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Virva Siira

VULNERABILITY SIGNS OF MENTAL DISORDERS IN ADOPTEES WITH GENETIC LIABILITY TO SCHIZOPHRENIA AND THEIR CONTROLS MEASURED WITH MINNESOTA MULTIPHASIC PERSONALITY INVENTORY

FACULTY OF MEDICINE,
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Abstract

Both genetic and environmental factors and gene-environment interaction have been found to contribute to the development of schizophrenia. Predisposition may manifest as prodromal vulnerability indicators before the onset of disease.

The aim was to search for vulnerability signs of schizophrenia spectrum disorders, to establish the origin of these signs, and to predict the future mental disorders of adoptees with these signs. The study is a part of the Finnish Adoptive Family Study of Schizophrenia. Genetic vulnerabilty indicators were studied by comparing MMPI (Minnesota Multiphasic Personality Inventory) subscales of high-risk adoptees (HR, biological mother with a diagnosis of schizophrenia spectrum disorder) and low-risk adoptees (LR, biological mother with no diagnosed schizophrenia spectrum disorder) in the sample of all adoptees (n = 182) and in the sample of initially mentally healthy adoptees (n = 136). The later mental health status of the initially mentally healthy adoptees (assessed with DSM-III-R criteria) was predicted by MMPI subscales during the 11-year follow-up. The origins of the vulnerability indicators were investigated by assessing gene-environment interaction using parental Communication Deviance (CD) as a measure of environmental risk (n = 99).

The MMPI subscales Hostility, Hypomania, and Social Maladjustment (these scales indicate emotional unresponsiveness, avolition, decreased energy, and introversion) were found to be vulnerability indicators of schizophrenia spectrum disorders. Social Maladjustment developed under gene-environment interaction when the environmental risk was assessed by CD. Psychopathic Deviate (asociality) was found to be a predictor of any later mental health disorder of the adoptees.

Genetic vulnerability to schizophrenia spectrum disorders, gene-environment interaction and later onset of psychiatric disorders were found to manifest in the adoptees' MMPI. These results suggest a need to use a combination of multiple methodologies in the screening of at-risk individuals and are useful in the clinical practice of preventive mental health care.

Keywords: adoptive family study, Minnesota Multiphasic Personality Inventory, vulnerability to schizophrenia

Siira, Virva, Skitsofreniaan perimän kautta altistuneiden adoptiolasten ja heidän verrokkiensa mielenterveyden häiriöiden ennusmerkit Minnesota Multiphasic Personality Inventory testissä

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Tiivistelmä

Skitsofreniaan sairastumisessa keskeisiä ovat perintö- ja ympäristötekijät sekä näiden yhdysvaikutus. Skitsofrenia kehittyy siten, että jo ennen sairauden puhkeamista on olemassa alttiutta ilmentäviä, sairautta ennakoivia prodromaali piirteitä.

Tämän tutkimuksen tarkoituksena oli etsiä skitsofreniaspektrin häiriöihin sairastumiseen liittyviä haavoittuvuutta ilmentäviä merkkejä, selvittää kuinka nämä kehittyvät ja ennustaa niillä adoptiolasten myöhempiä mielenterveydenhäiriöitä. Tutkimus on osa suomalaista adoptiolapsiperhetutkimusta. Perinnöllistä haavoittuvuuden ilmenemistä tutkittiin vertailemalla riskiadoptiolasten (biologisella äidillä oli skitsofreniaspektrin häiriö) ja heidän verrokkiensa (biologisella äidillä ei ollut skitsofreniaspektrin häiriötä) MMPI (Minnesota Multiphasic Personality Inventory) testin osa-asteikkoja kaikkien adoptiolasten ryhmässä (n = 182) ja tutkimuksen aloitusvaiheessa psyykkisesti terveiden adoptiolasten ryhmässä (n = 136). Tutkimuksen aloitusvaiheessa psyykkisesti terveiden adoptiolasten MMPI testin osa-asteikoilla ennustettiin 11 vuoden seurannassa heidän DSM-III-R kriteerein arvioitua mielenterveyttään. Perimän ja perheympäristön (adoptiovanhempien kommunikaatiohäiriöt) yhdysvaikutuksella pyrittiin selittämään haavoittuvuutta ilmentävien piirteiden syntyä (n = 99).

MMPI testin osa-asteikot Hostility, Hypomania ja osittain myös Social Maladjustment (astekot ilmentävät emotionaalisen vastavuoroisuuden puutetta, tahdottomuutta, energian puutetta ja sosiaalista vetäytyneisyyttä) osoittivat perinnöllistä haavoittuvuutta skitsofreniaspektrin häiriöihin. Social Maladjustment kehittyi perinnöllisen riskin ja adoptiovanhempien poikkeavan kommunikaation yhdysvaikutuksen seurauksena. Psychopathic Deviate (asosiaalinen käyttäytyminen) ennusti adoptiolasten myöhempää sairastumista mihin tahansa mielenterveydenhäiriöön.

Perinnöllinen alttius skitsofreniaspektrin häiriöihin, perintö- ja ympäristötekijöiden yhdysvaikutus sekä myöhempi sairastuminen mielenterveyden häiriöihin ilmenivät MMPI testin tuloksissa. Tuloksia voidaan käytää hyväksi mielenterveydenhäiriöiden ennaltaehkäisyssä.

Asiasanat: adoptioperhetutkimus, Minnesota Multiphasic Personality Inventory, skitsofrenian haavoittuvuustekijät

To Leo, Akseli, Samuli and Taneli

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Oulu, September 2007 Virva Siira

Abbreviations

MMPI	Minnesota Multiphasic Personality Inventory
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
PD	Personality Disorder
NOS	Not Otherwise Specified
HR	High-risk
LR	Low-risk
CD	Communication Deviance
OR	Odds ratio
ANOVA	Analysis of variance
AA	All adoptees
MHA	Mentally healthy adoptees
MHF	Mentally healthy adoptees at follow-up
APDF	Any psychiatric disorder at follow-up
L	Lie scale
F	Frequency scale
K	Correction, Clinical Defensiveness scale
4	Psychopathic Deviate (Pd) scale
HOS	Manifest Hostility scale
HYP	Hypomania scale
PHO	Phobias scale
PSY	Psychoticism scale
REL	Religious Fundamentalism scale
SOC	Social Maladjustment scale
2+7+8+0	Golden-Meehl Indicators scale (sum of Depression (2), Psychasthenia (7), Schizophrenia (8) and Social Introversion (0)
8-6	46 items from different MMPI scales, mainly from the scales 6 Paranoia and 8 Schizophrenia, Minneapolis Veterans Administration Hospital-MMPI Research Laboratory scale
Pz	Paranoid Schizophrenia scale
SzP	Schizophrenia Proneness scale

List of original publications

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

I Siira V, Wahlberg K-E, Miettunen J, Läksy K, Tienari P (2004) Psychometric deviance measured by MMPI in adoptees at high risk for schizophrenia and adoptive controls. J Pers Assess 83:14-21.

II Siira V, Wahlberg K-E, Miettunen J, Läksy K, Tienari P (2006) MMPI measures as signs of predisposition to mental disorder among adoptees at high risk for schizophrenia. Psych Res (in press).

III Siira V, Wahlberg K-E, Miettunen J, Tienari P, Läksy K (2006) Differentiation of adoptees at high versus low genetic risk for schizophrenia by adjusted MMPI indices. Eur Psych 21:245-250.

IV Siira V, Wahlberg K-E, Hakko H, Läksy K, Tienari P (2006) Interaction of genetic vulnerability to schizophrenia and Communication Deviance of adoptive parents associated with MMPI schizophrenia vulnerability indicators of adoptees. Nord J Psychiatry (in press).

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1 Introduction

Schizophrenia is a mental disorder influenced by genetic vulnerability, other biological factors, and psychosocial factors of the environment. According to the vulnerability models of schizophrenia, vulnerability indicators manifest before the clinically observable illness and increase the individual's predisposition to develop symptoms of schizophrenia in a stressful environment. Depending on the individual threshold of tolerating stress, the increased impact of genetic vulnerability and environmental stressors and the diminished effect of personal and environmental protectors may lead to emergence or absence of symptoms of psychosis.

Psychometric deviation in personality traits as measured by Minnesota Multiphasic Personality Inventory (MMPI) (Dahlstrom *et al.* 1982) has been investigated as a way to characterize schizophrenic disorders. Research has indicated that this psychological test classifies a large number of the pathological personality traits evident in schizophrenia. These can be identified before the onset of schizophrenia, during the disease, and after active psychosis. Subscales of MMPI have also been used as vulnerability indicators in schizophrenia.

Moldin *et al.* (1990a) and later Bolinskey *et al.* (2001) used a set of schizophrenia-related MMPI subscales in their studies of vulnerability indicators in schizophrenia. Their psychometric index of schizophrenia-related MMPI scales includes a validity scale, clinical scales, special scales, and a new derivation scale. These scales in the present study measure vulnerability in terms of personality aberrations.

The adoption study method offers advantages in research on psychosocial stress factors of schizophrenia. The effect of heritability and the environment can be studied separately since the genes of adopted-away children of parents with schizophrenia come from their biological parents, while the adoptive parents shape their rearing environment. Psychometric deviance in the personality traits of adoptees indicating vulnerability to schizophrenia or other psychiatric disorders has not been studied very much. Earlier studies have explored the differences between genetic high-risk and low-risk groups and predicted the later mental status of children at high genetic risk and their controls. The interaction of genetic and environmental factors in the development of vulnerability indicators measured by MMPI within an adoptee sample has not been reported earlier.

Communication Deviance (CD) (Wynne *et al.* 1977) in the rearing parents has been found to increase the probability of schizophrenia in adopted-away

offspring of mothers with schizophrenia as an environmental stress factor. CD is a measure of communication style in the rearing environment. Clear parental communication in the rearing of children supports the cognitive development of thought, while deficits in parental communication have a disturbing effect on the child's development.

In the present study, we investigated which MMPI subscales are related to the genetic risk of schizophrenia, which MMPI subscales predict later onset of schizophrenia and other mental disorders, and whether genetic vulnerability and environmental risk separately or their interaction manifest in the MMPI subscale scores of adopted-away offspring of mothers with schizophrenia and their controls. Our sample is a subsample of the nationwide Finnish Adoptive Family Study of Schizophrenia.

2 Review of the literature

2.1 Schizophrenia

2.1.1 Psychopathology and course of schizophrenia

Schizophrenia is a mental disorder that can make the patient's life difficult in many different ways. The premorbid manifestations of psychopathology in schizophrenia are diverse, including clinical, behavioral, biological, motor, perceptual, and neuropsychological processes (Bilder *et al.* 2006, Jones *et al.* 1994, Lewis *et al.* 2000, Picchioni *et al.* 2006). Personal symptoms that are markers of vulnerability and/or indicators of risk and/or early signs of the disorder may begin before the characteristic manifestations of obvious illness (Nuechterlein 1987, Yung & McGorry 1996). This prodromal phase begins from the first observable signs of illness and ends up at the onset of psychosis (Larsen *et al.* 1996, Yung & McGorry 1996).

Active psychosis is manifested as problems in reality testing (Bleuler 1911/1950), such as problems in thinking (delusions) and impaired perception (hallucinations). Other typical symptoms of schizophrenia are incoherence, loosening of associations, inappropriate or flat affect, and possibly catatonic behavior (American Psychiatric Association 1987). It is typical of schizophrenia that diminished executive processes impair functioning at work, interpersonal relations, and self-care.

The symptoms of schizophrenia can be longstanding. Long-term follow-up studies have shown that active symptom progression takes 3-5 years, after which the changes are usually less invalidating (Ciompi 1980, Eaton *et al.* 1992a, 1992b). The risk for relapse of psychotic symptoms is greatest within the first few years after onset. Studies have indicated that the detection of prodromal signs and early psychopharmacological and psychosocial interventions provide the best treatment results in schizophrenia (Falloon *et al.* 1996, McGlashan 1998, McGorry *et al.* 2000, Yung *et al.* 1998).

2.1.2 Epidemiology of schizophrenia

The lifetime risk on schizophrenia is about 1% in the general population. The incidence rate ranges from 0.17 to 0.54 in a population of 1000 per year

(Jablensky 2003). Studies have found that first-degree relatives of schizophrenia patients have an approximately tenfold risk for illness (Gottesman 1991, Kendler 2004), and the risk for schizophrenia is somewhat higher in men compared to women (Aleman *et al.* 2003). The onset is also earlier in men (20-28 years) than in women (24-32 years) (Häfner 2003).

2.1.3 Etiology of schizophrenia

Schizophrenia has been suggested to be multifactorial/polygenetic in nature (Gottesman 1994, Gottesman & Shields 1967, Reich *et al.* 1972, Tsuang 2000). Research has indicated that schizophrenia is influenced by genetic vulnerability as well as biological and psychosocial factors (Fanous *et al.* 2005, Kendler *et al.* 2000, Singh *et al.* 2004, Tienari *et al.* 2004).

Genetic risk factors in schizophrenia have been studied widely. The risk of schizophrenia increases in proportion to familial closeness and the number of affected relatives (Erlenmeyer-Kimling *et al.* 1997, Gottesman 1991, McGuffin *et al.* 1984, Tienari *et al.* 2003). Recent findings in molecular biology show the importance of epigenetic studies for describing modifications of the genome in schizophrenia (Petronis 2004).

Although offspring of parents with schizophrenia have a higher risk for the disease compared to the general population, schizophrenia generally does not transmit directly, as do Mendelian disorders (Gottesman 1991). Estimations of the risk for schizophrenia demonstrate that, of all children born to one parent with the disease, 87%, will not develop clinically observable schizophrenia (Gottesman & Erlenmeyer-Kimling 2001). An adoption study that excluded the rearing contributions of the biological mothers with schizophrenia indicated that 5.34% of adopted-away offspring developed narrowly defined schizophrenia compared to the low-risk adoptees, of whom 1.74% had the same disorder (Tienari *et al.* 2003). Relatives of schizophrenic probands have been reported to be at increased risk to Schizotypal Personality Disorder (PD), Schizoid PD, and Paranoid PD, which are included in the category of Cluster A personality disorders (Baron *et al.* 1985, Tienari *et al.* 2003). There are no reports of a general liability to psychiatric disorders in schizophrenia. However, some studies have found that the frequency of psychiatric disorders is higher in offspring born to mothers with schizophrenia than among offspring at low genetic risk (Niemi *et al.* 2004, Parnas *et al.* 1993, Schubert & McNeil 2003).

According to the original determination, the ”schizophrenia spectrum” includes all disorders that are “to some extent genetically transmitted” (Kety *et al.* 1968). The search for the genetically related disorders of schizophrenia continues to resolve this still open question (Erlenmeyer-Kimling *et al.* 1997, Tienari *et al.* 2003).

Obstetric complications and adverse events during pregnancy have been found to increase the risk of schizophrenia (Jones *et al.* 1998, McNeil & Cantor-Graae 1999, Zornberg *et al.* 2000). Studies have demonstrated that there is an association between prenatal exposure to influenza and later schizophrenia (Huttunen *et al.* 1994, Sorensen *et al.* 2004). Fetal hypoxia has been found to be more frequent in patients with schizophrenia than in their siblings and normal controls (Cannon *et al.* 2002).

Early theories of psychosocial factors describe linear family relationships between a pathogenic mother (Fromm-Reichman 1948) and her child and ‘double bind’ interaction, where the child is unable to respond adequately to deviant information from a parent, which contributes to the development of schizophrenia (Bateson *et al.* 1956). In addition, chronic marital conflict, marital skew (Lidz *et al.* 1965), and pseudomutuality between family members have been found in the families of patients with schizophrenia (Wynne *et al.* 1958). Unwillingness to define roles in the family due to a threat of family breakdown has been found to be associated with the onset of schizophrenia (Selvini-Palazzoli *et al.* 1980, 1989). Later studies of schizophrenia have emphasized biopsychosocial factors within the system theory framework (Benjamin 1982, Engel 1977, Wynne 1987).

2.1.4 Gene-environment interaction

Modern concepts of the development of schizophrenia focus on the joint effects of genetic and environmental risk factors (Cooper 2001). Current theories suggest that several risk factors are needed, and that different risk factors are emphasized individually in the onset of schizophrenia (Cullberg 1993a, 1993b, Rutter & Silberg 2002). Theories of gene-environment interaction in the vulnerability to schizophrenia demonstrate that genes and the environment can interact in several different and potentially subtle ways (Kendler & Eaves 1986, Rutter *et al.* 2001).

The model of additive effects of the genotype and the environment implies that genetic and environmental factors enhance each other’s effects in the development of schizophrenia (Kendler & Eaves 1986). According to this model, protective and predisposing environmental factors have similar effects on the

vulnerability to schizophrenia, independently of what genetic factors are involved. In addition, the probability of an individual's exposure to a given environment is independent of his/her genotype. According to the second model, genetic control of sensitivity to the environment means that, instead of directly altering the probability of illness, the genes control the degree to which the individual is sensitive to the risk-increasing or risk-reducing aspects of the environment. A 'sensitive' genotype contributes the greatest increase of liability in a predisposing environment and the greatest decrease in a protective environment. Thus, a sensitive person gets more benefit than other persons from a protective environment (Wahlberg *et al.* 1997). Exposure to a predisposing environment is thought to be independent of genetic factors in these models.

A third possibility is that there is genetic control of exposure to the environment in the development of schizophrenia (Kendler & Eaves 1986). Genes and the environment correlate in such a way that genes only influence the liability to illness by regulating the probability of exposure to a predisposing environment. As an example, we assume that a gene has been identified which contributes the probability of having impulsive and unstable personality traits and many life events, such as job and relationship changes. We also assume that the AA genotype has the highest and the aa genotype the lowest liability to impulsiveness and life events. Because adverse life events predispose an individual to depression, the AA genotype has the highest and the aa genotype the lowest liability for this disorder. There is no difference in the risk of illness between these genotypes in the presence of a life event. In this model, as a moderator, the genotype specifies in whom or under what conditions a mediator that is an environmental variable will lead to the development of a mental disorder (Kraemer *et al.* 2001).

2.1.5 Summary of the development of schizophrenia

The development of schizophrenia proceeds through several phases with different symptoms, but not all affected individuals go through every phase. Genetic vulnerability increases the risk of schizophrenia, but not all high-risk individuals develop schizophrenia. The current theories of schizophrenia implicate that early detection of prodromal symptoms and early treatment may help to prevent the chronicity of schizophrenia and even prevent the onset of the actual disorder. Thus, more information about the riskfactors, their interaction, and their

predictive validity is needed to clarify the causal chain leading to the onset of symptoms of schizophrenia or other mental disturbances among individuals.

2.2 Vulnerability to schizophrenia

The pattern by which psychic processes develop the symptoms of schizophrenia has been called ‘predisposition’ or ‘underlying primary features’ by Bleuler (1911/1950). The term ‘liability for schizophrenia’ used by Falconer (1965) includes the contribution of all genetic and environmental influences that make an individual more or less likely to get the disease. It has been suggested that the diathesis is polygenetically determined, and that the constitutional predisposition to develop schizophrenia is inherited, while the disorder itself is not. (Gottesman & Shields 1967)

Several vulnerability models of schizophrenia have been developed to describe the process whereby a genetic liability to schizophrenia leads to the disease under the influence of environmental stress (Nuechterlein 1987, Rosenthal 1970, Zubin & Spring 1977). The diathesis-stress model presented by Rosenthal (1963, 1970) emphasizes that inborn vulnerability and environmental stressors heighten each other until schizophrenic symptoms appear. According to the vulnerability model outlined by Zubin and Spring (1977), episodes of the schizophrenic disorder are regarded as states and vulnerability as an enduring trait. Exogenous and/or endogenous stress factors elicit symptoms of schizophrenia, so that finally, depending on the intensity of the stress and the personal threshold for tolerating it, symptomatic episode of schizophrenia will or will not emerge. Wynne (1978) adds the epigenetic dimension to the concept of vulnerability, meaning that vulnerability develops under the interchange of constitutional and experiential influences of an individual.

Nuechterlein (1987) includes biological and behavioral personal vulnerability factors, personal protectors, environmental stressors, and environmental protectors into a framework of a possible causal chain leading to schizophrenic episodes. These episode indicators are present only during the psychotic episode, while the stable vulnerability indicators are trait-like abnormalities that exist independently of the symptomatic state. The mediating vulnerability factors show deviance from normality in both psychotic and asymptomatic states.

The increased impact of genetically mediated personal vulnerability factors of schizophrenia and/or environmental stressors and the diminished effect of personal and environmental protectors may manifest as overloaded cognitive

processing capacity and autonomic hyperarousal, leading to prodromal symptoms of schizophrenia and further to the onset or relapse of the disorder (Nuechterlein 1987). In addition, according to Zubin and Spring (1977), the concept of adaptation is useful in describing the relationship of vulnerability and life event stressors in schizophrenia. It means the extent to which an individual responds adequately and appropriately to stimuli of the environment, not only as a living organism, but also as a learning individual with coping skills and competencies.

As stated earlier, modern gene-environment interaction theories of schizophrenia describe the joint effect of genes and environmental factors (Kendler & Eaves 1986). These theories imply the vulnerability concept in the development of the schizophrenia.

2.2.1 Personal vulnerability indicators

Vulnerability indicators have been suggested to develop in transactions of the individual with the physiological and psychosocial environment, where each new developmental phase is built on outcome of earlier transactions (Cicchetti & Cohen 1995, Wynne 1978). Personal vulnerability factors manifest at the behavioral and biological levels (Green 1998, Nuechterlein 1987). Genetic liability to schizophrenia has been measured by using liability or vulnerability indicators, markers, or factors and predictors, signs, and traits as variables (Ellison *et al.* 1998, Erlenmeyer-Kimling 2000).

Biological vulnerability markers are anatomical and chemical abnormalities. Recent genetic linkage and association methods have provided increased evidence for several chromosomal loci related to schizophrenia susceptibility (Harrison & Weinberger 2005, Lipska *et al.* 2006). Dopamine dysregulation in the cerebral neurotransmitter system has been proposed as an underlying trait associated with vulnerability to schizophrenia (Hirvonen *et al.* 2005, Laurelle 2000). Structural brain abnormalities have been suggested to be genetically mediated and, thus, possible markers of vulnerability (Cannon *et al.* 1994, Lawrie *et al.* 1999).

Biobehavioral vulnerability markers are considered to be close to the underlying biological factors of schizophrenia because they manifest in the child's early development (Cornblatt *et al.* 1999, Cornblatt & Obuchowski 1997). Early problems in neurological and motor development have predicted later development of schizophrenia in the offspring of parents with schizophrenia (Fish *et al.* 1992, Hans *et al.* 1999). Studies have indicated that attention and information processing deficits measured by the SOA (span of apprehension),

CPT (continuous performance test), and neuropsychological tests are associated with schizophrenia and may be vulnerability indicators (Asarnow *et al.* 1991, Erlenmeyer-Kimling *et al.* 2000, Maier *et al.* 1992, Nuechterlein *et al.* 1986, Nuechterlein *et al.* 1994a). In addition, high-risk studies have demonstrated visual dysfunction and eye movement abnormalities measured by SPEM (smooth pursuit eye movement) to be associated with later onset of schizophrenia (Ross *et al.* 1996, Schubert *et al.* 2005).

Research has demonstrated that high-risk children who will develop schizophrenia later have more thought disorder and more problems in verbal memory, gross motor skills, and attention than children without genetic risk (Erlenmeyer- Kimling 2000, Ott *et al.* 2001). Thought disorders have been found to be stable over time and to predict a subsequent onset of psychiatric disorder among high-risk and low-risk adoptees (Metsänen *et al.* 2006, Metsänen *et al.* 2004).

Behavioral vulnerability markers are found in the clinical assessment of personality, in psychiatric symptoms, and in the deviance of motor, perceptual, or neuropsychological processes (McGlashan & Johannessen 1996). High-risk studies have indicated that behavioral, emotional, and social adjustment problems precede later onset of schizophrenia and are thus possible vulnerability indicators (Amminger *et al.* 2000, Marcus *et al.* 1987, Olin *et al.* 1995). Childhood behavioral problems without substance abuse, anxiety at age of the 16, and interaction of the genetic risk with the rearing environment as well as disruptive school behavior have been shown to predict schizophrenia (Amminger *et al.* 1999, Carter *et al.* 2002, Kugelmass *et al.* 1995). High-risk studies have used MMPI in the search for psychometric deviance in personality traits as liability indicators for schizophrenia (Bolinskey *et al.* 2001, Carter *et al.* 1999).

2.3 Environmental stress in schizophrenia

In psychiatry, stress has been conceptualized as an external event that causes psychological distress. Stressful life events may include the death of an important person, marriage, the birth of a child, or loss of employment.

Studies have shown that psychosocial stress may precede the onset of full-blown schizophrenia (Bebbington *et al.* 1993, Corcoran *et al.* 2003). In addition, studies have demonstrated that psychosocial stress is often a precursor of the relapse of schizophrenic symptoms (Brown & Birley 1968, Ventura *et al.* 1992).

However, stressful events are associated with personal adaptive capabilities in the relapse of schizophrenia among some patients (Pallanti *et al.* 1997).

A hostile, critical, and overinvolved family emotional climate, as measured by high expressed emotion (EE,) has been found to predict relapse of schizophrenia (Kavanagh 1992, Leff & Vaughn 1985). Within a family with a member who has schizophrenia, low expressed emotion may be a protective factor (Nuechterlein *et al.* 1994b). Further, a study of EE demonstrated that controlling behaviors by family members may predict relapse of schizophrenia. (Hooley & Campbell 2002). If parents do not regard their offspring as medically ill, they may not be willing to change their own behavior. Thus, the controlling and critical comments made by family members about the patient's odd behavior may be due to their efforts to support the patient to have behave normally. In terms of the Attributional Model, criticism is not determined only by parental or the patient's characteristics, but by the definition given to the behavior of the offspring (Hooley 1987). These efforts may sometimes help the patient, but critical comments may also be overstimulating, leading to aggravation of symptoms (Wahlberg & Wynne 2001). Another study of a stressful family situation demonstrated that measures of interpersonal criticism predict psychotic thinking among patients with working memory deficits (Rosenfarb *et al.* 2000).

2.3.1 Parental Communication Deviance

Communication Deviance (CD) is extensively studied vulnerability factor of the rearing environment in schizophrenia research (Miklowitz & Stackman 1992). The concept has been applied to measurements of disordered verbal discourse processes manifesting among parents of offspring with schizophrenia. Wynne and Singer (Singer & Wynne 1965a, b, Singer & Wynne 1966, Wynne & Singer 1963a, b) demonstrated that a high level of CD is an indicator of the parents' inability to share and maintain a focus of attention and meaning with the child, which endangers the child's cognitive, emotional, and personality development. Deviant parental communication implies that the child has problems understanding what is spoken about and thus experiences these situations as confusing. The child's perception is directed to details of the communication instead of the focus of attention shared with the parents. This may make the child predisposed to schizophrenia and other psychotic disorders.

CD is a composite index of communication patterns measuring reciprocal interpersonal process between rearing parents and their children (Wahlberg *et al.*

2001, 2004). CD of the rearing parents establishes a long-term, stressful learning environment of the child, characterized by a major, enduring relationship between the parents and the offspring (Singer *et al.* 1978, Wynne *et al.* 1977). Research has demonstrated that CD of adults is a stable, trait-like feature rather than a temporary state (Nugter *et al.* 1997, Velligan 1995, Wahlberg *et al.* 2001). In addition, it has been shown to be permanent in interactive situations with variable compositions of family members (Keskitalo 2000) and also stable over time (Wahlberg *et al.* 2000).

Communication Deviance in schizophrenia and other mental disturbances

Several researches have indicated that CD is associated with schizophrenia. Singer and Wynne (1963) found the parents of children with schizophrenia to have higher CD compared to the parents of withdrawn children or autistic children. Later studies have demonstrated that high parental CD is significantly more frequent in families with schizophrenic offspring than in families with normal, neurotic, or borderline offspring (Wynne *et al.* 1977) or in families with depressive offspring (Asarnow *et al.* 1988). A prospective study showed that initially nonpsychotic, distressed adolescents with high-CD parents developed more schizophrenia spectrum disorders than adolescents with low-CD parents during 15-year follow-up (Goldstein 1987). Recently, a high rate in CD has been found to be associated with a family history of schizophrenia spectrum disorders among the parents and siblings of parents with schizophrenic offspring (Subotnik *et al.* 2002).

However, parental CD is not a specific characteristic of schizophrenia. Studies have shown CD also to be present in parents who have offspring with other severe psychiatric disorders (Miklowitz *et al.* 1991, Wahlberg *et al.* 2004). In addition, studies have addressed the different cognitive and psychosocial impairments among children that might be associated with high rates of CD in parents hospitalized for mental disturbances (Doane *et al.* 1982, Wynne 1987). Docherty (1995) replicated the original finding on the usefulness of CD in predicting thought disorder of offspring. It has also been demonstrated that a high rate of parental CD is associated with attentional disturbances and learning disabilities of offspring (Ditton *et al.* 1987, Nuechterlein *et al.* 1989, Wagener *et al.* 1986).

Studies of high-risk adoptees offer the best evidence for independent measures of genetic and environmental effects in schizophrenia, since the biological parents with schizophrenia are not the rearing parents (Tienari *et al.* 2000, Tienari & Wynne 1994). Thus, the genotype of an adoptee comes from the biological parents, while the rearing environment is shaped by the adoptive parents. The results of the recent adoption study indicate that, in addition to schizophrenia spectrum disorders, high-risk adoptees with high-CD adoptive parents also have more other mental disorders than low-risk adoptees with high-CD adoptive parents (Wahlberg *et al.* 2004).

Finnish adoption research has also indicated that there is gene-environment interaction in the development of thought disorder as an indicator of schizophrenic vulnerability (Wahlberg *et al.* 1997, 2004). Metsänen (2007, Metsänen *et al.* 2007) also reported an association between the thought disorder of adoptees and the CD of their parents. Wahlberg (1994, Wahlberg *et al.* 1997) showed that CD of adoptive parents is associated with thought disorders of high-risk adoptees, but also that high-risk adoptees are more sensitive to the family environment than their control adoptees. High-risk children develop thought disorders if their adoptive parents have high CD scores. However, high-risk adoptees of low-CD adoptive parents develop less often thought disorders than their adoptive controls of low-CD adoptive parents, indicating increased sensitivity to protective environments among high-risk adoptees. This is in line with the model of genetic sensitivity to the environment (Kendler & Eaves 1986).

2.4 Psychometric deviance of personality traits in schizophrenia as assessed by MMPI

The most commonly known instrument for assessing psychometric deviance in personality traits and vulnerability to schizophrenia is the Multiphasic Minnesota Personality Inventory (MMPI) (Dahlstrom *et al.* 1982, Marks *et al.* 1974). MMPI has been established as a reliable and valid instrument for measuring schizophrenic psychopathology (Gottesman & Shields 1972, Graham 1987, Meehl 1972). It is a standardized psychological test applying an objective interpretation and quantitative assessment of personality traits (Greene 1980, Walters 1983, Walters 1988). As a multifaceted inventory, it allows for

heterogeneity in the description of the clinical symptoms of patients with schizophrenia (Merrit *et al.* 1998, Zalewski & Gottesman 1991).

Earlier studies indicate that the MMPI criteria used to establish a diagnosis of schizophrenia have varied (Haier *et al.* 1979, Johnson *et al.* 1980). Six rules (1. T-score > 70 on at least four scales, 2. F > 65, 3. Sc > Pt, 4. Pa or Ma > 70, 5. Pa or Sc or Ma > Hs and D and Hy, 6. D > Hs and Hy) for the MMPI developed by Peterson (1954) have been used successfully to discriminate between individuals with and without schizophrenia (Affleck & Garfield 1960, Giannetti *et al.* 1978, Goodson & King 1976). Schizophrenia and neurosis have been differentiated with a configural scale and a linear index derived from MMPI (Goldberg 1965, Taulbee & Sisson 1957). MMPI scales have been shown to differentiate symptomatic schizophrenia patients from manic inpatients (Walters & Greene 1988). In addition, a MMPI index developed by Newmark *et al.* (1975) and MMPI high-point pairs have been used in differential diagnosis of schizophrenia (Gilberstadt & Duker 1965, Marks *et al.* 1974).

The methodology in the search for indicators of the schizophrenic phenotype changed in terms of personality aberrations when researchers began to use several MMPI validity, clinical, and special scales instead of focusing on traditional univariate analysis (Moldin 1985, Walters 1983). Moldin *et al.* (1987a) differentiated schizophrenia from affective disorders and from normality with an MMPI index of this kind. MMPI measures were useful in describing the phenomenology specific for schizophrenia, such as the predominance of disturbances in thought, social relations, motivation, and affective expressivity. A combination of signs derived from MMPI was effective in discriminating schizophrenia from psychotic and non-psychotic affective disorders and normality (Moldin *et al.* 1987b). In addition, a psychometric index composed of schizophrenia-related MMPI special scales (Rosen 1962, Wiggins 1966) has been demonstrated to increase the efficacy of diagnosing schizophrenia (Moldin *et al.* 1991).

2.5 MMPI-measured psychometric deviance in personality traits as potential vulnerability indicator

2.5.1 MMPI group differences in offspring of parents with schizophrenia and their controls

MMPI (Dahlstrom *et al.* 1982) has been used to assess psychometric deviance in individuals presumed to be at risk for schizophrenia due to a genetic association with a parent diagnosed with schizophrenia (Walters 1988). Research has indicated that the rate of MMPI-measured psychometric deviance in terms of disturbances in thinking, social relatedness, volition, and affective expressivity is significantly higher among offspring of parents with schizophrenia (23%) than in psychiatric (7%) or normal controls (2%) (Moldin *et al.* 1990a). Another study of Moldin *et al.* (1990b) indicated that the distribution of MMPI-measured psychometric deviation was bimodal in a group of 171 children including offspring at a high genetic risk (HR) for schizophrenia, offspring at a genetic risk for affective illness (PC, psychiatric control), and offspring at no increased risk for psychiatric morbidity (NC, normal control). The study demonstrated a valid and non-arbitary distinction between a subgroup of MMPI-deviant subjects, including 54% of HR subjects, and a larger homogenous group of MMPI-nondeviant HR, PC, and NC subjects. Thus, MMPI is useful in resolving within-group heterogeneity in high-risk research of schizophrenia, because only a subgroup of those at risk will get the disorder. Psychometric deviance in personality traits assessed by MMPI has been found to be strongly familial and thus an effective indicator for liability to schizophrenia (Moldin *et al.* 1990c).

These studies used high-risk samples with offspring born to and reared by mothers with schizophrenia. Thus, the possible disturbing environmental influence of parental psychiatric illness on the development of a vulnerability indicator was not excluded.

2.5.2 Confounding variables in MMPI research

MMPI has been reported for a variety of populations, including both clinical and normal groups (Friedman *et al.* 1989). Much of the research on MMPI and schizophrenia, however, have been done exclusively on young, male, and white individuals with schizophrenia (Walters 1988). Thus, the generalizability of the results may be questionable between demographically different studies. The

mostly studied moderator variables of MMPI and schizophrenia are age, gender, race, education, and marital status.

Several studies have failed to demonstrate differences in the profiles of females and males with schizophrenia (Newmark *et al.* 1980, Wauck 1950). Only one study has demonstrated that female and male psychotics have high scores on the different MMPI scales (Goodson & King 1976). Some MMPI indices have been found to be more effective in identifying males with schizophrenia and schizophrenia spectrum disorders than corresponding females (Haier *et al.* 1978, Watson 1971).

Studies have indicated that MMPI is more effective in differentiating between young individuals with and without schizophrenia than corresponding elderely groups (Dawis 1972, Wauck 1950). This result was replicated in a sample of patients with acute schizophrenia, suggesting that the leveling off of MMPI scores among elderely individuals with schizophrenia is not due to long-term hospitalization or chronicity of the disorder (Davis *et al.* 1973). In addition, the MMPI index developed by Newmark *et al.* (1978) has been shown to be more useful in identifying schizophrenia among young adults (Newmark *et al.* 1980) than among adolescents (Newmark *et al.* 1983) or older individuals with schizophrenia (Newmark & Hutchins 1980).

All earlier studies of moderator variables in schizophrenia and MMPI have included only patients with schizophrenia (Walters 1988). The effect of the demographic variables may be different in a sample of offspring without psychiatric disorders and born to parents with schizophrenia. In their research for vulnerability indicators of schizophrenia among mentally healthy offspring born to parents with schizophrenia, Moldin *et al.* (1990a, b, c) and Bolinskey *et al.* (2001) utilized gender, age, and socioeconomic status in adjusting MMPI T scores to control for the possible effect of demographic variables.

Studies have found that demographic variables may potentially modify the relationship between MMPI and vulnerability to schizophrenia. However, earlier studies using adjusted MMPI variables in the search for vulnerability indicators did not include adopted-away children of mothers with schizophrenia.

2.5.3 Predicting later mental health by MMPI

The predictive validity for schizophrenia of different compositions of Moldin's (1990a) MMPI variables from a shortened 304-item version of MMPI was reported by Carter *et al.* (1999). The subjects who later developed schizophrenia

in a sample of adolescents at high risk for schizophrenia scored significantly higher on the F scale (Frequency) and the PSY scale (Psychoticism) than those with no mental illness at follow-up. When a high-risk preschizophrenic group was divided into paranoid and non-paranoid subgroups, the F scale, PSY scale, and Pz scale (Paranoid Schizophrenia) significantly discriminated paranoid preschizophrenics from nonparanoid preschizophrenics and subjects with no mental illness at follow-up.

Most recently, Bolinskey *et al.* (2001) used Moldin's psychometric index (1990a) and a new SzP scale (Schizophrenia Proneness) to predict later schizophrenia among offspring born to one parent with schizophrenia. They found that a revised psychometric index including the Lie (L), Correction (K), 2+7+8+0 (Golden-Meehl Indicators, sum of the Depression, Psychasthenia, Schizophrenia, and Social Introversion), Social Maladjustment (SOC), Psychoticism (PSY), Phobias (PHO), 8-6, and Schizophrenia Proneness scales (SzP) differentiated statistically significantly high-risk children who later developed schizophrenia from other high-risk children and from children with another diagnosis or no diagnosis.

These studies confirmed that MMPI may be used as a measure of signs of predisposition to schizophrenia among high-risk populations. The predictive validity of schizophrenia-related MMPI variables to any psychiatric disorder has not yet been investigated.

2.5.4 MMPI and adoption studies of schizophrenia

Two studies, on children at high risk for schizophrenia not reared by a parent with psychiatric illness, reported the results of MMPI assessments among children. Firstly, the study of MacCrimmon *et al.* (1980) demonstrated that MMPI scales differentiated the fostered offspring of mothers with schizophrenia from non-foster controls, but not from a foster control group. The study speculated that the result may be due to the shared traumatic life experiences of the fostered subjects, who had been placed in foster care because of the inability of a single parent in rearing his or her children. Another study included adopted-away offspring of parents with schizophrenia who were assessed by the MMPI scales (Haier *et al.* 1978). The MMPI criteria of schizophrenia-related psychopathology differentiated more adopted-away offspring of parents with schizophrenia than their controls based exclusively on the Psychological Disturbance Index. The results indicated that MMPI criteria combined with interview-based diagnoses

detected schizophrenia spectrum disorders in 22% of the subjects at high risk for schizophrenia and in 6% of the control subjects.

The offspring in these two studies were not reared by mentally ill parents, and they had thus avoided the possible disturbing environmental influences of psychiatric illness. However, neither of these studies included direct measures of environmental risk factors.

3 Aims of the study

The aim was to find signs of vulnerability to schizophrenia, to establish the origin of these signs, and to predict the future mental disorders of adoptees with these signs. The detailed aims of this study were:

1. Are signs of psychometric deviance measured by MMPI subscales indicators of vulnerability to schizophrenia spectrum disorders (I, III).
2. Can a schizophrenia spectrum disorder or another mental disorder of adoptees be predicted by MMPI subscales (II).
3. Is the interaction between the genetic risk for schizophrenia and the family environmental risk measured as Communication Deviance (CD) of the adoptive rearing parents associated with the MMPI-assessed vulnerability of the adoptee (IV).

4 Material and methods

4.1 Study design

The present study of vulnerability to schizophrenia represents a longitudinal and prospective adoption and high-risk study design. More specifically, the adoptive study method was used, where the genetic factors of the adopted-away child come from the biological parents and the environmental factors are determined by the adoptive parents.

4.2 Study population, sample selection, and methods of the Finnish Adoptive Family Study of Schizophrenia

This research is part of the National Finnish Adoptive Family Study of Schizophrenia. The original sample, which was assembled and studied based on the initiative of Professor (emeritus) Pekka Tienari, included all Finnish adopting-away biologic mothers who had been hospitalized for schizophrenia or paranoid psychosis during the years 1960-1979 and their adopted-away children and these children's adoptive families (Tienari *et al.* 1981, 1987, 2000, 2003, Tienari & Wynne 1994) (Figure 1). At the initial phase of the original sample selection, control adoptees and adoptive parents were identified through the files of a national adoption agency. The purpose of this nationwide research project was to describe the relationship between the genetic and environmental factors contributing to the development of mental health among the adopted-away offspring of mothers with schizophrenia.

Adoptive families were ordinary, usually childless Finnish families. The study children had been adopted by these non-related families before the age of 4 years. The adoptive parents were unaware of their adoptive child's background. Most of the adoptions were organized through a private organization "Save the Children Finland" (Pelastakaa Lapset ry). A smaller proportion of the children were adopted through municipal social boards. The original high-risk sample consisted of the adopted-away children born to hospitalized female patients, because the adoptions were committed by the biological mothers, and only these adoptions could be checked through formal registers. Only 57% of the adopted-away children's fathers have been identified through legally available files of the judicial district, adoption agency records, or information given by the adopting-

away mothers in the research interviews. Thus, the fathers' mental disorders were not used as a criterion in sample selection.

Research interviews were carried out blindly (the interviewers were unaware of the adoptees' genetic background) during the years 1977-1989 by psychiatrists and psychologists trained in the assessment methodology of the study. All the adoptive families were interviewed at their homes. The interviews and tests were tape-recorded for later blind re-ratings, reliability checks, and re-classifications. Information of genetic and early environmental variables, individual and familial intermediate vulnerability variables, and psychiatric status was collected in terms of the vulnerability model of schizophrenia.

Data on the psychiatric status of the adopting-away parents was obtained firstly through hospital diagnoses. The Research Diagnostic Criteria (RDC) (Spitzer *et al.* 1978) were applied to the initial and follow-up hospital records. Also, the modified Present State Examination (PSE) (Wing *et al.* 1974) was used in the psychiatric interviews to ensure the RDC and the final operational diagnostic criteria for Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (American Psychiatric Association 1987).

The initial evaluations of the adoptive families were performed using joint spousal and family interviews, spousal and consensus Rorschach protocols (Loveland *et al.* 1963), and the Interpersonal Perception Method (Laing *et al.* 1966). The adoptees and both adoptive parents were interviewed individually with a semi-structured diagnostic procedure. Abbreviated versions of Wechsler's Adult Intelligence Scale (WAIS) and Wechsler's Intelligence Scale for Children (WISC) and individual Rorschach tests were also admistered. The initial MMPI assessments were carried out during the years from 1978 to 1990 for the adopted children.

4.2.1 Follow-up study of adoptees

The follow-up evaluations of the adoptees were carried out after a median interval of 12 years from the initial assessments. The adoptees were re-interviewed and re-tested using the extended lifetime version of PSE, SCID-II (Spitzer *et al.* 1989), and the structured interview for schizotypy (SIS) (Kendler *et al.* 1989). In addition, the follow-up assessments of the adoptees included psychological and neuropsychological testing.

The follow-up diagnostic information for all study subjects was collected through the Hospital Discharge Register, the Pension Register, the National

Health Insurance Files, the National Criminal Register, and the National Register of Causes for Death. Based on the register follow-up until the year 2000, most of the adoptees had passed the age of the maximum risk for schizophrenia.

After research interviews and register checks, all diagnoses were assigned using the DSM-III-R criteria. The final sample included 190 offspring at high genetic risk (HR) born to biological mothers with DSM-III-R diagnoses of the broad schizophrenia spectrum and 192 adoptees at low genetic risk (LR), whose biological mothers had a nonspectrum diagnosis or no psychiatric disorder (Kendler *et al.* 1996, Tienari *et al.* 2000, 2003, 2004).

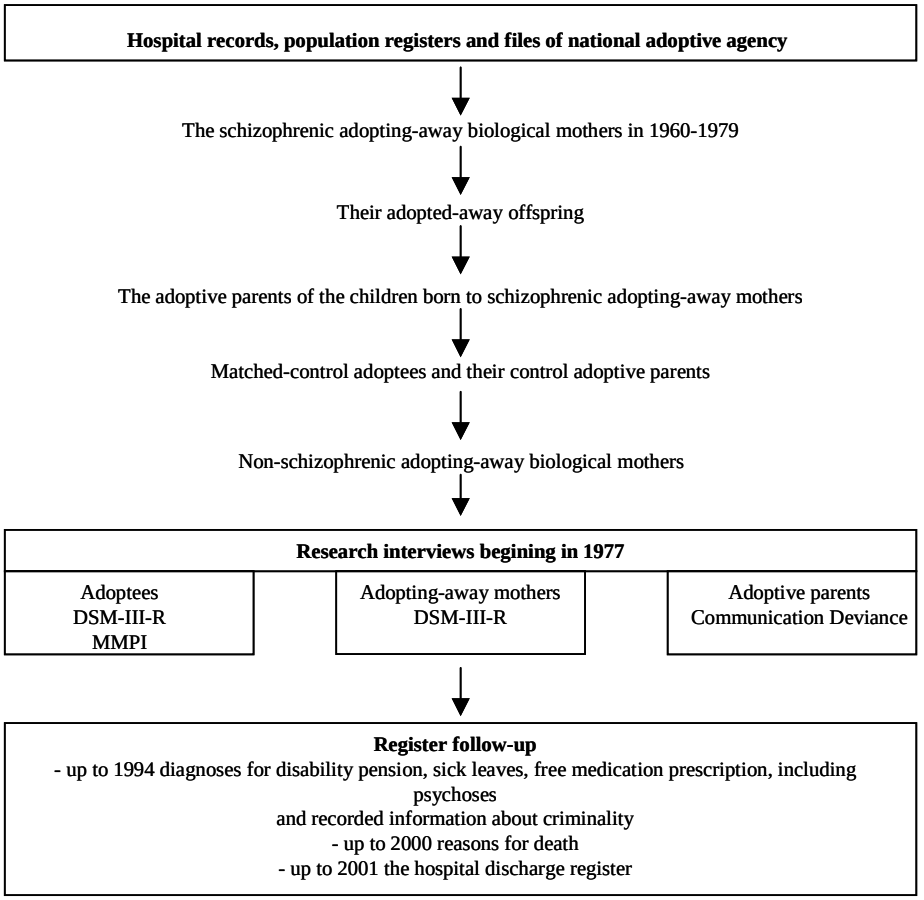

Fig. 1. Flowchart of data collection in the Finnish Adoptive Family Study of Schizophrenia and in the original publications I-IV

4.2.2 Study samples in the original publications I-IV

The subjects of the present study are a subsample of the Finnish Adoptive Family Study of Schizophrenia. Altogether 189 adoptees of the original sample of 382 adoptees completed the MMPI at the initial assessment. After exclusion based on the MMPI validity criteria (Figure 2), 182 MMPI profiles of adoptees were included.

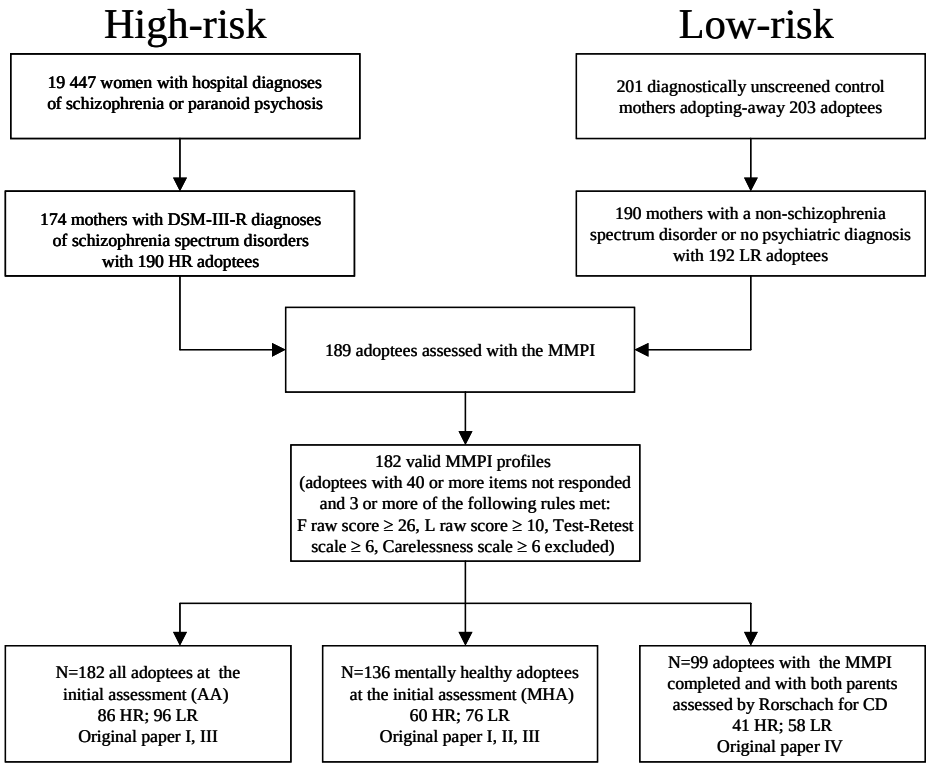

Fig. 2. Flowchart of sample selection in the Finnish Adoptive Family Study of Schizophrenia and the study samples in the original publications I-IV

There were no statistically significant differences between the HR and LR groups in the study samples, except in the social status of the adoptive family in the sample of all adoptees (AA) (Table 1). The study samples are representative of the total adoptee sample as regards gender, age at placement, and social class

of the adoptive family. However, the adoptees in these samples were younger (AA sample mean age 25 years, sd±10.16; MHA sample mean age 25 years, sd±10.16; CD and MMPI sample mean age 20 years, sd±6.67) than those in the whole sample. In addition, the adoptees of the CD and MMPI samples had a lower number of psychiatric diagnoses (p=0.05, χ^2 test, two-tailed significance) and were more often LR adoptees than those who were excluded from the study (p=0.03, χ^2 test, two-tailed significance). The effects of the adoptee's age and psychiatric status were statistically accounted in the multivariate model.

Table 1. Demographic characteristics of high-risk (HR) and low-risk (LR) adoptees in the study samples.

Demographic characteristics	Study samples		
	All adoptees (AA) (n=182) (I,III)[b]	Mentally healthy adoptees (MHA) (n=136) (I,II,III)[c]	Communication Deviance and MMPI (n=99) (IV)[d]
HR			
Mean age ± Sd at MMPI assessment (years)	26±9.95	25±10.06	20±6.60
Mean age ± Sd at placement (months)	19±15.71	18±15.39	16±15.95
Gender M:F	34:52	27:33	18:23
Social class of the adoptive family (%)[a]			
I	15	14	20
II	38	41	34
III	30	36	39
IV	17	10	7
LR			
Mean age ± Sd at MMPI assessment	25±10.19	24±9.33	21±6.77
Mean age ± Sd at placement (months)	16±13.69	17±13.83	15±13.31
Gender M:F	44:52	34:42	26:32
Social class of the adoptive family (%)[a]			
I	12	13	3
II	51	51	59
III	33	33	36
IV	4	3	2

[a]The social status of the adoptive families was rated according to the four-level Finnish socioeconomic classification based on the main provider's occupation and education (Handbook for Office of Statistics 17, 1983). A low number indicates a high social class.

[b]The AA sample included adoptees (n=46) who had DSM-III-R diagnoses of psychiatric disorder.

[c]The MHA sample included adoptees without psychiatric disorder at the initial assessment.

[d]The sample of 99 subjects included adoptees (n=20) who had been diagnosed with a psychiatric disorder at the initial assessment, but had not been hospitalized because of their illness.

4.3 Variables

4.3.1 MMPI test; schizophrenia-related scales and scoring

The MMPI test is an objective structured personality inventory with a large item pool (Dahlstrom *et al.* 1982, Friedman *et al.* 1989). It has been used in the assessment of self-concept, behavior, and social relationships in a self-report manner. Form R of the MMPI test was administered to the adoptees at their homes by psychiatrists trained by clinical psychologists. Fourteen schizophrenia-related scales of MMPI were included in this study (Table 2). Thirteen MMPI scales were originally included in the Moldin-Gottesman psychometric index by Moldin *et al.* (1990a), and the fourteenth scale, Schizophrenia Proneness (SzP), was developed by Bolinskey *et al.* (2001). The behavioral correlates of these scales consist of a wide array of disturbances in thinking, social relatedness, volition, and affective expressivity (Bolinskey *et al.* 2001, Moldin *et al.* 1990c).

Table 2. MMPI variables of the psychometric index (Moldin *et al.* 1990c) and SzP (Bolinskey *et al.* 2001) and their behavioral correlates associated with schizophrenia

MMPI variable	Behavioral correlates
L (Lie) scale (Dahlstrom *et al.* 1982, Friedman *et al.* 1989)	Lack of insight, cognitive and emotional inflexibility/rigidity, egocentricity, excessive denial, and poor stress tolerance
F (Frequency) scale (Dahlstrom *et al.* 1982, Friedman *et al.* 1989)	Poor judgment, poverty of speech and content of speech, lack of insight, and overt psychotic symptoms (delusions, hallucinations), severe disorganization, impaired attention/concentration, social withdrawal
K (Correction, Clinical Defensiveness) scale (Dahlstrom *et al.* 1982, Friedman *et al.* 1989)	Social withdrawal, emotional detachment/inhibition, lack of insight, phobic behaviors, emotional and cognitive inflexibility/rigidity, excessive denial, uncooperativeness, oversensitivity, emotional overcontrol, formal thought disturbances, paranoid ideation, "schizoid" traits, extreme defensiveness
4 (Psychopathic Deviate) scale (Dahlstrom *et al.* 1982, Friedman *et al.* 1989)	Asocial behavior, antisocial/acting-out impulses, poor judgment/insight, emotional immaturity, egocentricity, insensitivity, restless, hostility, superficial relatedness, avolition, shallow affect, impatience, deficient warmth, resentfulness, emotional unresponsiveness/instability, denial, irresponsibility
2+7+8+0 scale (Golden-Meehl Indicators), sum of scales 2 (Depression), 7 (Psychasthenia), 8 (Schizophrenia) and 0 (Social Introversion) (Golden & Meehl 1979)	Anhedonia, interpersonal aversiveness, formal thought disturbances, ambivalence, poor affective control, social withdrawal, poor relatedness, 'schizoid ' traits, phobic behaviors, avolition, oversensitivity, flat affect, apathy, paranoid ideation, somatic complaints, emotional instability, excessive anxiety, fearfulness
Rosen's Pz (Paranoid Schizophrenia) (Rosen 1962)	Paranoid and bizarre delusions, hallucinations, social withdrawal, emotional reserve/inhibition, somatic complaints, sexual concerns, lack of insight, poor self-control, autistic thinking, phobic behaviors
8-6 scale (Minneapolis Veterans Administration Hospital-MMPI Research Laboratory, 1975)	Florid hallucinations, paranoid delusions, disordered/autistic thought, irritable mood, "schizoid" traits, oversensitivity, social withdrawal, emotional immaturity/inhibition, poor judgment, apathy, avolition, blunted or inappropriate affect, negativism, impaired attention/concentration
HOS (Manifest Hostility) scale, scored in the opposite direction, (Wiggins 1966)	Passivity, emotional unresponsiveness, aloofness, emotional overcontrol, restricted affectivity
HYP (Hypomania) scale, scored in the opposite direction, (Wiggins 1966)	Emotional unresponsiveness, avolition, low energy, restricted affectivity
PHO (Phobias) scale, (Wiggins 1966)	Anhedonia, marked social anxiety and withdrawal, generalized and incapacitating anxiety, oversensitivity/fearfulness, phobic behaviors
PSY (Psychoticism) scale (Wiggins 1966)	Hallucinations and delusions, confuse and autistic thinking.
REL (Religious Fundamentalism) scale, (Wiggins 1966)	Conceptual disorganization, unusual thought content and intolerance
SOC (Social Maladjustment) scale, (Wiggins 1966)	Introversion, apathy, social inhibition and withdrawal
SzP (Schizophrenia Proneness), (Bolinskey *et al.* 2001)	Derived from Rosen's Pz scale by reducing the items overlapping with Wiggins PSY scale

In the present study, 64 (35.2%) profiles were derived from the 566-item MMPI Form R and 118 (64.8%) from the 400-item (short) Form R. The 400-item form is sufficient for scoring the basic and clinical scales. These were L, F, K, 4, and

2+7+8+0 in this study. The following special scales: Pz, 8-6 scale, the six Wiggins scales, and SzP comprised items not included in the abbreviated version of Form R. The prorating of the omitted items was completed according to the procedure previously proposed by Moldin *et al.* (1991). The scores of the full-length scales were estimated from the scores of the abbreviated scales using information from those who replied to all items (n=64). Pearson's correlations between the estimated and observed full-length scores were 0.99 on the PSY, 0.97 on the SOC, 0.97 on the Pz, 0.96 on the 8-6, 0.93 on the SzP, 0.92 on the HYP, 0.91 on the HOS, 0.91 on the REL, and 0.84 on the PHO scales, supporting the prorating.

After the estimation of the abbreviated MMPI profiles, raw scores were converted to standard K-corrected adult T scores, Pz +1K scores (Rosen 1962), and Wiggins adult T scores (Wiggins 1966). In lieu of the T score, the raw scores for the 8-6 scale and the SzP scale were applied to the statistical analyses. The 0.4×K correction was employed for the 4 scale and the 1×K correction for 7 and 8 on the 2+7+8+0 scale according to the standard profile sheet.

4.3.2 DSM-III-R diagnoses

The genetic risk assignments of the adoptees in this study are based on the DSM-III-R diagnoses (Tienari *et al.* 2003). HR adoptees had biological mothers with diagnoses of a broad putative schizophrenia spectrum including schizophrenia, odd-cluster personality disorder (plus avoidant PD), nonschizophrenic nonaffective psychosis, and affective psychosis (Kendler *et al.* 1996, Tienari *et al.* 2003). LR adoptees had biological mothers with no psychiatric diagnoses or with non-schizophrenia spectrum diagnoses. The DSM-III-R diagnoses of the adopting-away high-risk and low-risk biological mothers of the present study are presented in Table 3.

The principal (most severe lifetime) diagnoses were assigned in terms of the DSM-III-R criteria for Axis I or Axis II psychiatric disorders based on all available data for all subjects. The DSM-III-R diagnoses were made at a definite certainty level, meaning that the disorder had to be diagnosed as probable or definite.

The reliability of the psychiatric diagnoses was carefully assessed in the Finnish Adoptive Family Study. The Finnish raters and Drs Kenneth Kendler and Lyman Wynne from the United States of America reviewed 40 randomly selected case summaries. A test of inter-rater reliability was carried out cross-nationally for

the Finnish and American raters. Agreement was evaluated for the principal diagnoses within each hierarchic diagnostic class. The kappa coefficient for inter-rater reliability between the raters was 0.80.

Table 3. The DSM-III-R diagnoses of the high-risk (HR) adopting-away mothers with schizophrenia spectrum disorders and the low-risk (LR) control adopting-away mothers without schizophrenia spectrum disorders in the study samples

Diagnostic categories of the biological mothers	Number of cases (n=182) (I,III)	Number of cases (n=136) (I,II,III)	Number of cases (n=99) (IV)
HR			
Schizophrenia	60	39	29
Schizo-Affective Disorder	2	1	1
Schizophreniform Psychosis	7	6	4
Schizotypal PD	4	4	3
Paranoid PD	1	1	
Schizoid PD	1	1	1
Delusional Disorder	2	1	
Psychosis NOS	2		1
Bipolar Psychosis	1	1	1
Depressive Psychosis	3	3	
Avoidant PD	3	3	1
Total HR	86	60	41
LR			
Antisocial PD	1	1	
Alcohol use	3	2	3
Obsessive-Compulsive PD	1	1	
Passive-Aggressive PD	1	1	1
PD not otherwise specified	1	1	1
Mild mood disorder	2	1	1
Dysthymic disorder	3	3	3
Anxiety Disorders	5	3	3
Other diagnoses	3	2	1
Brain organic	1	1	
No diagnosis	35	31	21
No hospitalization	40	29	24
Total LR	96	76	58

4.3.3 Communication Deviance

The CD scale was used as a family environmental variable in the present study. Parental communication was assessed by the CD scale adapted from the Singer-Wynne Rorschach scoring manual (Klopfer & Davidson 1962, Singer & Wynne 1966, Singer *et al.* 1978) (The written instructions for the Rorschach test Appendix 1). This manual has been translated in Finnish and adapted to the Finnish Adoptive Family Study by Dr Karl-Erik Wahlberg and Dr Pirjo Keskitalo.

The CD of both adoptive parents was scored from the individual Rorschach test protocols that had been tape-recorded and transcribed according to standardized instructions. The 42-item version of the CD score sheet was divided into six conceptually different subgroups as presented in Table 4 (M.T. Singer and L.C. Wynne, unpublished 1986 version).

CD was scored from the transcribed individual Rorschach records of the adoptive parents by two psychologists blind to the psychiatric diagnoses, clinical functioning, or relatedness of the biological or adoptive family of any subject (Wahlberg 1994). For the reliability of the CD, the psychologists reviewed jointly every 25th Rorschach records and discussed the differences in the scoring. The intra-class correlation coefficient for CD between the psychologists was 0.95 for these 51 records.

One of the raters (K-E Wahlberg) has been trained in the scoring of CD by Dr Singer and Dr Wynne (Wahlberg 1994). The CD scores were calculated separately for each adoptive parent (Wahlberg *et al.* 2004). The items of the CD were searched from the transcribed text, and the presence of an item was scored as one point. All speech in response to each Rorschach test card given by the subject was recorded as a transaction. The frequency of the scored items was divided by the number of transactions to get the total CD for each parent. The obtained quotients were summed up and used as the CD for each adoptive parental pair. The sample included four single-parent families with no adoptive father at any stage. The CD of adoptive fathers who had never existed (single- parent families) was replaced by multiplying the CD of the adoptive mother by 2 to represent the parental CD.

Table 4. The items of the CD categories

CD categories
I Disruptions of the task and the relationship with the tester
Put-down of the tester of the task
Interruptions of the examiner's speeches
Extraneous questions and remarks
Nonverbal disruptive behavior
Environmental task disruptions
Disruptive humor
Disruptive swearing
Other conversation stoppers
II Problems of commitment and ability to sustain the task set
Abandoned, abruptly ceased, uncorrected remarks
Responses in negative form
Subjunctive, "if" responses
Question responses
Nihilistic remarks about task or life in general
Inability or failure to verify own responses
Forgetting responses
Answering unasked questions
Hopping around among responses
Negativistic, temporary card rejection followed by a response
Concrete-set responses
Assigning to other responsibility for the percept
III Unclear and unstable referents
Unintelligible remarks: a) brief, without context, or b) the total effect ending with an unintelligible referent
Unstable percepts
Inconsistent and ambiguous referents
Incompatible alternatives or incompatible aspects of images
Derogatory, disparaging, critical disqualifications of a response
Nihilistic remarks
Partial disqualification
IV Language anomalies
Ordinary words or phrases used oddly, incorrectly, or out of context
Odd sentence construction
Private, contrived terms and labeling
Clang associations, rhymed phrases, and word play
Reiteration
V Reasoning problems and contradictions
Contradictory information
Retractions and denials
Odd, tangential, inappropriate responses to questions or remarks
Peculiar logic; illogical combinations or percepts
Non sequitur reasoning
Assigning meaning on the basis of nonessential attributes of the cards
Contaminations
VI Indefinite and cryptic comments
Gross indefiniteness and lack of specificity
Cryptic remarks
Abstract, global terms and technical phrases

4.4 Statistical methods

The data were analyzed using independent samples t-tests, cross-tabulations, and appropriate regression models adjusted for confounding. The statistical software used for the data analyses was SPSS for Windows (versions 9.0, 11.0 and 12.0) (SPSS Inc. 2003). The MMPI subscales were adjusted for the following demographic variables: adoptee's gender, age at MMPI assessment, age at placement in the adoptive family (I-IV), social class of the adoptive family at the time of placement (I, III, IV), genetic risk status of the adoptees (II), and the effect of the adoptee's psychiatric status (IV) (Bolinskey *et al.* 2001, Moldin *et al.* 1990a, b, Walters 1988). High MMPI subscale scores (I, III) and MMPI scores above the cut-off point of the 75th percentile (II, IV) were used to show the schizophrenic direction for all scales except HOS and HYP, for which low MMPI subscale scores (I, III) and MMPI scores below the 25th percentile (II, IV) showed the schizophrenic direction. Because the distribution of sample means of each MMPI variable followed the normal distribution (i.e. skewness ≤ 2.0 or kurtosis ≤ 7.0 (Curran *et al.* 1996), parametric statistical methods were chosen for the comparisons of the means of the MMPI subscales between the HR and LR adoptees (Bland 1995) (I-III).

Original publication I. The independent samples t-tests for mean age differences as continuous variables and Chi-square analyses for gender and social class differences as classified variables were used to compare the demographic characteristics of the original sample and the sample of MMPI-assessed adoptees. Cohen's d was calculated for the effect sizes (Cohen 1988). In addition, focused contrast effect sizes were calculated for social class (four categories) using the instructions presented by Meyer *et al.* (2003).

Original publication II. Factorial ANOVA (Armitage & Berry 1987) was used to investigate whether there are any main effects or interactions between the follow-up diagnoses and the genetic risk status of the adoptees on each MMPI subscale. In addition, post hoc tests with Bonferroni correction for multiple comparisons were used to determine the pairs of means with significant differences.

Original publication III. Regression coefficients for each MMPI subscale were calculated by linear regression analysis in order to control the effects of the demographic variables. The adoptee's gender, age at MMPI assessment, age at placement into the adoptive family, and the adoptee's social class were considered as independent variables and the MMPI T scores (or scale 8-6 and SzP raw score)

as the dependent variable. An adjusted MMPI score R_i was calculated from each observed MMPI scale T or raw score S_i as follows: $R_i = S_i - (B_{sex_i} * sex) + (B_{age_i} * age) + (B_{sclass_i} * sclass) + (B_{arriv_i} * arriv) + constant_i)$, where B = regression coefficient (Bolinskey *et al.* 2001, Moldin *et al.* 1990a). The regression equations needed to calculate the residual scores of the MMPI subscales are presented in Appendix 2. The statistical differences in the adjusted means of the MMPI subscales between the HR and LR groups were tested by Student's t-test (Bland 1995, McCullagh & Nelder 1989).

Original publication IV. Logistic regression analyses were used to study the association of the MMPI-measured vulnerability factors with the genetic risk status of the adoptees and parental CD. The results of logistic regression models were presented using the Odds Ratios (ORs) with 95% confidence intervals (95% CI) and associated p-values. In the statistical analyses, the cut-off point of the 75th percentile was chosen to indicate the most deviant quartile of parental CD.

4.5 Ethical considerations and personal involvement

The study design of the Finnish Adoptive Family Study of Schizophrenia was approved by the Ethics Committee of the Faculty of Medicine, University of Oulu, on 2 May 1988. This permission by the Ethics Committee of the Faculty of Medicine also covers the present research.

Since 1977, verbal informed consent has been obtained in the course of the Finnish Adoptive Family Study of Schizophrenia. This procedure was reviewed by the Ethics Committee of the Faculty of Medicine, University of Oulu, on 15 October 1991.

The study design of the present thesis was accepted by the Postgraduate Research Committee of the Faculty of Medicine, University of Oulu, on 27 March 2001. The author was accorded permission to use the data, and since 2000, the author has participated in the Finnish Adoptive Family Study of Schizophrenia project as a researcher. The author has participated in the design, data analysis, and reporting of all original papers I-VI of the present thesis.

5 Results

5.1 Psychometric deviance measured by MMPI in adoptees at high-risk for schizophrenia and their adoptive controls (I, III)

5.1.1 Psychometric deviance of all adoptees

The first aim of the present study was to compare HR and LR adoptees in search for indicators of vulnerability to schizophrenia spectrum disorders as assessed by the MMPI subscales. Fourteen schizophrenia-related MMPI scales were compared between adopted-away high-risk (HR) offspring of biologic mothers and low-risk (LR) control adoptees using Student's t-test. The HR adoptees in the sample of all adoptees (AA) (n=182) had higher MMPI scores on Lie (L) (p=0.01) and lower scores on Hostility (HOS) (p=0.01) than the LR adoptees. In addition, although showing only a trend toward statistical significance, the HR adoptees had lower scores on Hypomania (HYP) (p=0.06). Also, the LR adoptees scored higher than the HR adoptees on Phobias (PHO) (p=0.06) (I Table 2).

Schizophrenia-related MMPI scales were adjusted for the adoptee's gender, age at MMPI assessment, age at placement in the adoptive family, and social class of the adoptive family at the time of placement. The HR adoptees in the sample of AA (n=182) had higher adjusted MMPI scores on the Lie (L) scale (p=0.01) and lower scores on the Hostility (HOS) (p=0.01) and Hypomania (HYP) scales (p=0.04) than the LR adoptees. The LR adoptees scored higher than the HR adoptees on Phobias (PHO) (p=0.04) (III Table 2).

5.1.2 Psychometric deviance of mentally healthy adoptees at the initial assessment

Vulnerability to schizophrenia spectrum disorders was also investigated using a subsample of adoptees with mental disorder diagnoses excluded (i.e. mentally healthy adoptees at the initial assessment, MHA). When fourteen schizophrenia-related MMPI scales were compared in the MHA subsample (n=136) using Student's t-test, the HR adoptees had lower scores on the Hostility (HOS) (p<0.01) and Hypomania (HYP) (p=0.03) scales than the LR adoptees. The LR adoptees scored higher than the HR adoptees on Phobias (PHO) (p=0.05). The

HR adoptees had higher scores on Lie (L) than the LR adoptees, although the difference did not reach statistical significance (p=0.06) (I Table 4).

When schizophrenia-related MMPI scores adjusted for the adoptee's gender, age at MMPI assessment, age at placement in the adoptive family, and social class of the adoptive family at the time of placement were used, the HR adoptees in the MHA subsample (n=136) had lower scores on the Hostility (HOS) (p<0.01) and Hypomania (HYP) scales (p=0.02) than the LR adoptees. The HR adoptees also showed a trend toward higher scores on Lie (L) (p=0.06) compared to the LR adoptees. The LR adoptees scored higher than the HR adoptees on Phobias (PHO) (p=0.05) (III Table 3).

5.2 MMPI measures as signs of predisposition to mental disorder among adoptees (II)

The second aim of the study was to assess the MMPI-derived subscale's predictive power for schizophrenia spectrum disorder or any psychiatric disorder in the adoptees at follow-up (APDF). Firstly, the fourteen schizophrenia-related MMPI scales were investigated in three groups of adoptees who were mentally healthy at the initial assessment (MHA). The adoptees were divided into the following groups based on the follow-up diagnoses: 1. adoptees mentally healthy (n=99), 2. adoptees with psychiatric disorder, but not schizophrenia (n=31), and 3. adoptees with broad schizophrenia spectrum disorder (n=6). Because no MMPI schizophrenia-related scale predicted the onset of broad schizophrenia spectrum disorder, the predictive power of the MMPI subscales was investigated in two groups of adoptees, which were: 1. adoptees mentally healthy at follow-up (MHF) (n=99) and 2. adoptees diagnosed with any psychiatric disorder at follow-up (APDF) (n=37) in this study.

Factorial ANOVA was done to analyze for possible main effects or interactions between the follow-up diagnoses (MHF, APDF) and the genetic risk status (HR, LR) of the adoptees on each MMPI schizophrenia-related scale. The overall results of factorial ANOVA (Table 6) showed significant findings only on the Psychopathic Deviate (scale 4) (p<0.01) and Hostility (HOS) scales (p=0.01). Univariate F-tests showed a significant effect of genetic risk (HR vs. LR) on the Frequency (F) scale (mean for HR vs. LR = 60.93 vs. 63.89, p=0.03), the Hostility scale (46.27 vs. 51.92, p<0.01), the Hypomania (HYP) scale (48.18 vs. 52.11, p=0.05), the Phobias (PHO) scale (44.22 vs. 47.68, p=0.02), and the Psychoticism (PSY) scale (50.02 vs. 52.99, p=0.05). Furthermore, a significant

main effect of the follow-up diagnosis (mentally healthy vs. any psychiatric disorder) was found on the Schizophrenia Proneness (SzP) scale (10.68 vs. 11.36, p=0.02) and the Psychopathic Deviate scale (60.33 vs. 59.60, p<0.01).

A logistic regression analysis – with adjustment for the adoptee's gender, age at MMPI assessment, age at placement in the adoptive family, and genetic risk of schizophrenia – was used to examine the association of each MMPI subscale with the adoptees' later psychiatric disorder. As seen in Table 5, the adoptees with high scores on Psychopathic Deviate (scale 4) at the initial assessment had a 2.8-fold score (OR 2.79, p=0.02) for any psychiatric disorder at follow-up compared to the rest of the adoptees. No other MMPI subscale was significantly associated with the later psychiatric disorder of the adoptees.

Table 5. Proportions (*n*, %) of deviant MMPI scores at the initial assessment of the adoptees and adjusted odds ratios when predicting any psychiatric disorder of the adoptees at follow-up (II).

Variable	Group				Adjusted Odds Ratio (95% Confidence Interval)
	Adoptees initally healthy at follow-up (n=99)		Any psychiatric disorder at follow-up (n=37)		
	n	%	n	%	
L	28	28.3	9	24.3	0.66 (0.26-1.66)
F	25	25.3	12	32.4	1.61 (0.68-3.82)
K	27	27.3	7	18.9	0.49 (0.18-1.30)
4	20	20.2	15	40.5	2.79 (1.17-6.62) *
2+7+8+0	22	22.2	12	32.4	1.77 (0.74-4.22)
8-6	28	28.3	11	29.7	1.13 (0.48-2.68)
SzP	30	30.3	13	35.1	1.50 (0.65-3.49)
Pz	23	23.2	11	29.7	1.47 (0.61-3.55)
HOS	19	19.2	10	27.0	1.31 (0.54-3.33)
HYP	18	18.2	10	27.0	1.32 (0.51-3.38)
PHO	27	27.3	13	35.1	1.77 (0.73-4.25)
PSY	24	24.2	14	37.8	2.13 (0.91-5.00)
REL	29	29.3	11	29.7	0.97 (0.41-2.29)
SOC	29	29.3	11	29.7	0.92 (0.39-2.19)

* *P*<0.05. The adoptees' gender, age at MMPI assessment, age at placement in the adoptive family, and genetic risk of schizophrenia were used as confounding variables.

Table 6. Descriptive statistics of the adoptees' MMPI scores (Mean, Sd) and p-values of the factorial ANOVA used to analyze the main effects and interactions between the follow-up diagnoses (MHF, APDF) and the genetic risk (HR, LR) of the adoptees on each MMPI schizophrenia-related scale (II)

Variable	Cutoff score[a]	HR adoptees (n=60)				LR adoptees (n=76)				Fb	p-value
		Adoptees mentally healthy at follow-up (n=38)		Any psychiatric disorder at follow-up (n=22)		Adoptees mentally healthy at follow-up (n=61)		Any psychiatric disorder at follow-up (n=15)			
		Mean	Sd	Mean	Sd	Mean	Sd	Mean	Sd		
L	56.00	51.71	7.34	52.95	10.16	49.18	7.35	50.87	8.54	1.53	0.21
F	68.00	60.87	10.72	61.05	8.56	62.44	12.65	69.80	14.82	2.26	0.09
K	61.75	57.92	8.48	56.36	8.58	55.25	7.98	54.87	8.91	0.94	0.43
4	67.00	59.82	9.26	61.23	9.87	57.28	11.26	68.53	11.50	4.73	< 0.01
2+7+8+0	252.75	232.53	27.59	230.82	35.25	227.03	36.10	250.53	28.87	2.04	0.11
8-6	26.00	23.18	3.97	21.00	4.75	22.26	4.68	24.73	5.90	2.23	0.09
SzP	13.00	10.26	3.85	11.41	3.96	10.87	3.99	13.33	3.92	2.29	0.08
Pz	59.75	54.74	7.33	54.32	6.79	53.59	8.28	59.40	9.86	2.14	0.10
HOS	41.00	47.05	8.51	44.91	7.87	51.34	11.05	54.27	11.88	4.10	0.01
HYP	44.00	49.16	11.00	46.50	10.12	52.25	9.63	51.53	11.89	1.93	0.13
PHO	51.00	44.82	9.21	43.18	7.35	47.02	11.75	50.33	9.70	1.81	0.15
PSY	57.00	50.95	10.04	48.41	8.81	52.21	12.63	56.13	13.35	1.44	0.23
REL	46.00	39.08	9.93	38.82	11.05	38.64	10.12	38.67	8.55	0.02	1.00
SOC	61.00	54.26	9.72	54.50	12.22	51.95	9.94	55.07	5.75	0.76	0.52

[a]Cut-off score used to indicate the high and low scores on the MMPI subscales in subsequent logistic regression analyses. [b] Factorial ANOVA, statistical significance of the corrected model, df=3. MHF=Mentally healthy adoptees at follow-up, APDF=Any psychiatric disorder at follow-up.

The analyses were replicated for the HR and LR adoptees separately. In the group of HR adoptees (n=60), none of the deviant scores on the MMPI subscales were shown to predict future mental disorder of the adoptees (II Table 4). Among the LR adoptees (n=76), high scores on Psychopathic Deviate (scale 4) ($p<0.01$) and on Golden-Meehl Indicators (sum of scales 2+7+8+0) ($p=0.01$) at the initial assessment were associated with an increased likelihood of any psychiatric disorder at follow-up (II Table 5).

5.3 Origins of schizophrenia-related scales (IV)

The third aim of the study was to find out possible interaction between the genetic risk for schizophrenia and the family environmental risk measured as Communication Deviance (CD) of the adoptive rearing parents associated with the MMPI-assessed vulnerability of the adoptee. The individual and interactional effects of the genotype and the environment were investigated in HR and LR adoptees' vulnerability to schizophrenia spectrum disorders. Confounding variables consisted of the adoptee's gender, age at MMPI assessment, age at placement in the adoptive family, social class of the adoptive family at the time of placement, and the adoptee's psychiatric status.

The HR adoptees (n=41) had a statistically significantly increased risk for vulnerability on the Lie (L) ($p=0.05$), Correction (K) ($p=.01$), and Hostility (HOS) ($p=0.01$) scales of MMPI compared to the LR adoptees (n=58) in the adjusted logistic regression analysis (IV Table 2). Thus, the genetic risk associated positively with the adoptees' vulnerability on these scales. In addition, a positive association was found on the Hypomania (HYP) scale ($p=0.22$), while a negative association was found on the other MMPI subscales.

High scores of the adoptive parents' CD (Communication Deviance) (n=99) were found to have a trend towards statistical significance with the vulnerability of the adoptees on the scales Lie (L) ($p=0.08$), Psychopathic Deviate (scale 4) ($p=0.28$), HYP ($p=0.34$), and Religious Fundamentalism (REL) ($p=0.06$) (IV Table 3).

The adjusted odds ratios for the joint effect of the genetic and environmental risks ranged from 0.91 to 8.52 on the MMPI subscales, when the genetic risk, the environmental risk, and their interaction were simultaneously entered into a logistic regression model (Figure 3).

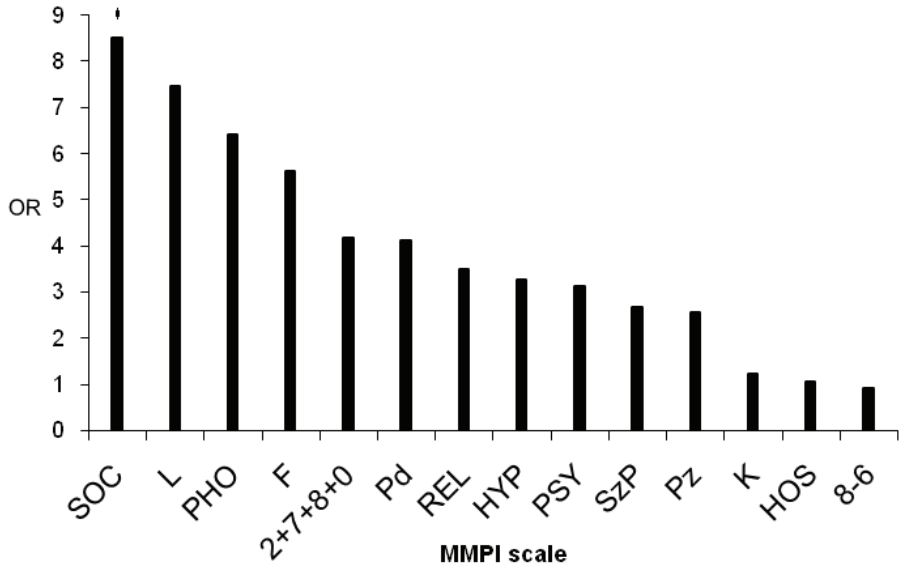

Fig. 3. Adjusted odds ratios of gene-environment interaction for deviant MMPI scores of adoptees (n =99) (IV). p<0.05.

The joint effect of the genetic and environmental risks was significant on Social Maladjustment (SOC) (p=0.05) in the adjusted logistic regression analysis (IV Table 4), meaning that the HR adoptees with rearing parents who had high CD had a significantly increased risk of Social Maladjustment compared to the respective LR adoptees. In addition, a trend towards statistical significance was found on the Lie (L) (p=0.08) and Phobias (PHO) (p=0.08) scales.

6 Discussion

6.1 MMPI measured vulnerability signs of schizophrenia (I, III)

Psychometric deviance assessed by MMPI was compared among HR and LR adoptees in search for signs of genetic vulnerability to schizophrenia spectrum disorders. Firstly, the sample of all adoptees (AA) was used with the observed MMPI scale scores and with corresponding adjusted scores to control the effects of confounding variables (gender, age at MMPI assessment, age at placement, and social class). Secondly, signs of genetic vulnerability among the adoptees who were mentally healthy (MHA) at the initial assessment were studied to exclude the possible effect of symptoms of mental disorder. Here, too, observed and adjusted MMPI scores were used. Thus, the earlier HR studies were partially replicated using a sample of adopted-away offspring of mothers with schizophrenia (Bolinskey *et al.* 2001, Carter *et al.* 1999, Moldin *et al.* 1990a).

Hostility (HOS) was found to be a vulnerability indicator in all of the comparisons. Thus, the possible genetic vulnerability assessed especially by Hostility is independent of the adoptees' clinical status. This scale probably measures stable, trait-like features of psychometric deviance that are indicators of genetic vulnerability to schizophrenia spectrum disorders (Nuechterlein & Dawson 1984, Zubin & Spring 1977). Hypomania (HYP) also indicated the possible vulnerability to schizophrenia spectrum in both samples when observed and adjusted MMPI scores were used, except in the non-adjusted AA sample. Hypomania may also measure trait-like abnormalities that are indicators of genetic vulnerability to schizophrenia spectrum. Hostility and Hypomania indicate emotional unresponsiveness, restricted affectivity, and decreased energy. These findings are consistent with the earlier HR study, which also controlled the effects of demographic variables (Moldin *et al.* 1990a).

Lie (L) was found to be a vulnerability indicator only in the sample of adoptees including disturbed subjects, and it is therefore probably not a vulnerability indicator. This is contradictory to the earlier research that found Lie to belong to the set of MMPI schizophrenia-related scales indicating vulnerability specific to schizophrenia before the onset of mental disorder (Bolinskey *et al.* 2001). The Lie scale is associated with a lack of insight and stress tolerance, cognitive and emotional inflexibility, egocentricity and excessive denial. Lie may

reflect the presence of adoptees with mental health disorders and indicate rather symptoms of a disorder or a prodromal phase than genetic vulnerability.

Contrary to the earlier findings (Bolinskey *et al.* 2001), mentally healthy LR adoptees had higher scores on the Phobias scale (PHO) than corresponding HR adoptees. Since the finding was replicated when the adjusted scores were used, the result does not depend on the adjustment of the scores. Thus, our result indicates Phobias not to be a genetic vulnerability indicator of schizophrenia spectrum disorder. Bolinskey *et al.* found Phobias to differentiate the high-risk individuals who later develop schizophrenia from those who remain mentally healthy. An analysis with the Chi-square test performed item by item for Phobias showed that LR adoptees had a variety of signs of classical phobias (wide-open places, snakes, windstorm) in the present study. The behavioral correlates of the high scores on Phobias associated with schizophrenia are anhedonia, anxiety, oversensibility and phobic behavior (Moldin *et al.* 1990c), which may be different from more classical phobic fears. Another reason may be due to the fact that the MMPI was here administered to adopted-away children of mothers with schizophrenia, unlike in the study by Bolinsky et al., where the sample included HR children reared by a parent with schizophrenia. The behavioral correlate of the Phobias may not be consistent within these samples because the effect of gene-environment interaction may be stronger on this scale than on the other MMPI schizophrenia-related scales.

6.2 Psychometric deviance of MMPI as a prospective sign of mental disorder (II)

Firstly, schizophrenia-related MMPI scales were used in the search for predictors of later schizophrenia spectrum disorders among HR and LR adoptees. The lack of predictive value of Hostility and Hypomania was surprising, since they were genetic vulnerability indicators among HR adoptees. The result may be due to several reasons. Predictions with MMPI subscales may have been unsuccessful due to the limited number of adoptees (n=6) with broad schizophrenia spectrum disorder at follow-up. Secondly, the psychometric deviance measured with these scales does not necessarily lead to signs and symptoms in the absence of disruptive environmental influences, and the environmental risk was not assessed here. Thirdly, all adoptees had not yet got follow-up diagnoses during the present follow-up period, but their mental health status may have changed later.

The Golden-Meehl Indicators scale (sum of scales 2+7+8+0) has been considered specific only for later onset of schizophrenia among children at high-risk for schizophrenia (Bolinskey *et al.* 2001, Carter *et al.* 1999). The earlier findings were not confirmed in this study. The earlier high-risk studies included children who had been reared by a parent with schizophrenia, and the possible influence of a protective rearing environment was not assessed in these studies. A child born to a mother with schizophrenia and reared by adoptive parents may avoid the possible disturbing environmental influences of the psychiatric illness. Thus, the results obtained from samples with different rearing environments in terms of, for instance, parental mental health status (Bolinskey *et al.* 2001, Tienari *et al.* 2004, Wahlberg *et al.* 1997) are not fully comparable.

HR and LR adoptees' schizophrenia-related MMPI scales were used to search for predictors of any subsequent psychiatric disorder, including broad schizophrenia spectrum disorders and other psychiatric disorders. The adoptees' deviant scores on Psychopathic Deviate (scale 4) and Hostility (HOS) at the initial assessment were found to be associated with psychiatric disorder at the follow-up assessment. However, after adjustment for demographic and other variables, Psychopathic Deviate was only a predictor of future mental disturbances among the adoptees who were mentally healthy at the initial assessment. This scale measures traits associated with asocial behavior, egocentricity, impatience, and shallow affect (Dahlstrom *et al.* 1982, Moldin *et al.* 1990c). Other high-risk studies have also shown that behavioral, emotional, and social adjustment problems precede schizophrenia and psychotic symptoms (Amminger *et al.* 2000, Kugelmass *et al.* 1995, Olin *et al.* 1995). Thus, Psychopathic Deviate may be useful as a sign of predisposition to later onset of psychiatric disorder.

MacCrimmon *et al.* (1980) demonstrated that a foster group at high risk for schizophrenia and a foster control group had equally high scores on Psychopathic Deviate (scale 4) as a community control group. The explanation for this result may be that fostered children are alike in that they share the traumatic loss of parents and the placement into a new family. Therefore, the results of an adoptive sample including children who have experienced these traumas, do not represent the results of children who have been living with their biological parents.

We did not find any of the MMPI schizophrenia-related variables to be predictors of later psychiatric disorder among our HR adoptees. Instead, Psychopathic Deviate (scale 4) and Golden-Meehl Indicators (sum of scales 2+7+8+0) were predictors of any psychiatric disorder at follow-up among our LR

adoptees. The result of the LR adoptees remained unchanged after adjustment for the confounding variables. The Golden-Meehl Indicators obtained here for any follow-up psychiatric disorder among the LR adoptees are consistent with the earlier findings from non-genetic high-risk studies (Chapman *et al.* 1982, Golden & Meehl 1979).

The unsuccessful prediction of mental disorders among the HR adoptees may be explained by the assumption that the development of schizophrenia reflects gene-environment interaction, which was not studied here. Recent adoption studies have indicated that the onset of schizophrenia spectrum disorders in HR adoptees depends more on the interaction between genetic and environmental factors than the onset of corresponding disorders in control adoptees (Tienari *et al.* 2004, Wahlberg *et al.* 1997, 2000, 2004). HR adoptees with genetic vulnerability have been found to be more sensitive to the negative or positive effects of the gene-environment interaction than LR adoptees. Thus, a favorable rearing environment in the adoptive family may prevent the expression of vulnerability indicators in HR adoptees.

6.3 Origins of schizophrenia-related MMPI scales (IV)

The origins of the fourteen schizophrenia-related MMPI scales were predicted with the separate and joint effects of genetic and environmental factors. Genetic risk alone predicted Lie (L), Correction (K), and Hostility (HOS) to be vulnerability indicators among HR adoptees. This replicates the earlier finding that Hostility may be an indicator of the genetic liability to schizophrenia spectrum disorders (I, III).

The schizophrenia-related MMPI scales were not associated with the environmental risk of extremely high parental CD. There are at least two possible explanations for our results. Firstly, the reason could be the limited sample size of 99 adoptees, including only 26 adoptees with high-CD adoptive parents. Another hypothesis is that some children may notice and be aware of the confused communication patterns of their parents and may learn to cope with that, which may manifest as low scores on the MMPI-measured vulnerability indicators of schizophrenia.

The joint effect of genetic risk and parental CD increased the risk of MMPI-measured vulnerability on Social Maladjustment (SOC) up to eightfold among the HR adoptees who had high-CD rearing parents compared to the respective LR adoptees. This result indicates that HR children reared by adoptive parents who

communicate in a diffuse and confusing way have an increased risk for social and behavioral problems. Social Maladjustment indicates introversion, apathy, social inhibition, and withdrawal. These problems have been found to precede often the onset of schizophrenia and psychotic symptoms (Amminger *et al.* 2000, Kugelmass *et al.* 1995, Olin *et al.* 1995). Thus, high scores on the Social Maladjustment scale may be one way to predict future psychotic disorder, even though this could not be confirmed in the present study. Bolinskey *et al.* (2001) included Social Maladjustment in their psychometric index in identifying premorbidly the HR children who later developed schizophrenia-related psychoses. However, the comparability of these studies with the present study is limited since the earlier studies did not differentiate between environmental and genetic factors. A high level of CD shown by the adoptive parents of HR adoptees may increase the risk of the child to develop first vulnerability signs and later psychosis. It is noteworthy that CD alone is not an important factor in this process, but that interaction with genetic liability enhances its significance in the development of Social Maladjustment as a probable trait of the child in the family.

The Social Maladjustment scale measures introversion, apathy, social inhibition, and withdrawal. This vulnerability sign has earlier been found to predict schizophrenia (Bolinskey *et al.* 2001). Our previous finding showed Psychopathic Deviate to be a predictor of any psychiatric disorder. The behavioral correlates of this scale are associated with asocial behavior, egocentricity, impatience, and shallow affect, showing that it measures a different aspect of asociality compared to the Social Maladjustment scale. The relationship between social inhibition, antisocial impulses, and gene-environment interaction in the development of vulnerability signs and predictors of schizophrenia need to be investigated in more detail in the future.

6.4 Strengths and limitations of the study

A major strength of the present study was the possibility to investigate the genetic and environmental effects on schizophrenia separately and in the context of gene-environment interaction, using a subsample from the globally known and, for some time, unique Finnish Adoptive Family Study of Schizophrenia. The genes of the adopted-away children come from their biological parents and, their rearing environment is shaped by their adoptive parents. Thus, the combination of high-risk and adoption study designs makes it possible to distinguish the effect of the

genotype on an adopted child more clearly than the corresponding effect on a child living with a mother who has schizophrenia.

Earlier prospective family studies that have used MMPI to predict future psychiatric disorder have included children born to and raised by mothers with schizophrenia in the HR sample (Bolinskey *et al.* 2001, Carter *et al.* 1999). Most of the subjects had passed the age of the maximum risk to develop schizophrenia during the sufficiently long follow-up time in the Finnish Adoptive Family Study of Schizophrenia and in the current studies. This made it possible to study the continuity between premorbid deviance in personality traits and later mental health. In addition, to our knowledge, this is the first study to investigate the origins of MMPI-assessed vulnerability using parental CD as an environmental risk factor among HR adoptees.

The main limitation of the present study was the small number of MMPI-assessed adoptees, despite the extensive original sample. Because of the longstanding nature of multiple assessments, some subjects lacked the energy to complete the test or responded only to the 400-item (short) Form R instead of the full-length 566-item MMPI. We corrected the missing items by prorated scores for the Pz scale, the 8-6 scale, the six Wiggins scales, and the SzP scale, which may have impaired the reliability of the results. However, the high correlations between the prorated and observed MMPI scale scores support these estimations.

Some earlier studies (Bolinskey *et al.* 2001, Moldin *et al.* 1990a, Rosen 1962) have used a psychiatric comparison group. In this study, we had offspring born to mothers with broad schizophrenia spectrum disorders as a HR group. As a LR group, we had offspring born to mothers with a non-spectrum diagnosis or with no psychiatric disorder without a separate psychiatric comparison group because of the limited number of LR adoptees. The study might have had more discriminatory power if a psychiatric control group had been used.

Most genetic studies have operationalized schizophrenia based on the international diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). Recently, genetic studies revealed an overlap in the genetic susceptibility to schizophrenia and bipolar disorder, suggesting the possibility of a shared disease entity (Owen *et al.* 2007). Also, an overlap between the diagnoses of schizophrenia, dissociative disorders, and post-traumatic stress disorder (PTSD) has been demonstrated (Muenzenmaier *et al.* 2005, Read *et al.* 2005). Modification of the concept of the psychosis has been proposed for the future DSM revision based on the most recent studies (Regier 2007).

In this study, the diagnoses were assigned in terms of the DSM-III-R criteria (American Psychiatric Association 1987). Diagnostic reliability was assessed in co-operation by the Finnish and American raters. The DSM-III-R diagnoses of broad schizophrenia spectrum were used as a criteria for the group of disorders with high genetic risk to schizophrenia (Kendler *et al.* 1996, Tienari *et al.* 2003).

The present sample included only women able to reproduce despite schizophrenia. This may implicate that they have a higher degree of functionality than women with schizophrenia in general, who tend to have impaired reproductive fitness. However, inclusion of offspring of biologic mothers with schizophrenia spectrum disorders is the most important precondition of any study on the genetic effects and familial pathways of the transmission of schizophrenia. We nearly always know the biologic mother of a child, but we cannot be equally sure about the biologic father, which is why this criterion was used.

Adult T scores or raw scores of MMPI were used in the present study for all adoptees, although not all subjects were not old enough for the use of adult norms. Adult MMPI norms have been found to increase the probability of adolescents' deviant scores with regard to schizophrenia-related processes (Archer 1987). To avoid this problem, the adoptee's age at the MMPI assessment was statistically accounted for in the appropriate regression models.

7 Conclusions

7.1 Main results

Hostility (HOS), Hypomania (HYP), and probably also Social Maladjustment (SOC) were found to be vulnerability indicators of schizophrenia. Psychometric deviance of these scales indicates emotional unresponsiveness, decreased energy, and social inhibition. These aberrations in personality traits are all prodromal symptoms of schizophrenia. We may hypothesize that all of these traits are associated with a genetic risk and parental communication deviance of HR children. However, the present results did not show the genetic risk and parental CD and their interaction to be associated with Hostility and Hypomania, but with Social Maladjustment, which indicates that similar prodromal symptoms may develop under the effect of gene-environment interaction.

The early presence of any psychometric deviance in MMPI measures did not predict schizophrenia spectrum disorders among HR adoptees. This may be due to the limited number of HR adoptees with schizophrenia at follow-up. However, Psychopathic Deviance (scale 4) was a predictor of future psychiatric disorders. Psychopathic Deviate may not be associated specifically with schizophrenia, but genarally with the development of mental health disorders. Recent adoption studies have indicated that the interaction between genetic and environmental factors may be a predictor of later onset of schizophrenia spectrum disorders in HR adoptees (Tienari *et al.* 2004, Wahlberg *et al.* 1997, 2000, 2004). The present result is in line with these earlier studies, showing that genetic risk and parental CD also have an effect on Social Maladjustment as a measure of prodromal symptom.

7.2 Clinical implications and implications for future research

In clinical practice, genetic vulnerability to schizophrenia spectrum disorder may manifest as MMPI measures of Hostility (HOS), Hypomania (HYP), and possibly also Social Maladjustment (SOC). These scales indicate emotional unresponsiveness, decreased energy, and social inhibition. However, these scales do not predict all subsequent psychiatric disorders. Instead, asocial behavior and antisocial acting-out impulses assessed by Psychopathic Deviate (scale 4) may predict later mental disorder. A new important clinical implication is that the

genetic risk together with deviant communication in the family may manifest as increased social inhibition and withdrawal problems measured on the Social Maladjustment scale with deviant communication in the family. MMPI measures of Hostility, Hypomania, and Social Maladjustment are proxy to the findings of premorbid and prodromal clinical symptoms of schizophrenia. Thus, when these features are found among a HR population, both the individual and the family could be referred for preventive mental health care. The present results support the combination of multiple methodologies for the screening of at-risk individuals.

The results on MMPI-measured vulnerability indicators obtained in the context of gene-environment interaction offer a frame of reference to the clinician. We can hypothesize that children with genetic liability tend to develop psychometrically deviant personality traits as vulnerability signs in families where the parents communicate in a confusing way. Thus, in addition to an individual change, the interactional patterns of the family members need to be assessed. Clarification of the communication pattern in family therapy may lead to corrective experiences and help the child to cope with his/her difficult traits. Thus, the child gets support in the process of personality development from her/his parents. This may stop the development of vulnerability signs in personality traits and thereby help to prevent later psychosis.

In future studies, the predictive validity of MMPI in schizophrenia needs to be studied using a composite index of multiple indicators among the adoptive family sample. Also, it would be interesting to combine different psychological tests in search for vulnerability indicators of schizophrenia. A further challenge is to clarify gene-environment interaction in the development of vulnerability indicators into predictors measurable by MMPI.

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Appendix 1 Writing instructions for the Rorschach test (these instructions are not complete)

Typing:

The typing must be verbatim. The typist should neither “fix up” odd statements nor distort through additions or omissions what a speaker has said. Reading the scoring manual which follows, permits typists to see how raters will eventually score the typescripts. The need for accurate transcribing errors, either correcting or distorting what a speaker actually said are to be avoided. These two problems are discussed below.

1. Avoid fixing and correcting. Do not correct into better English, nor make into better sense what is heard. Type without revising, substituting, or rearranging what is said by speakers. Both beginning raters and typist should be familiar with the typing remarks and descriptions which usually accompany viewing the Rorschach cards. Speakers are often pointing to parts of the blots or describing features of the cards which may be puzzling if one is not familiar with the typical exchanges which occur during the procedure. Do not “fix” either normal ellipses, breaks in thought, nor unusual phrasings such as illustrated below. Type what has actually said.

Here are a few examples of exact wordings, odd as they may be, which can tempt a typist to edit, but which should be typed as heard.

I see ribs and of the esophagus.

These are protozoa, though alive they are.

A murial (sic) with outstretched arms. (i.e., mural.)

That is a carticaytchure (sic) of a man. (i.e., caricature)

To do with birth again I feel; they’re sort of uh, about to give birth itself I think to one another.

2. Avoid distorting what is heard. If a typist faithfully avoid correcting what is heard, only two other major problems occur; either the typing of sounds which some persons append to words, or the failing to properly insert words which are said rapidly as a speaker glides from one word of phrase to the next. The following examples illustrate inclusion and omission errors:

a. Inclusion errors: Certain persons add an extra “uh” sound at he end of words terminating in hard sounds as “k”, “g”, “ing”, and similar sounds. These sounds in ordinary conversation go unnoticed as part of the speaker’s regionalism or idiosyncratic style, but are audible on tapes and are to be ignored. However, those must be distinguished from those genuine separate “uh” sound which serve as space fillers and non-word verbalizations, and which should be included in the typescript.

(a) Original incorrect typing of “regionalism”: “That uh looks uh like a dog uh with uh collar.”

(b) Correct version gained from listening to tape with knowledge about the criteria above: “That looks like a dog, a dog with a collar.”

Inclusions such as in (a) above are not likely to be scored, but add to the work of reading and evaluating a record. For global ratings such can mislead a reader into thinking a speaker was extremely hesitant. The features below are likely to cause incorrect scoring with the manual which follows this introduction.

b.Omissions: Failing to hear words of failing to indicate phrasing and pauses can mislead raters.
(1) Word omissions: Short words are often elided as they are spoken. They are formed, but faint and blended into the preceding word’s ending or blended into the start of the following word. The sentences below suggest a cryptic speaker:

(a)“Two figures bending forward touching something, tearing apart”.

(b)“Here star which actually somewhat sevenpointed star”.

Rechecking the tape revealed the speaker had said many more words than a new typist had transcribed. She had not heard the underlined words which were present in elided form as shown here:

(a) “There are two figures bending forward touching something and tearing it apart.”

(b)“Here’s a star, which is actually, it’s somewhat a sevenpointed star.”

The speakers actually had fully formedand smoothly stated remarks.

(2) Phrasing omissions: A speaker groups his ideas in phrases and the typescript should reflect accurately these groupings. Example (a) below illustrates a failure to indicate phrasing. Example (b) shows what checking and audiotape revealed.

(a) “Two large feet with a show with a high heel.”

(b) “ Two large feet with uh, shoes with a high heel.”

Here a reader sees a speaker corrected his thoughts and phrased clearly whereas the typing originally suggested on long peculiarly strung together utterance.

In summary, tapes must be checked, certain linguistic principles understood, and ideas properly grouped until a faithful transcript of the tapes occurs.

Appendix 2 Regression equations for each of the constituent MMPI scale

Scale	
L	L – ((-1.3*SEX) + (0.05*AGE) + (-0.41*SCLASS) + (0.03*ARRIV)+ 51.4)
F	F – ((-0.65*SEX) + (0.01*AGE) + (1.2*SCLASS) + (0.02*ARRIV)+ 62.4)
K	K – ((0.54*SEX) + (-0.05*AGE) + (-1.3*SCLASS) + (-0.005*ARRIV)+ 55.8)
Pd[1]	Pd – ((0-.9*SEX) + (0.06*AGE) + (1.5*SCLASS) + (0.10*ARRIV)+ 57.3)
$2+7^2+8^2+0$	2+7+8+0 – ((3.5*SEX) + (0.35*AGE) + (4.7*SCLASS) + (0.25*ARRIV)+ 210.9)
SOC	SOC – ((0-.35*SEX) + (0.09*AGE) + (0.33*SCLASS) + (0.09*ARRIV)+ 48.8)
REL	REL – ((3.2*SEX) + (0.005*AGE) + (-2.1*SCLASS) + (-0.02*ARRIV)+ 36.9)
PSY	PSY – ((1.9*SEX) + (-0.04*AGE) + (1.5*SCLASS) + (0.03*ARRIV)+ 48.0)
PHO	PHO – ((5.0*SEX) + (0.007*AGE) + (-2.1*SCLASS) + (0.02*ARRIV)+ 40.6)
HOS	HOS – ((0.11*SEX) + (-0.14*AGE) + (0.10*SCLASS) + (-0.06*ARRIV)+ 53.6)
HYP	HYP – ((3.4*SEX) + (-0.06*AGE) + (0.60*SCLASS) + (0.04*ARRIV)+ 44.7)
Pz[2,3]	Pz – ((3.1*SEX) + (0.07*AGE) + (-0.48*SCLASS) + (0.01*ARRIV)+ 48.3)
SzP[4]	SzP – ((1.8*SEX) + (0.03*AGE) + (0.2*SCLASS) + (0.08*ARRIV)+ 7.2)
8-6[2,4]	8-6 – ((1.3*SEX) + (-0.01*AGE) + (-0.55*SCLASS) + (-0.01*ARRIV)+ 21.2)

Notes: All scores are standard non-K corrected T scores unless otherwise noted. [1] With .4*K correction, [2] With 1*K correction,

[3] T scores based on revised Minnesota VA norms, [4] Raw score

SEX : 1=male, 2=female

AGE: age at MMPI (years)

SCLASS: social class, 1 = I-II, 2 = III-IV

ARRIV: age at arrival (months)

SAMPLE: 182 cases

Original publications

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

I Siira V, Wahlberg K-E, Miettunen J, Läksy K, Tienari P (2004) Psychometric deviance measured by MMPI in adoptees at high risk for schizophrenia and adoptive controls. J Pers Assess 83:14-21.

II Siira V, Wahlberg K-E, Miettunen J, Läksy K, Tienari P (2006) MMPI measures as signs of predisposition to mental disorder among adoptees at high risk for schizophrenia. Psyc Res (in press).

III Siira V, Wahlberg K-E, Miettunen J, Tienari P, Läksy K (2006) Differentiation of adoptees at high versus low genetic risk for schizophrenia by adjusted MMPI indices. Eur Psych 21:245-250.

IV Siira V, Wahlberg K-E, Hakko H, Läksy K, Tienari P (2006) Interaction of genetic vulnerability to schizophrenia and Communication Deviance of adoptive parents associated with MMPI schizophrenia vulnerability indicators of adoptees. Nord J Psychiatry (in press).

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

933. Kangasniemi, Mari (2007) Monoliittisesta trilogiseen tasa-arvoon. Tasa-arvo hoitotyön etiikan tutkimuksessa

934. Ronkainen, Johanna (2007) Costs in today's radiology. ABC analysis of typical situations in the transitional period

935. Vainionpää, Aki (2007) Bone adaptation to impact loading—Significance of loading intensity

936. Mousavinasab, Firoozeh (2007) Effects of lifestyle and genetic factors on the levels of serum adiponectin, a novel marker of the metabolic syndrome, in Finnish servicemen

937. Kääriäinen, Maria (2007) Potilasohjauksen laatu: hypoteettisen mallin kehittäminen

938. Itäranta, Petri (2007) Wnt4 and Wnt6 secreted growth and differentiation factors and neural crest in the control of kidney development

939. Hirsso, Päivi (2007) Alopecia; its prevalence and association with cardiovascular diseases, risk factors and quality of life—cross-sectional population-based studies

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