

Riikka Roisko

PARENTAL COMMUNICATION
DEVIANCE AS A RISK FACTOR
FOR THOUGHT DISORDERS
AND SCHIZOPHRENIA
SPECTRUM DISORDERS
IN OFFSPRING

THE FINNISH ADOPTIVE FAMILY STUDY

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE,
INSTITUTE OF CLINICAL MEDICINE,
DEPARTMENT OF PSYCHIATRY;
OULU UNIVERSITY HOSPITAL



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The Finnish Adoptive Family Study

Academic Dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium I, Building PT1 of the Department of Psychiatry (Peltolantie 17), on 7 November 2014, at 12 noon

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Abstract

Both genetic and biological and psychosocial environmental risk factors contribute to the aetiology of schizophrenia spectrum disorders. Among the much studied environmental risk indicators are parental Communication Deviance (CD) and the winter or spring birth of a child. Genetic and environmental risk factors do not function in isolation from each other, but gene-environment interactions play a major role in the aetiology of psychotic disorders. The aim of this doctoral thesis is to investigate the role of parental CD as a risk factor (together with other risk indicators) for thought disorders and schizophrenia spectrum disorders in an adoptive child.

A systematised review was performed concerning the association between parental Communication Deviance and schizophrenia spectrum and thought disorders in offspring. A meta-analysis could only be performed for the association of parental CD with schizophrenia spectrum disorders in offspring. A large overall effect size was found (0.79, 95%CI 0.21–1.37). The studies included in the systematised review suggest that frequent parental CD and thought disorders in the offspring are connected with each other.

The two original studies are based on the data derived from the total sample of the Finnish Adoptive Family Study ($n=382$). First, the association between parental Communication Deviance scored from individual and family Rorschach protocols and the characteristics of the adoptive child and the parents themselves was investigated. The variability of CD in the adoptive parents in individual and family Rorschach situations was most closely associated with the characteristics of the parents themselves. The association of an adoptive child's thought and schizophrenia spectrum disorders with the child's genetic risk for schizophrenia spectrum disorders, winter or spring birth, and parental Communication Deviance, and their interactions was also explored. The adoptive child's thought disorders were associated only with parental CD. None of the risk indicators or their interactions predicted the adoptee's schizophrenia spectrum diagnosis.

In conclusion, the results indicate that the amount of Communication Deviance is a stable trait of an individual. It may be considered as a risk indicator for schizophrenia spectrum disorders in offspring and, with a lower level of confidence, also for thought disorders in offspring.

Keywords: adoption study, Communication Deviance, gene-environment interaction, high-risk study, Rorschach, schizophrenia spectrum, season of birth, TDI, thought disorder

Roisko, Riikka, Vanhempien hajanainen kommunikaatio lapsen ajatushäiriöiden ja skitsofreniaspektrin sairauksien riskitekijänä. Suomalainen adoptiolapsiperhetutkimus

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta, Kliinisen lääketieteen laitos, Psykiatria; Oulun yliopistollinen sairaala

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Tiivistelmä

Skitsofreniaspektrin sairauksien varsinaisia syytekijöitä ei tunneta, mutta niillä on lukuisia sekä perimään että biologiseen ja psykososiaaliseen ympäristöön liittyviä riskitekijöitä. Nykytietämyksen mukaan riskitekijät eivät vaikuta sairauden syntyyn itsenäisesti, vaan perimän ja ympäristön vuorovaikutuksella on merkittävä osuus. Paljon tutkittuja ympäristöön liittyviä riskitekijöitä ovat lapsen talvi- tai kevätsyntymä ja vanhempien hajanainen kommunikaatio. Tässä väitöskirjassa tutkitaan vanhempien hajanaista kommunikaatiota adoptiolapsen ajatushäiriöiden ja skitsofreniaspektrin sairauksien riskitekijänä.

Vanhempien hajanaisen kommunikaation ja lapsen skitsofreniaspektrin sairauksien ja ajatushäiriöiden yhteydestä laadittiin systemaattinen katsaus. Meta-analyysi voitiin tehdä vain skitsofreniaspektrin sairauksiin liittyen. Vanhempien hajanaisen kommunikaation ja lapsen skitsofreniaspektrin sairauksien välisellä yhteydellä havaittiin olevan suuri efektikoko (0,79, 95 % luottamusväli 0,21–1,37). Katsaukseen sisällytetyt tutkimukset viittaavat siihen, että vanhempien hajanaisella kommunikaatiolla ja lapsen ajatushäiriöillä on myös yhteys.

Väitöskirjan alkuperäistutkimukset perustuvat Suomalaisen adoptiolapsiperhetutkimuksen aineistoon ($n=382$). Aluksi tutkittiin vanhempien yksilö- ja perhe-Rorschach-tilanteissa mitatun hajanaisen kommunikaation määrän ja lapsen ja vanhempien ominaisuuksien välistä yhteyttä. Hajanaisen kommunikaation määrän vaihtelu selittyi pääosin vanhempien ominaisuuksilla. Seuraavaksi tutkittiin adoptiolapsen ajatushäiriöiden ja skitsofreniaspektrin sairauksien yhteyttä lapsen skitsofreniaspektrin sairauksille altistavan perimän, talvi- tai kevätsyntymän ja vanhempien hajanaisen kommunikaation kanssa. Huomioon otettiin myös riskitekijöiden yhteisvaikutukset. Mikään riskitekijä tai niiden yhteisvaikutus ei ollut yhteydessä lapsen skitsofreniaspektrin sairauteen. Lapsen ajatushäiriöt olivat yhteydessä ainoastaan vanhempien hajanaiseen kommunikaatioon.

Tutkimuksen tulokset osoittavat, että vanhempien hajanainen kommunikaatio on kohtalaisen muuttumaton piirre, joka on lapsen skitsofreniaspektrin sairauksien riskitekijä. Tulokset viittaavat myös siihen, että vanhempien hajanainen kommunikaatio voi olla lapsen ajatushäiriöiden riskitekijä.

Asiasanat: adoptiolapsitutkimus, ajatushäiriö, hajanainen kommunikaatio, perimän ja ympäristön vuorovaikutus, riskilapsitutkimus, Rorschachin mustetahrastei, skitsofreniaspektri, syntymävuodenaika, TDI

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Oulu, September 2014

Riikka Roisko

Abbreviations

ANCOVA	Analysis of Covariance
APA	American Psychiatric Association
AS	Affective Style
CD	Communication Deviance
CI	Confidence interval
DNA	Deoxyribonucleic acid
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders. 3rd edition, revised
DSM-5	Diagnostic and Statistical Manual of Mental Disorders. 5th edition
EE	Expressed Emotion
ES	Effect size
ICD-10	International Statistical Classification of Diseases, Injuries and Causes of Death, 10th edition
PAR	Population attributable risk
PSE	Present State Examination
RDC	Research Diagnostic Criteria
RNA	Ribonucleic acid
SCID-II	Structured Clinical Interview for DSM-III-R Personality Disorders
SIS	Structured Interview for Schizotypy
SNP	Single nucleotide polymorphism
TAT	Thematic Apperception Test
TDI	Thought Disorder Index
TD _R	Thought disorder on the Rorschach; sum of weighted TDI scores divided by the number of Rorschach responses
WHO	World Health Organisation

List of original publications

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

- I Roisko R, Wahlberg K-E, Miettunen J & Tienari P (2014) Association of parental Communication Deviance with offspring's psychiatric and thought disorders. A systematic review and meta-analysis. *Eur Psychiatry* 29: 20-31.
- II Roisko R, Wahlberg K-E, Hakko H, Wynne L & Tienari P (2011) Communication Deviance in parents of families with adoptees at a high or low risk of schizophrenia spectrum disorders and its associations with attributes of the adoptee and the adoptive parents. *Psychiatry Res* 185: 66-71.
- III Roisko R, Wahlberg K-E, Hakko H & Tienari P (2014) Association of adoptive child's thought and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders, season of birth and parental Communication Deviance. Manuscript.

Contents

Abstract	
Tiivistelmä	
Acknowledgements	7
Abbreviations	9
List of original publications	11
Contents	13
1 Introduction	17
2 Review of the literature	19
2.1 Schizophrenia.....	19
2.1.1 Risk factors for schizophrenia.....	20
2.2 Schizophrenia spectrum disorders.....	24
2.3 Thought disorders	26
2.3.1 Definition and assessment of thought disorders.....	26
2.3.2 Aetiology of thought disorders.....	29
2.3.3 Stability of thought disorders	30
2.3.4 Relationship between thought disorders and psychiatric disorders	31
2.3.5 Thought disorder as a putative schizophrenia endophenotype	33
2.4 Communication Deviance.....	33
2.4.1 Definition and assessment of Communication Deviance	33
2.4.2 Stability of Communication Deviance	35
2.4.3 Relationship of parental Communication Deviance to psychiatric and thought disorders in offspring	39
2.4.4 Parental communication and cognitive development of the child.....	41
2.5 General systems theory, biopsychosocial model, and vulnerability theories.....	42
3 Aims of the study	45
3.1 Aims of the study	45
3.2 Hypotheses.....	45
4 Material and methods	47
4.1 Meta-analysis (I).....	47
4.1.1 Data collection.....	47
4.1.2 Study selection	47

4.1.3	Statistical methods.....	47
4.2	Study design.....	48
4.3	Study population (II and III).....	48
4.3.1	The Finnish Adoptive Family Study.....	48
4.3.2	Publication II: Association of parental Communication Deviance with the attributes of the adoptive child and adoptive parents.....	50
4.3.3	Publication III: Association of adoptive children’s thought disorders and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders and season of birth and parental Communication Deviance	51
4.4	Variables (II, III).....	53
4.4.1	Communication Deviance	53
4.4.2	Season of birth.....	57
4.4.3	Thought Disorder Index.....	57
4.4.4	Schizophrenia spectrum diagnosis.....	60
4.5	Statistical methods (II, III).....	61
5	Ethical considerations and personal involvement	63
6	Results	65
6.1	Systematized review and meta-analysis of the association between parental Communication Deviance and thought disorders and psychiatric disorders in offspring (I).....	65
6.1.1	Search results.....	65
6.1.2	Association of parental Communication Deviance with psychiatric disorders in offspring	65
6.1.3	Association of parental Communication Deviance with thought disorders in offspring.....	66
6.2	Association of parental Communication Deviance with the attributes of the adoptive child and adoptive parents (II).....	67
6.3	Association of adoptive children’s thought disorders and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders and season of birth and parental Communication Deviance (III).....	69
7	Discussion	71
7.1	Systematised review and meta-analysis (I).....	71
7.1.1	Main findings.....	71
7.1.2	Discussion of results.....	71

7.2	Association of parental Communication Deviance with the attributes of the adoptive child and adoptive parents (II).....	73
7.2.1	Main findings	73
7.2.2	Discussion of results.....	73
7.3	Association of adoptive children’s thought disorders and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders and season of birth and parental Communication Deviance (III)	75
7.3.1	Main findings	75
7.3.2	Discussion of results.....	76
7.4	Theoretical discussion.....	77
7.5	Strengths and limitations of the study.....	80
7.5.1	Systematised review and meta-analysis of the association between parental Communication Deviance and psychiatric and thought disorders in offspring (I)	80
7.5.2	Association of parental Communication Deviance with the attributes of the adoptive child and adoptive parents (II)	81
7.5.3	Association of adoptive children’s thought disorders and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders, season of birth, and parental Communication Deviance (III).....	82
8	Conclusions	85
8.1	Main conclusions	85
8.2	Clinical implications	85
8.3	Future studies	86
	References	89
	Original publications	107

1 Introduction

Schizophrenia-like conditions have been described worldwide throughout recorded history (Bhati 2013). Schizophrenia was distinguished from other types of severe mental illness and the term “schizophrenia” was introduced in the early 20th century (Bleuler 1950). Later it was found that schizophrenia is not a conceptually or dimensionally separate entity from other psychotic disorders, but there is overlap in risk factors, diagnostic criteria, and the clinical picture of severe psychiatric disorders. The term “schizophrenia spectrum” was introduced about 50 years ago (Kety *et al.* 1968) and, since then, many definitions of schizophrenia spectrum have emerged, but no uniform view on the boundaries of schizophrenia spectrum has been established.

Despite the long history of the concept of schizophrenia and an intensive search for the causes of schizophrenia, which has been going on for decades, its aetiology has remained an unresolved problem. Family, twin, and adoption studies have shown that schizophrenia and other severe psychiatric disorders with psychotic features run in families (Shih *et al.* 2004). The high estimates of heritability based on family studies have been criticised as underestimating the role of the environment (Brown 2011). Molecular genetic studies have shown that both rare genetic variants with strong effects (Sullivan *et al.* 2012) and common variants with small effects (Sullivan *et al.* 2012, Ripke *et al.* 2013) contribute to the genetic basis of heritability of schizophrenia. However, genotypic relative risks for even the most significant and replicated loci for schizophrenia have been small, at about 1.10 (Kim *et al.* 2011). The strongest risk indicator for schizophrenia, having a first-degree relative with a schizophrenia diagnosis, increases the risk of schizophrenia in an individual tenfold (from about 1% to 10%). Genetic liability seems not to be specific to schizophrenia, but shared for broadly defined schizophrenia spectrum disorders (Bigdeli *et al.* 2014) or even for psychiatric disorders in general (Lee *et al.* 2013).

In addition to genetic factors, several biological and psychosocial environmental risk factors contribute to the aetiology of psychotic disorders. These include pre- and perinatal factors, such as prenatal infections (Brown & Derkits 2010), nutritional deficiencies (especially hypovitaminosis D, McGrath *et al.* 2010), winter or spring birth (Torrey *et al.* 1997), migration (Cantor-Graae & Selten 2005), and urbanicity (Vassos *et al.* 2012). Various risk factors during childhood and adolescence have also been shown to be associated with schizophrenia and other psychotic disorders, such as childhood adversities

(Tienari *et al.* 2004, Varese *et al.* 2012), cannabis use (Arseneault *et al.* 2002), disadvantaged socioeconomic position (Wicks *et al.* 2010), and communication deviance in the rearing parents (Miklowitz & Stackman 1992). Many of the environmental risk indicators have been shown to interact with genetic risk factors. Even though the era of gene-environment interaction studies is just about to emerge, evidence indicates that gene-environment interactions play a major role in the aetiology of psychotic disorders (Kendler & Eaves 1986, Tienari *et al.* 2004, Kendler 2005, van Os *et al.* 2010).

The aim of this doctoral thesis is to investigate the role of parental Communication Deviance as a risk factor for thought disorders and schizophrenia spectrum disorders in an adoptive child. To achieve this aim, it is first determined what is known about the association of parental Communication Deviance and psychiatric disorders and thought disorders in offspring, by means of a systematic review and meta-analysis. Second, it is assessed if the amount of parental Communication Deviance is independent of characteristics of the adoptive child and the parents themselves. This aim is connected to the issue of the direction of the effect between parental CD and the psychopathology of the child. Third, the association of parental Communication Deviance, together with the genetic risk status of a child and their season of birth, with thought disorders and schizophrenia spectrum disorders in an adoptive child is investigated. The thesis consists of three original publications, each of which deals with one aim of the study, and a compilation.

This doctoral thesis is a part of the Finnish Adoptive Family Study (Tienari *et al.* 1987, Tienari *et al.* 2000). The data on the subjects of the Finnish Adoptive Family Study have been collected from tests, personal and family interviews, and registers. The Finnish Adoptive Family Study is a prospective longitudinal high-risk study, which aims to investigate the contribution of genetic risk and adoptive family environmental variables (including parental Communication Deviance) to the psychopathology of the adoptive child.

2 Review of the literature

2.1 Schizophrenia

Schizophrenia was recognised and differentiated from manic-depressive psychosis by Emil Kraepelin in early 20th century (Kraepelin 1919), but it was Eugen Bleuler (1950) who first used the term “schizophrenia”. Nowadays, schizophrenia is defined as a combination of delusions, hallucinations, disorganised speech, disorganised or catatonic behaviour, and negative symptoms that are present for at least one (ICD-10, WHO 1994) or six months (DSM-5, APA 2013) without considerable affective symptoms. Lifetime prevalence of schizophrenia worldwide is estimated to be 0.57 (mean), lifetime morbid risk 0.7%, and incidence 23.7/100 000 (mean), but both estimates show prominent variation between study sites and being higher, for example in urban sites and among migrants (McGrath *et al.* 2008). In a Finnish study, the lifetime prevalence of schizophrenia was 0.87%, but if register diagnoses were also included in the analyses, 1.00% (Perala *et al.* 2007). In the same study, lifetime prevalence of any psychotic disorder was estimated to be 3.06% and 3.48%, respectively. Subclinical psychotic symptoms are far more common in the general population, with a median prevalence rate of about 5% and a median incidence rate of about 3% (van Os *et al.* 2009).

The search for the causes of schizophrenia has been going on for decades, but its specific aetiology has remained an unresolved problem. Schizophrenia seems to be an aetiologically heterogeneous syndrome with genetic and environmental risk factors, the latter consisting of both biological and psychosocial factors (Tandon *et al.* 2008). It has been suggested that one major reason for the lack of success of research on aetiology of mental disorders (including schizophrenia) is current diagnostic system which, with its descriptive diagnoses, does not reflect relevant neurobiological and behavioural systems (Cuthbert & Insel 2013). To overcome this obstacle, the National Institute of Mental Health (NIMH) began the Research Domain Criteria (RDoC) project about five years ago (Cuthbert & Insel 2013). The RDoC project ultimately aims to develop a research classification system based on dimensions of neurobiology and observable behaviour which is supposed to reveal the aetiology and pathophysiology of mental disorders better than research relying on the current descriptive, categorical diagnostic system.

2.1.1 Risk factors for schizophrenia

Genetics and epigenetics

Family, twin, and adoption studies have shown that schizophrenia, as well as other severe psychiatric disorders with psychosis (e.g. bipolar disorder), runs in families (Shih *et al.* 2004). If one of the monozygotic twins has schizophrenia, the other has a relative risk of 50–70 for the disorder. As the percentage of shared genetic material decreases, an individual's relative risk of schizophrenia decreases: it is 9–18 if a family member with schizophrenia is a dizygotic twin pair or another first degree relative, and it further decreases if second or third degree relatives are concerned (Tandon *et al.* 2008). Based on twin studies, the heritability of the liability for schizophrenia (the proportion of variance in liability for an illness in the general population that is accounted for by genetic effects) is estimated to be as high as 80% (Sullivan *et al.* 2003). Adoption studies also show that schizophrenia runs in families (Heston 1966, Rosenthal *et al.* 1971, Kety *et al.* 1975, Kendler & Gruenberg 1984). However, those adoption studies in which specified environmental factors have also been explored strongly suggest the contribution of both genetic and environmental factors in the aetiology of schizophrenia and schizophrenia spectrum disorders (Wender *et al.* 1968, Wynne *et al.* 1978, Tienari *et al.* 2004, Wicks *et al.* 2010).

Advances in technology and science have made it possible to try to elucidate the genetic basis and exact mechanisms of the heritability of schizophrenia, and both rare genetic variants with strong effects (Sullivan *et al.* 2012) and common variants with small effects (Sullivan *et al.* 2012, Ripke *et al.* 2013) have been found. However, so far, even the most significant and replicated loci for schizophrenia typically have genotypic relative risks of about 1.10 (Kim *et al.* 2011).

In addition to structural changes in DNA, the transcription of genes into proteins may be affected by epigenetic changes. Three systems are known to be used in epigenetic silencing of genes: DNA methylation, RNA-associated silencing, and histone modification (Egger *et al.* 2004). Through epigenetic mechanisms, environmental factors can affect gene expression (Weaver *et al.* 2004) and give rise to diseases (Egger *et al.* 2004). Though there has been wide speculation about the role of epigenetic mechanisms in schizophrenia, research into it is, however, still in its infancy, and much more research is needed to

elucidate the significance of epigenetic mechanisms in the neurobiology of schizophrenia (Dempster *et al.* 2013).

Research into the genetics of schizophrenia, as well as other psychotic disorders, has been hampered by their heterogeneous phenotypes. The endophenotype concept in psychiatry was introduced in the 1970s, but it laid dormant for decades until its re-introduction in 2003 (Gottesman & Gould 2003), since when it has enjoyed a revival (Miller & Rockstroh 2013). Endophenotypes for psychopathology are conceived as measurable components, unseen to the naked eye, that causally connect genetic liability to clinical disorder (Gottesman & Gould 2003, Miller & Rockstroh 2013). The vast majority of studies of schizophrenia endophenotypes are concerned with measures of anatomical and physiological variants and neurocognitive measures (Allen *et al.* 2009), but indices of disordered thought have also lately been explored as an endophenotype for schizophrenia and schizophrenia-related disorders (Gooding *et al.* 2012, Gooding *et al.* 2013).

Environmental risk factors

Even though schizophrenia (like other severe psychiatric disorders, e.g. bipolar disorder) is considered a highly heritable disease, environmental factors are also recognised to have relevance in the aetiology of schizophrenia.

Several pre- and perinatal risk factors have been associated with schizophrenia: prenatal infections [especially influenza (Brown & Derkits 2010)], maternal stress (Myhrman *et al.* 1996, van Os & Selten 1998, Khashan *et al.* 2008, Malaspina *et al.* 2008), prenatal nutritional factors (famine; iron, folate, and vitamin D deficiency) (Susser *et al.* 1996, McGrath *et al.* 2010, McGrath *et al.* 2011), winter or spring birth (Torrey *et al.* 1997), migration (Cantor-Graae & Selten 2005), urbanicity (Vassos *et al.* 2012), advanced paternal age (Miller *et al.* 2011), and complications in pregnancy and delivery (Cannon *et al.* 2002). Both low and high birth weight have been shown to increase the risk for later schizophrenia (Cannon *et al.* 2002, Moilanen *et al.* 2010). Individuals who later develop schizophrenia also show premorbid cognitive, physical, and social impairment and subtle and nonspecific behavioural deviations (Tandon *et al.* 2008, Welham *et al.* 2009). Various risk factors during childhood and adolescence have also been shown to be associated with schizophrenia and other psychotic disorders: childhood adversities (Tienari *et al.* 2004, Varese *et al.* 2012), cannabis use (Arseneault *et al.* 2002), disadvantaged socioeconomic position (Wicks *et al.*

2010), central nervous infections (Dalman *et al.* 2008), and communication disorders in the rearing parents (Wynne *et al.* 1977, Goldstein 1985, Miklowitz & Stackman 1992, de Sousa *et al.* 2014). In addition to parental Communication Deviance, measures of family affective tone are much studied as family environmental risk factors. The most studied measure of family affective tone is Expressed Emotion (EE) (Brown *et al.* 1972, Vaughn & Leff 1976a). EE is a measure of the degree to which a relative of a recently hospitalized schizophrenic patient holds highly critical and/or emotionally overinvolved or overprotective attitudes towards the patient. It is not considered as an aetiological risk factor for psychiatric disorders, but as a predictor of relapse in schizophrenia and also in mood disorders, including bipolar disorder (Hooley 2007). Carers' critical comments (but not the overall EE) increase the risk of relapse in first-episode psychoses 2.3-fold (Alvarez-Jimenez *et al.* 2012).

The season of birth is one of the intensively studied biological risk indicators in schizophrenia. In a comprehensive review (Torrey *et al.* 1997), it was concluded that the rate of increase of winter-spring births in schizophrenia and also in bipolar and schizoaffective disorder (from November to April, the peak from January to February) is 5-10% compared with the expected number of births during the season. The result on the increase in winter-spring births in schizophrenia has since been replicated in a large register-based study (Mortensen *et al.* 1999), but the finding was not constant in all study populations in a replication attempt (Pedersen & Mortensen 2001). The increase in winter-spring births in schizophrenia has only been detected in the northern hemisphere (McGrath & Welham 1999, Davies *et al.* 2003). Even though the absolute increase in risk of schizophrenia related to winter-spring birth is small, it is not insignificant, because a considerable proportion of the population is exposed to risk. For this reason, the population attributable fraction (PAF) according to season of birth is estimated to be as high as 10% (Torrey *et al.* 1997, Mortensen *et al.* 1999), while PAF according to the strongest risk factor known, namely family history, is 5.5%. It has been suggested that the season of birth effect would be present only in those population groups where there is no genetic liability to psychotic disorders, but the results of the studies concerning this issue are controversial (Torrey *et al.* 1997, Mortensen *et al.* 1999, Kinney *et al.* 2000, Carrion-Baralt *et al.* 2006).

The studies on the season of birth in other psychiatric diagnoses are sparse, but the results suggest that similar excess in winter-spring births as in schizophrenia may be present in affective psychoses (Castrogiovanni *et al.* 1998,

Hultman *et al.* 1999). There is only one study that has explored the association of psychotic-like experiences and season of birth (Tochigi *et al.* 2013), in which a significant excess of winter births (from November to March) was observed in the prevalence of psychotic-like experiences. There is evidence that another indicator of vulnerability to schizophrenia, schizotypy, is also associated with winter or early spring birth (Lahti *et al.* 2009, Hori *et al.* 2011, Bolinsky *et al.* 2013).

While there is a multitude of studies concerning the association of the season of birth and psychiatric disorders, much less is known about how the season of birth effect is mediated. It is proposed that it represents a proxy for certain meteorological factors, prenatal infections, nutritional deficiencies, the effect of external materials (e.g. heavy metals), factors on the paternal side, maternal hormones, and seasonal variation in procreation (Tochigi *et al.* 2004). Accumulating evidence supports the hypotheses that the season of birth effect is mediated by either prenatal infections or vitamin D deficiency, the latter of which could also explain the variability in the risk of schizophrenia according to place of birth and migrant status (McGrath *et al.* 2004, Kinney *et al.* 2009). Results of both epidemiological and animal experimental research support the hypothesis on the association between developmental vitamin D deficiency and increased risk of schizophrenia (McGrath *et al.* 2010, Eyles *et al.* 2013).

Joint effects of genotype and environment

The high estimates of heritability based on family studies have been criticised as underestimating the role of the environment by ignoring gene-environment interactions and gene-environment correlations (Brown 2011). There is growing evidence that the aetiology of psychotic disorders can be accounted for neither in genetics nor in environmental factors alone, but rather the joint effects of genes and environment play a major role (van Os *et al.* 2010). The three basic models for the joint effects of genotype and environment are: 1) additive effects of genotype and environment, 2) genetic control of sensitivity to the environment, and 3) genetic control of exposure to the environment (also called GxE correlation) (Kendler & Eaves 1986). Evidence supports the hypothesis that the mechanism of interaction in most cases is genetic control of sensitivity to the environment (van Os *et al.* 2008). There are several adoption studies that provide evidence on the interaction of inherited vulnerability and risk factors in the psychosocial environment (parental Communication Deviance, adverse rearing environment, and disadvantaged socioeconomic position) in the manifestation of

thought disorders and psychotic and other psychiatric disorders (Wahlberg *et al.* 1997, Wahlberg *et al.* 2004, Tienari *et al.* 2004, Wicks *et al.* 2010). There is also direct molecular evidence on gene-environment interactions in psychosis (Caspi *et al.* 2005), but candidate gene-by-environment studies have been criticised as not being robust because of marked publication bias among replication attempts and underpowered samples (Duncan & Keller 2011). However, this purely statistical (theory-free) approach that requires huge samples has been also criticised. Theory-free approach is not considered to be either sufficient or even necessary for evaluating research into GxE interaction hypotheses involving candidate genes with known functions and association to the outcome measure. (Caspi *et al.* 2010).

2.2 Schizophrenia spectrum disorders

The history of the idea of schizophrenia spectrum disorders extends over one hundred years. Both Kraepelin and Bleuler observed that some relatives of schizophrenia patients, though never psychotic themselves, displayed symptoms similar to but milder than those in schizophrenia. However, it was not until 1968 that the term “schizophrenia spectrum” was introduced (Kety *et al.* 1968), referring to these signs and symptoms observed in relatives of schizophrenia patients. Schizophrenia spectrum disorders are regarded as reflectors of shared genetic vulnerability with schizophrenia.

The main body of literature concerning the existence and boundaries of schizophrenia spectrum is based on family, twin, and adoption studies (Tienari *et al.* 2003, Shih *et al.* 2004, Goldstein *et al.* 2010, Rasic *et al.* 2014). In the vast majority of these studies, environmental risk indicators are not taken into account, even though, especially in studies of biological families, genetic and environmental risk factors cannot be disentangled. There is also some direct molecular evidence that supports the hypothesis of shared genetic liability to broadly defined schizophrenia spectrum disorders (Bigdeli *et al.* 2014) or even to psychiatric disorders in general (Lee *et al.* 2013).

Since the 1960s, many definitions of schizophrenia spectrum have emerged, and no uniform view on the boundaries of schizophrenia spectrum has been established. There has been discussion on whether genetic vulnerability is specific only to non-affective psychoses, to any psychiatric disorder with psychosis or psychotic-like experiences, or if there is a vulnerability to psychiatric disorders in general.

Kety and his co-workers (1968, 1978) originally applied a rather narrow definition of schizophrenia spectrum disorders, including chronic schizophrenia, acute schizophrenic reaction, border-line state, and inadequate personality, with the latter two categories being reminiscent of diagnoses of DSM-5 schizoid and schizotypal personality disorders. A highly similar narrow definition of schizophrenia spectrum can be found in DSM-5, in which schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, and delusional disorder are included in the spectrum, and schizotypal personality disorder is also recognised as a spectrum disorder (Bhati 2013).

One extensively studied definition of schizophrenia spectrum is that of Kendler and colleagues, which assumes shared genetic liability for several disorders with varying degrees of severity. It is based on family studies, and the spectrum includes schizophrenia, schizoaffective disorder, other non-affective psychoses and also affective psychoses (Kendler *et al.* 1993a, Kendler *et al.* 1995b) and schizotypal, paranoid, schizoid, and avoidant personality disorders (Kendler *et al.* 1993b, Kendler *et al.* 1995b, Asarnow *et al.* 2001, Fogelson *et al.* 2007).

The broad definition of schizophrenia spectrum is supported by growing evidence of the existence of a psychosis continuum (van Os *et al.* 2009) that extends from transitory subclinical psychotic experiences to clinical psychotic disorders. Subclinical psychotic symptoms are much more common than clinical psychoses in general population (a median prevalence rate of about 5% and a median incidence rate of about 3%), although 75–90% of cases are transitory, and they share risk factors with schizophrenia (van Os *et al.* 2009). A dose-response but not necessarily linear association between increasing severity of psychosis and proxies of genetic factors (mental illness in family members, family history of common mental disorder and severe mental illness) has been found (Binbay *et al.* 2012). In the same study by Binbay and colleagues (2012), several environmental risk indicators were also found to be associated with severity of outcome, with associations being either linear or extralinear, depending on the type of risk indicator.

Even though the vast majority of literature supports the hypothesis that genetic vulnerability is shared among psychotic disorders, there is also evidence of more general vulnerability to psychiatric disorders. In a large register-based study (Mortensen *et al.* 2010), the highest relative risk of schizophrenia was associated with schizophrenia in a first-degree relative, but categories of mental disorder (severe enough to lead to psychiatric hospitalisation or out-patient

contact) among first-degree relatives were also associated with increased risk. It was concluded that population attributable risk (PAR, an estimate of the fraction of the total number of cases of schizophrenia in the population that would not have occurred if the effect of the specific risk factor had been eliminated) due to family histories that include schizophrenia is 6.0%, but PAR attributed to mental disorder and suicide is 27.1%. In a meta-analysis of family high-risk studies (Rasic *et al.* 2014), it was shown that high-risk children of parents with severe mental illness (schizophrenia, bipolar disorder, or major depressive disorder) had a significantly increased risk of developing severe mental illness as compared to control children. The results of a huge register-based study with more than 2 million nuclear (also adoptive) families (Lichtenstein *et al.* 2009) showed that first-degree biological relatives of probands with schizophrenia or bipolar disorder were at increased risk of both of these disorders. It was concluded that schizophrenia and bipolar disorder partly share a common genetic cause.

The available molecular evidence also supports the hypothesis about a shared genetic vulnerability between several disorders: schizophrenia polygene scores (SNP) differed significantly across diagnostic categories, being highest in those with a very narrow schizophrenia-spectrum, lowest in those with no psychiatric illness, and in-between with a more or less broad schizophrenia spectrum. All the relatives of affected subjects, including those with no diagnosis at all, had higher scores than relatives in the control sample (Bigdeli *et al.* 2014). In a genome-wide association study of genetic relationship between five psychiatric disorders [schizophrenia, bipolar disorder, major depressive disorder (MDD), autism spectrum disorders (ASD) and attention-deficit-hyperactivity disorder (ADHD)], SNP-based coheritabilities were found to be high between schizophrenia and bipolar disorder; moderate between schizophrenia and MDD, bipolar disorder and MDD, and ADHD and MDD; and low (but significant) between schizophrenia and ASD (Lee *et al.* 2013).

2.3 Thought disorders

2.3.1 Definition and assessment of thought disorders

The presence of disordered thought and language in schizophrenia has been recognised as early as the disease itself. Kraepelin (1919) described dementia praecox as a progressive mental and social deterioration, including deterioration

in the capacity to think. Bleuler (1950), who introduced the term “schizophrenia”, went one step further and assumed thought disorder (an associative disturbance) to be a central feature of this disease. Kurt Schneider’s definitions of first and second rank symptoms of schizophrenia (1974) have had a great impact on diagnostic classification of mental disorders as the first rank symptoms were long considered to be specific to schizophrenia. Schneider’s list of first rank symptoms includes following indicators of disordered thought: thought withdrawal and other forms of thought interference, thought diffusion and delusional perception (Schneider 1974).

Despite a long history of a concept of and research on thought disorders, an exact definition of thought disorder has been lacking since the days of Kraepelin. One obvious reason that makes the definition of the essence of disordered thought complicated is insufficient scientific knowledge on the mechanisms of not disordered, “normal” thinking. Basically, two categories of definitions of thought disorders have been distinguished, the one being based on content (e.g. delusions) and the other on form of thought. The main interest of researchers has been focused on the latter, formal thought disorders (Harvey & Neale 1983).

Several features have been used to characterise formal thought disorders: associative disturbances, illogicality, concrete thinking, conceptual overinclusion, intermingling, autistic thinking, poverty of content of speech, incoherence, clanging, perseveration, echolalia, blocking, and poverty of speech (Marengo & Harrow 1988). Thought disorders have also been dichotomised to positive and negative types (Andreasen 1979b, Andreasen & Grove 1986, Marengo & Harrow 1988), the former meaning that disordered thinking replaces conventional thinking, and the latter that there are some deficiencies in thinking, such as poverty of content of speech. In addition to purely dividing manifestations of disordered thought into categories and counting their frequencies, thought disorder severity has also long been the subject of research (Harrow & Quinlan 1977, Johnston & Holzman 1979).

The presence of thought disorder is conventionally inferred from disordered speech, and there has been a long-lasting, still ongoing debate on the issue of whether thought disorder is actually a speech disorder, a linguistic rather than a psychological problem. There is some evidence that language as such is impaired in schizophrenia (DeLisi 2001), especially in the fields of semantics, discourse, and pragmatics (Radanovic *et al.* 2013). Motor features of disordered speech have also gained some attention, and subjects with thought disorders have been shown to have slow, redundant speech with more pauses between clauses than speakers

without thought disorders (Marengo & Harrow 1988). Crow (2008) has gone even so far that he claims that the nuclear symptoms of schizophrenia (and broadly defined psychosis) can be considered entirely as a disorder of language. The majority of researchers, however, presuppose thought disorders to be a psychological or psychiatric phenomenon.

During the more than one hundred years of observation and research on thought disorders, a substantial number of scales and other methods to assess the quantity and quality of thought disorders have been established. This is partly a reflection of the miscellaneous nature of definitions of disordered thought. The data for investigations have been collected from a variety of situations (Harvey & Neale 1983): from interaction with patients on a hospital ward in early studies, diagnostic interviews (Cancro 1968, Andreasen 1979a), and from projective testing sessions (Friedman 1952, Harrow *et al.* 1972, Johnston & Holzman 1979, Liddle *et al.* 2002). Some researchers, especially in the field of psycholinguistics (DeLisi 2001), have prioritised gathering samples of natural language using several methods.

The data collected from the aforementioned situations has been analysed using numerous methods. Early studies were merely descriptions of thought disorder (Kraepelin 1919) or observed certain features of what was considered to be disordered thought (for example, associative loosening, Bleuler 1950, Cancro 1968). Later, however, many scales for rating the quantity and quality of disordered thought have been developed. Examples of these scales are Index of Primitive Thought (Friedman 1952), the Scale for the Assessment of Thought, Language, and Communication (TLC, Andreasen 1979a), the Thought Disorder Index (TDI, Johnston & Holzman 1979), the Kiddie Formal Thought Disorder Rating Scale (K-FTDS, Caplan *et al.* 1989), and the Thought and Language Index (TLI, Liddle *et al.* 2002). Inherent in symptom severity rating scales like the Brief Psychiatric Rating Scale (BPRS, Overall & Gorham 1962) and the Positive and Negative Syndrome Scale (PANSS, Kay *et al.* 1987) are also items that measure thought disorders.

One of the most used rating scales for disordered thought is the TDI (Johnston & Holzman 1979). It tags, classifies, and measures instances of disordered thinking both qualitatively and quantitatively. It is conventionally used as an indicator of both subclinical and clinical psychopathology, but its utility as a vulnerability marker, an endophenotype, for schizophrenia has also been studied (Gooding *et al.* 2012). Any verbal sample can be used as material for TDI. In short, the revised version of the Thought Disorder Index (Solovay *et al.* 1986)

includes 23 categories weighted along a continuum of severity (0.25, 0.50, 0.75, and 1.0), where 0.25 represents minor idiosyncrasies, 0.50 indicates a loss of mooring, shaky reality contact, emotional overreaction and distinct oddness, 0.75 is associated with psychotic disruption and characterised by instability of thinking and perception, absurdity, and an unrestrained combinatory tendency, and the 1.0 level represents responses completely divorced from reality (Solovay *et al.* 1986). Specific items on the Thought Disorder Index scale (Fluid Thinking, Confusion and Idiosyncratic Verbalisation) have been shown to be connected to schizophrenia and are referred to as a schizophrenia subscale of TDI (Holzman *et al.* 1986).

2.3.2 Aetiology of thought disorders

Theories on the aetiology of thought disorders have been changing since the recognition of the phenomenon following shifts in general theories on psychiatry and psychology (Marengo & Harrow 1988). The first theories were based on the traditions of associationist psychology and psychoanalytic theory, after which there was a shift to behavioural and family models (Marengo & Harrow 1988). Family models assume that thought disorders are derivatives of deviant family communication, together with other family environmental and genetic factors (Wynne & Singer 1963a, 1963b, Singer & Wynne 1965a, 1965b, Wahlberg *et al.* 1997, Wahlberg *et al.* 2000).

It has long been known that schizophrenia runs in families, as well as thought disorders, and early on, disordered thought was suggested to be a hereditary factor in schizophrenia (McConaghy 1959, Johnston & Holzman 1979). Thought disorders have constantly been found in unaffected biological relatives and in individuals at high-risk of schizophrenia at a higher rate than in the general population (McConaghy 1959, Haimo & Holzman 1979, Parnas *et al.* 1982, Arboleda & Holzman 1985, Shenton *et al.* 1989, Kendler *et al.* 1995a, Baskak *et al.* 2008, Gooding *et al.* 2012, Gooding *et al.* 2013). This finding, as such, does not indicate whether it is due to genetic or environmental factors. The relative contribution of genetics and the environment to the development of thought disorders has been investigated in twin and adoption studies. Both types of studies of thought disorder are sparse, and the results are contradictory (Berenbaum *et al.* 1985, Kinney *et al.* 1997, Docherty & Gottesman 2000). There is some evidence that gene-environment interactions make a significant contribution to the aetiology of thought disorders (Wahlberg *et al.* 1997, Wahlberg *et al.* 2000).

Genome-wide association studies of thought disorders are just about to emerge. So far, formal thought disorder has been associated with four genetic loci (PKNOX2, MYH13, PHF2, and GPC6), of which PKNOX2 is associated with several psychiatric disorders, while the knowledge of associations of the other three genes with psychiatric disorders is still incomplete (Wang *et al.* 2012).

Several types of cognitive impairments have been suggested to underlie thought disorders in schizophrenia patients, namely impaired executive functioning, increased spreading activation, impaired semantic memory, and impaired language production (Kerns & Berenbaum 2002). In their review, Kerns and Berenbaum (2002) conclude that formal thought disorder is most strongly associated with impaired executive functioning and impaired semantic memory. In the systematic review and meta-analysis of semantic memory impairment in schizophrenia, formal thought disorders were linked to semantic memory only in tests of naming and verbal fluency, the latter of which also reflects executive dysfunction (Doughty & Done 2009).

The number of structural and functional imaging studies on thought disorders is far from that concerning schizophrenia. The main finding of structural imaging studies of schizophrenia patients with thought disorders is volume reductions in the left superior temporal cortex (mainly the superior temporal gyrus) in language-related cortical regions, following attenuated, diminished, or inverse left-right asymmetry (Leube *et al.* 2008, Sans-Sansa *et al.* 2013). In functional imaging studies, dysfunction and inverse left-right asymmetry in the left superior temporal gyrus has also been a constant finding (Leube *et al.* 2008).

2.3.3 Stability of thought disorders

There has been debate on whether thought disorders are just a temporary reflection of a psychotic state or a stable trait of an individual, manifesting itself in states of clinical remission. Follow-up times in studies on thought disorders have been mainly quite short, from weeks to months.

A few studies exploring disordered thought in children show that immature thinking, which in adults was to be classified as a thought disorder, is common among them and decreases with a child's age (Arboleda & Holzman 1984, Caplan 1994, Caplan *et al.* 2000). Among adult subjects, short-term follow-up studies (from about seven weeks to six months) show that indices of disordered thought (Harrow *et al.* 1972, Harrow & Quinlan 1977, Harrow *et al.* 1982, Andreasen & Grove 1986) tend to decrease over time. However, they do not completely

disappear and seem to be more persistent among patients with schizophrenia. Studies with longer follow-up times (from about a year to 7.5 years) continue to provide evidence on persistence of thought disorders among patients with a schizophrenia diagnosis, but not in other groups of patients (Harrow *et al.* 1973, Harrow *et al.* 1983, Harrow *et al.* 1986, Marengo & Harrow 1997). In an eleven-year follow-up study, thought disorders measured by TD_R (Solovay *et al.* 1986), the most significant predictor of thought disorder in follow-up were the baseline TD_R scores, regardless of genetic risk status or psychiatric status (Metsänen *et al.* 2005). The stability seemed to be related to the most severe TDI categories and one of the items on the schizophrenia scale, idiosyncratic verbalisation (Metsänen *et al.* 2006).

Randomised controlled studies on the effect of antipsychotic medication on quantity or quality of thought disorders are scarce. Two papers derived from the same dataset of patients with a schizophrenia diagnosis (Hurt *et al.* 1983, Gold & Hurt 1990) reported that TDI scores declined significantly over the course of treatment with haloperidol, along with declining BPRS scores. In another study of patients with a schizophrenia diagnosis, more severe thought disorders defined by BPRS subscales and TDI severity levels were reduced by neuroleptic medication, but not less severe thought disorders (Spohn *et al.* 1986).

2.3.4 Relationship between thought disorders and psychiatric disorders

Thought disorders were long believed to be pathognomonic and also specific to schizophrenia. This assumption, which later turned out to be false, was for the most part due to a systematic bias in study designs and settings. Only schizophrenia patients were included in the studies and, at the same time, all patients with a diagnosis of schizophrenia had thought disorders because the diagnosis could not be settled without them. The aforementioned hypothesis had to be rejected as a consequence of, first, including patients other than those with a schizophrenia diagnosis in thought disorder studies and, second, changes in diagnostic criteria for schizophrenia, so that not all patients with a diagnosis of schizophrenia essentially had thought disorders.

There is strong evidence that thought disorders are common in schizophrenia, but also in other severe psychiatric disorders like mania and schizoaffective disorder (Andreasen 1979b, Harrow & Quinlan 1977, Harrow & Prosen 1979, Johnston & Holzman 1979, Harrow *et al.* 1982, Harvey *et al.* 1984, Andreasen &

Grove 1986, Holzman *et al.* 1986, Wilcox *et al.* 2012). In the aforementioned studies, subjects with nonpsychotic psychiatric disorders, or without any psychiatric disorder, are employed as control groups. Although the levels of thought disorders are generally statistically significantly lower in these control groups, thought disorder is not absent even among them. Acute distress, acute disorder (other than psychotic), and anxiety are connected to elevated levels of thought disorders in clinically healthy subjects or in patients with nonpsychotic psychiatric disorders (Harrow & Quinlan 1977, Solovay *et al.* 1987). While broadly defined thought disorders have not succeeded in differentiating groups of patients with separate severe, psychotic disorders from each other, subtypes and severity scales of thought disorders have done so (Harrow *et al.* 1973, Harrow & Quinlan 1977, Andreasen 1979b, Küfferle *et al.* 1985, Andreasen & Grove 1986, Harrow *et al.* 1986, Shenton *et al.* 1987, Solovay *et al.* 1987, Marengo & Harrow 1997, Caplan *et al.* 2000).

Schizotypic individuals, and individuals at high risk of schizophrenia spectrum disorders, display thought disorders similar to those shown by patients with a schizophrenia diagnosis, including among young children (Arboleda & Holzman 1985, Caplan 1994, Coleman *et al.* 1996).

The association between thought disorders and the outcome of schizophrenia and other psychotic disorders has been a quite intensively studied area. There is a constant finding that severe thought disorder (Harrow *et al.* 1983, Harrow *et al.* 1986, Racenstein *et al.* 1999) and negative thought disorder (Andreasen & Grove 1986, Wilcox *et al.* 2012) are associated with a poor clinical and functional outcome. Thought disorders have also been connected to an extremely poor outcome (Keefe *et al.* 1987), and specifically to impairments in social functioning (Bowie & Harvey 2008) among patients with chronic schizophrenia. However, thought disorders do not predict poor outcome in isolation, but are accompanied by other symptoms of severe psychotic disorders.

In a study of clinically unaffected subjects, high levels of TDI in general, and specifically severity level 0.50 and item idiosyncratic verbalisation, predicted any psychiatric diagnosis in an 18-year follow-up (Metsänen *et al.* 2004). Among patients with a diagnosis of borderline personality disorder, a high level of thought disorders added significantly to the prediction model of future psychosis (O'Connell *et al.* 1989).

The diagnostic significance of thought disorders has diminished as diagnostic criteria have changed. In both the ICD-10 (World Health Organisation 1994) and

DSM-5 (American Psychiatric Association 2013) systems, thought disorders are incorporated only as one possible, but not necessary, symptom of schizophrenia.

2.3.5 Thought disorder as a putative schizophrenia endophenotype

An increasing interest in the search for schizophrenia endophenotypes has made research on thought disorders topical again. It is recommended (Gottesman & Gould 2003) that a proposed vulnerability measure should be defined as an endophenotype if it is: associated with illness, state independent (including adequate test-retest stability, adequate between-site reliability, and evidence that impairments in patients are not due to medications and they are observed regardless of the illness state), heritable in healthy populations and in schizophrenia families, and found in unaffected relatives at a higher rate than in the general population. The literature reviewed here suggests that specific measures of thought disorder (e.g. items derived from TDI) could serve as endophenotypic markers for schizophrenia or wider schizophrenia spectrum disorders.

2.4 Communication Deviance

2.4.1 Definition and assessment of Communication Deviance

Research on the familial environment of schizophrenia patients began in the 1940s (e.g. Fromm-Reichman 1948, Bateson *et al.* 1956, Lidz *et al.* 1957, Wynne *et al.* 1958). Singer and Wynne began to evaluate systematically in empirical studies the form of thinking and communicating (Wynne & Singer 1963a, 1963b, Singer & Wynne 1965a, 1965b). A tool to systematically evaluate disturbed communication, the Communication Deviance (CD) scale (Singer & Wynne 1966), was eventually developed to assess specifically the degree to which family members are unable to share and maintain a focus of attention during communication. Frequent Communication Deviance in rearing parents may be regarded as an aspect of the long-term learning environment that may contribute to establishing inefficient patterns of information processing and thinking (Wahlberg *et al.* 1997). No absolute cut-off point for parental CD that is disadvantageous to the cognitive development of the child has been defined. However, Communication Deviance cannot by any means be considered an either

sufficient or necessary prerequisite for psychopathology, but it is assumed to function with other risk factors, such as genetic vulnerability (Goldstein 1987a, Wahlberg *et al.* 1997, Wahlberg *et al.* 2000, Wahlberg *et al.* 2004).

Since the publication of the first Communication Deviance scale (Singer & Wynne 1966), an astonishing variety of different methods (both situations in which speech samples are gathered and scoring methods) of measuring the amount of CD have emerged. Communication Deviance has been measured both in experimental and natural-like interactive situations. In experimental conditions, either an individual or a varying number of family members or other significant others have participated in tests.

The first Communication Deviance scoring manual (Singer & Wynne 1966) was designed to apply to speech produced in individual Rorschach (Klopfer & Davidson 1962) and TAT (Thematic Apperception Test, Murray 1943) situations, using all ten cards of the Rorschach test or the first TAT card. It was obvious from the beginning of these CD studies that (disturbed) communication also needs to be examined in interactive situations, and a method was developed for this, known as spouse and family Rorschach (Loveland *et al.* 1963). Since then, Rorschach and TAT cards have been used in many ways in Communication Deviance studies (Jones 1977, Sass *et al.* 1984, Rund 1986, Ditton *et al.* 1987, Tompson *et al.* 1990, Rasku-Puttonen *et al.* 1994, Poikkeus *et al.* 1999) and several methods have been employed to gather “natural” speech samples, as experimental conditions have not been thought to give a realistic impression of communication and interaction between family members (Lieber 1977, Sass *et al.* 1984, Velligan 1988, Cole *et al.* 1993, Docherty 1993, Hamilton *et al.* 1993, Kymalainen *et al.* 2006). In addition to the above-mentioned Communication Deviance scale by Wynne and Singer (1966), there is a wide diversity of other scales for scoring communication obtained from different situations [Fauce & Singer 1975 (unpublished manuscript), Doane & Singer 1977 (unpublished manuscript), Jones 1977, Sass *et al.* 1984, Velligan 1985 (unpublished manuscript), Cole *et al.* 1986 (unpublished manuscript), Rund 1986, Tompson *et al.* 1990, Velligan *et al.* 1990]. The effect of variations in the size of the speech sample on the extent of Communication Deviance has been standardised in many ways, such as by dividing the number of deviances by the number of responses (Wynne *et al.* 1977), the word count (Hirsch & Leff 1971, Wynne *et al.* 1978), the number of typed lines (Doane & Mintz 1987, Velligan 1988), and the number of clauses (Docherty 1993).

Apart from the Communication Deviance scale, several other scales to measure parental communication disturbances defined in many ways have been developed. Some of the scales focus on attention during communication resembling the CD scale (Beavers *et al.* 1965, Behrens *et al.* 1965, Morris & Wynne 1965, Wild *et al.* 1965, Lieber 1977), while others have a focus more remote from the CD scale (Rund & Blakar 1986, Hølte & Wichstrøm 1990, Docherty *et al.* 1996). These scales have also been applied to studies comparing parents of schizophrenia patients (or, in one study, children at high risk of schizophrenia, Lieber 1977) to other groups of parents, with results replicating those concerning the association of Communication Deviance with offspring psychopathology.

2.4.2 Stability of Communication Deviance

Temporal and situational stability

There is evidence to show that Communication Deviance is an enduring trait of a person rather than a transient state. There are several studies concerning the temporal stability of the amount of Communication Deviance (Doane & Mintz 1987, Velligan *et al.* 1995, Nugter *et al.* 1997, Wahlberg *et al.* 2001), which show that CD is stable over time, with the longest follow-up times in studies being 11 to 15 years, and even resistant to change (Nugter *et al.* 1997). The cross-situational stability of Communication Deviance is a less studied area. There are only two published studies with opposite results in this area (Doane *et al.* 1982, Keskitalo 2000). Doane and colleagues (1982) found that the amount of parental Communication Deviance was not significantly related to the amount of CD in another setting (individual, spouse, and family Rorschach), while Keskitalo (2000), evaluating measures of CD in the same three Rorschach situations, found it to be permanent. In an unpublished study by Glaser (1976), there was a general improvement in CD scores in the parents of offspring with a schizophrenia diagnosis when family members all came together, as compared to CD scores in individual Rorschach situation. The same was true for the parents of offspring without a schizophrenia diagnosis.

Association of Communication Deviance with sociodemographic variables, language, and culture

Studies that specifically explore the effect of salient sociodemographic factors (parental sex, age, socioeconomic status, intelligence, and educational level) on Communication Deviance are sparse. However, sociodemographic factors and their confounding effect on results have been taken into account in a vast majority of studies by including them in the analyses either as a covariate, or by matching groups by these variables. In a meta-analysis concerning the association of parental communication and psychosis (de Sousa *et al.* 2014), the effect size was significant and large even after excluding studies that had not controlled for the parents' educational level. One study (Hamilton *et al.* 1993) specifically discusses, although it was not the primary aim of the study, the association of socioeconomic status (SES) measured by Hollingshead score (Hollingshead, unpublished manuscript) with the amount of Communication Deviance. In this study, subjects belonging to the high CD group had lower SES than those belonging to the low CD group. It is noteworthy that in almost all of the CD studies, the subjects or families studied fall into lower to upper middle socioeconomic classes, and rarely into lower or upper classes.

There are only two studies directly exploring the effect of age on the amount of CD (Doane & Mintz, 1987, Wahlberg *et al.* 2001). Doane and Mintz (1987) found that the amount of CD in adulthood is significantly higher than during adolescence among both males and females. The follow-up time was fifteen years. In this study, there was a statistically significant, but only modest correlation between adolescent and adult CD, but it derived from female scores only. In a study by Wahlberg and colleagues (2001), the amount of CD in older subjects (21 years or older at the starting point of the study) was higher than that of younger subjects (younger than 21 years). For the older participants, the stability correlations between CD measures at initial assessment and at 11-year follow-up were uniformly and significantly high, but not for the younger sample.

Studies on Communication Deviance have not shed light on the issue of whether CD of one or both rearing parents is required for there to be an increased risk of psychopathology in the offspring. In addition, the question of whether maternal and paternal Communication Deviance are equally significant has remained unanswered. In the vast majority of CD studies, both parents together are considered as a source of Communication Deviance, and parental CD is used as an independent variable. In a few studies where separate analyses of maternal

and paternal CD have been performed (e.g., Cole *et al.* 1993, Doane *et al.* 1982, Velligan *et al.* 1988), the effects of maternal or paternal Communication Deviance on offspring outcome variables differed. In a meta-analysis concerning the association of parental communication and psychosis (de Sousa *et al.* 2014), the effect size for mothers of psychotic offspring was statistically significantly larger than for fathers.

In the majority of Communication Deviance studies, the subjects are English speaking and live in the USA. There are two studies carried out in the USA with Anglo- and Mexican-American (Doane *et al.* 1989) and Afro-, Anglo-, and Mexican-American (Kymalainen *et al.* 2006) subjects. In the first study of parents of schizophrenics (Doane *et al.* 1989), there was no difference in the amount of CD between ethnic groups. In a study of relatives of schizophrenic or schizoaffective patients (Kymalainen *et al.* 2006) differences between ethnic groups were found. Anglo- and Afro-Americans displayed more CD than Mexican-Americans, while there were no differences between Anglo- and Afro-Americans in total amount of CD. The results of the latter study indicate that there may be differences between ethnic groups. In these studies, both English and Spanish were used. Communication Deviance studies have also been carried out in Finland (Rasku-Puttonen *et al.* 1994, Wahlberg *et al.* 1997, Poikkeus *et al.* 1999, Wahlberg *et al.* 2000, Wahlberg *et al.* 2001, Wahlberg *et al.* 2004, Metsänen *et al.* 2007, Siira *et al.* 2007), the Netherlands (Nugter *et al.* 1997), and Norway (Rund 1986, Rund & Blakar 1986). In these studies, Finnish, Dutch, and Norwegian were used, and manuals were translated if needed. The earlier findings that frequent Communication Deviance in rearing parents is associated with certain diseases and disorders in the child were replicated as far as schizophrenia and other psychiatric disorders (Rund 1986, Wahlberg *et al.* 2000), learning disabilities (Rasku-Puttonen *et al.* 1994, Poikkeus *et al.* 1999), and thought disorders (Wahlberg *et al.* 1997, Wahlberg *et al.* 2000, Metsänen *et al.* 2007) were concerned, which indicates that the concept of Communication Deviance may be applied to different languages. However, the USA, Finland, and Norway are all western countries, and it is not obvious that the data on Communication Deviance are applicable worldwide.

Association of Communication Deviance with other family interaction measures

Over the decades, there has been great interest in studying the interrelationship of Communication Deviance with other family interaction measures. The most studied interaction measures are Expressed Emotion (EE) (Brown *et al.* 1972, Vaughn & Leff 1976a) and Affective Style (AS) (Doane *et al.* 1981). Expressed Emotion is a measure of the degree to which a relative of a recently hospitalised schizophrenic patient holds highly critical and/or emotionally overinvolved/overprotective attitudes towards the patient. EE is traditionally measured using a Camberwell Family Interview conducted with the patient's relatives (Vaughn & Leff 1976b). The measure of Affective Style is highly similar: it is composed of statements of personal criticism, guilt induction, and intrusiveness directed at the offspring. As distinct from EE, measures of AS are derived from directly observed interaction. There has been discussion on whether Communication Deviance and measures of family affective tone (EE and AS) really reflect distinctive aspects of the intrafamilial environment, or whether they are simply reflections of each other (Doane *et al.* 1981).

The association of Communication Deviance and Expressed Emotion has been discussed in five studies (Miklowitz *et al.* 1986, Velligan *et al.* 1990, Cole *et al.* 1993, Docherty 1995, Kymalainen *et al.* 2006), even though in only two of the studies (Miklowitz *et al.* 1986, Docherty 1995), the primary aim was the exploration of the relation of CD and EE. In Miklowitz and colleagues' (1986) study of relatives of schizophrenia patients, high-EE relatives had higher levels of overall CD than did low-EE relatives. In Docherty's (1995) study of parents of schizophrenia patients, high and low EE groups did not differ significantly on the CD measure. In Kymalainen *et al.*'s (2006) study of relatives of schizophrenia or schizoaffective patients, rates of Expressed Emotion were modestly but statistically significantly correlated to the level of Communication Deviance. The same was true for fathers, but not mothers, in a study of parents of schizophrenia patients by Cole *et al.* (1993). In Velligan *et al.*'s (1990) study of parents of recent-onset schizophrenia patients, the correlation of two CD measures assessed in two different situations was higher than the correlation of Communication Deviance and Expressed Emotion measured in the same situation.

Only three studies have discussed the association of Communication Deviance and Affective Style (Doane *et al.* 1981, Goldstein 1981, Velligan *et al.* 1990). In both 1981 studies, the same set of parents of non-psychotic but

disturbed adolescents from the UCLA Family Project was studied. AS and CD measures were not significantly related. Velligan and colleagues (1990) found in their study of parents of recent-onset schizophrenic patients that the correlation of two CD measures assessed in two different situations was higher than the correlation of Communication Deviance and Affective Style measured in the same situation.

The results of the studies reviewed here indicate that AS and CD are independent of each other, but results concerning the relationship between EE and CD are more ambiguous. However, although Communication Deviance and measures of family affective tone were correlated to each other, one cannot necessarily deduce that they are of the same origin and reflect the same psychological and interactional phenomena. It may also indicate that several risk factors tend to cumulate in the same families.

2.4.3 Relationship of parental Communication Deviance to psychiatric and thought disorders in offspring

It was hypothesised originally that disturbed communication that affects the manner in which foci and attention are shared is connected with what was called “schizophrenic” thinking, meaning formal thought disorders, attention disorders, and the processing of information and meaning, and not with schizophrenia as a clinical diagnosis. Formal thinking disorders were considered to be central and primary compared to a descriptive diagnosis of schizophrenia (Wynne & Singer 1963a, b, Singer & Wynne 1965a, b, Singer 1977). Despite this, the majority of studies on the interrelationship of Communication Deviance and psychopathology in offspring concerns schizophrenia spectrum and other psychiatric disorders, and there are only a handful of studies concerning thought disorders and other impairments of cognitive functioning.

Frequent parental Communication Deviance has been connected with schizophrenia spectrum disorder in offspring in several studies (Wynne 1967, Hirsch & Leff 1971, Wynne 1978, Goldstein 1987a, Asarnow *et al.* 1988, Docherty 1993), and also with severity of schizophrenic disorder (Cole *et al.* 1993) and schizophrenia relapse (Velligan *et al.* 1996). In one study (Rund 1986), Communication Deviance did not appear to differentiate parents of offspring with schizophrenia diagnosis from parents of non-psychotic psychiatric patients or healthy subjects, but specifically the parents of offspring with other than paranoid schizophrenia from other groups of parents. Parental Communication Deviance is

not, however, specific to schizophrenia spectrum disorders, but it is present in other types of psychiatric disorders, although with lower frequency. A landmark study of families of psychiatrically ill patients (severe neurotics, borderlines, and schizophrenics) with those of control subjects who were either healthy or had a severe chronic medical condition (Wynne *et al.* 1977) indicated that the higher the parents' Communication Deviance ratio scores were, the more severe was the psychiatric illness of the offspring, without any sharp cut-off point between psychotic and non-psychotic conditions. A study by Wahlberg and co-workers (2004) showed that high parental CD and an increased genetic risk to schizophrenia in the child together predicted a psychiatric disorder in the adopted child in general. An interaction of a positive family history of severe mental disorder (including unipolar recurrent depression) in first or second-degree relatives of the patient and the parental CD level was a powerful indicator of a high risk of a schizophrenia spectrum diagnosis in a subgroup of subjects in the UCLA High-Risk Study (Goldstein 1987b).

In studies using different methods to measure thought disorders (Sass *et al.* 1984, Wahlberg *et al.* 1997, Wahlberg *et al.* 2000, Metsänen *et al.* 2007), there was an association between high levels of parental Communication Deviance and thought disorders in the offspring. There are also studies showing association between parental CD and several measures of cognitive impairment (Wagener *et al.* 1986, Ditton *et al.* 1987, Greenwald 1989, Nuechterlein *et al.* 1989, Rasku-Puttonen *et al.* 1994, Poikkeus *et al.* 1999).

There are several reviews of Communication Deviance in families who have a member with schizophrenia or other schizophrenia spectrum disorder (e.g. Wynne 1970, Doane 1978, Wynne 1981, Goldstein 1984, Miklowitz & Stackman 1992, McFarlane & Lukens 1994, Miklowitz 1994, Rund 1994, Kymalainen & Weisman de Mamani 2008). None of these reviews does, however, fulfil the criteria of systematized review, and no meta-analyses have been performed.

Since the development of the concept of Communication Deviance, there has been controversy over the explanation of the association between parental CD and psychopathology in offspring. It has been suggested that Communication Deviance may not be an independent environmental risk factor, but a parental marker of shared genetic vulnerability (which, in the offspring, manifests itself as a psychiatric disorder) or a reflection of the parent's own psychopathology (a subtle form of thought disorder) or, simply, just a reaction to the child's deviant behaviour.

2.4.4 Parental communication and cognitive development of the child

The view on the significance of environmental factors, including the role of the rearing parents' communication, in the cognitive development of a child has changed over time, which is often referred to as the nature versus nurture debate (Silvén 2002). The earliest theories on the cognitive development of the child were based on assumptions about innate learning mechanisms, which, together with simple feedback from the environment concerning behaviour, would increase the probability that the same behaviour would continue (nativism, associationism). These mechanically acquired associations were presupposed to explain cognitive development. According to these theories, a child did not have an active role in the development, but was seen as a passive recipient of feedback. This presupposition was later found to be too simple, and the next step was to develop a theory that assumed that the human child has a genetically transmitted readiness to construct knowledge (Silvén 2002). In addition, in attachment theories, it is supposed that an infant is born with a biologically adaptive motivational system that drives the infant to create attachments. The experiences of an infant shape the organisation of the system (Siegel 2001). The most famous representative of this branch of developmental psychology is Jean Piaget. According to his theory of the cognitive development of a child (Piaget 1952), the course of development is understood as a sequence of stage-like changes that are regulated by the processes of assimilating information from the environment into cognitive structures, and accommodating those structures in external reality.

In all the aforementioned theories, the role of the socio-cultural environment in constructing meanings was almost completely ignored. A shift in a paradigm occurred as Lev Vygotsky (1978) concluded that cognitive development is socially structured. He argued that in social situations, the more experienced others (at first the parents) take responsibility for the child's developing mind. At the beginning of the process, the more experienced one has a task fundamental to the cognitive development: they ought to direct the child's attention to relevant aspects of an event or task, and communicate about the problem at hand (Garton 1992). The cognitive development of a child is assumed to happen in the zone of proximal development, in interaction (Vygotsky 1978). The external support is gradually reduced as cognitive development progresses. The ideas of Vygotsky have gone on living in the theory of social constructivism, which perceives

cognition entirely as a product of culture, as a structure of meanings shared through spoken language (Silvén 2002).

Concerning social constructivism, the lack of a theory of processes leading to internalisation of knowledge was criticised (Silvén 2002). The search for these mechanisms led back to basically nativist theories, which presume innately structured, biological cognition. Later, however, the nativist approach has turned out to be an inadequate theory, and nativism, associationism, and constructivism have been combined in an effort to create a theory of cognitive development (Silvén 2002). As an attempt to clarify the mechanisms of cognitive development by computational modelling of developmental changes, the connectionist approach was developed in the 1980s (Yermolayeva & Rakison 2014). Connectionism supposes that cognitive development is regulated by multilevel biological and psychosocial interactions, but it has not yet been able to create a comprehensive theory on the cognitive development of a child (Yermolayeva & Rakison 2014).

2.5 General systems theory, biopsychosocial model, and vulnerability theories

Even though a general systems theory was introduced in the 1950s (von Bertalanffy 1956), theories of the aetiology of psychiatric disorders have followed the reductionist tradition as they have tried to divide a complex system, like a human being, into its parts, and have assumed one-way causal chains. The definitions of the cause have depended both on general theories in psychiatry and psychology, and also on the level of technical development. The technological level has set limits, for instance for possible statistical analyses, research on genetics, and neuroimaging studies. On the contrary, general systems theory emphasises that a system, a whole, is more than its parts. According to this theory, systems (like a human being) are open and interact with their environment, acquiring new properties, and resulting in continual evolution. In medicine, a biopsychosocial model that is based on general systems theory was developed in the 1970s (Engel 1977). In psychiatry, vulnerability-stress theory (Rosenthal 1970, Zubin & Spring 1977, Nuechterlein 1987), which in turn is based on the biopsychosocial model, is widely accepted. According to vulnerability-stress theory, psychiatric disorders develop as several environmental risk factors interact with genetic or other kinds of biological vulnerability. However, even vulnerability-stress theory is reductionist in nature, as it presupposes a genetic or

other biologically acquired vulnerability as a beginning, a necessary prerequisite for a disorder to emerge. Evolutionary-neurodevelopmental theory (or differential susceptibility to environment, Ellis *et al.* 2011) supposes that some individuals are more susceptible than others to both negative and positive environmental conditions, but the theory is not established and models of development of susceptibility are still in a formative phase.

Accumulating evidence on the significance of gene-environment interactions (van Os *et al.* 2008) and epigenetics (Dempster *et al.* 2013) in the aetiology of psychiatric disorders seems to necessitate a shift in a paradigm away from reductionism, towards a systems theoretical view. As Miller and Rockstroh (2013, p. 198) elegantly state in their discussion of endophenotype research:

“We are going to need a lot more arrows in our models, we are going to have to let go of the serial causation model, and we are going to have to stop confining genes to the entry points of the models we do use. Endophenotype research has twin goals of identifying the genetic contributions to psychopathology and identifying the mechanisms by which those contributions contribute. Genes are not the beginning of the causal chain. There is no chain, and there is no beginning.”

3 Aims of the study

3.1 Aims of the study

The Finnish Adoptive Family Study aims ultimately to assess the extent to which genetic and adoptive family environmental variables, including parental Communication Deviance, interact and contribute to psychopathology and impairments of adoptees, and whether a healthy and protective family environment could reduce the effects of genetic risk. As a part of this ultimate goal, the aim is also to explore the direction of effects between genetic and family environmental factors in a prospective longitudinal high-risk study design. The aims of this doctoral thesis were:

1. To determine what is currently known about the association of parental Communication Deviance with psychiatric disorders and thought disorders in offspring (I).
2. To study the association of parental Communication Deviance with the attributes of the adoptee and the adoptive parents themselves (II).
3. To study the association of the adoptee's thought and schizophrenia spectrum disorders with genetic and environmental risk indicators of psychotic disorders, and their interactions. The risk indicators studied were the adoptee's genetic high risk of schizophrenia spectrum disorders, winter or spring birth, and parental Communication Deviance (III).

3.2 Hypotheses

The hypotheses of this study were:

1. There is an association between frequent parental Communication Deviance and thought and psychiatric disorders in offspring. This hypothesis was based on the results of several former non-systematised reviews (Wynne 1970, Doane 1978, Wynne 1981, Goldstein 1984, Miklowitz & Stackman 1992, McFarlane & Lukens 1994, Miklowitz 1994, Rund 1994, Kymalainen & Weisman de Mamani 2008).
2. An adoptee's genetic high risk of schizophrenia spectrum disorders, or any other characteristic of the adoptee, has no effect on the frequency of Communication Deviance in the adoptive mother, father, or parents together. Null results were hypothesised because, based on the earlier evidence,

Communication Deviance seems to be relatively stable over time and even resistant to change (Doane & Mintz 1987, Velligan *et al.* 1995, Nugter *et al.* 1997, Wahlberg *et al.* 2001).

3. The risk of thought and schizophrenia spectrum disorders in the adoptee increases not only when one of the risk indicators (the adoptee's genetic high risk of schizophrenia spectrum disorders, winter or spring birth, and parental Communication Deviance) is present, but especially when there is an interaction of two risk indicators. This hypothesis was based on the evidence that, in the light of recent research into schizophrenia, it is unlikely that any single cause, biological or psychosocial, can be found for it, but an interaction between several risk factors is likely to be essential for its onset (Tandon *et al.* 2008).

4 Material and methods

4.1 Meta-analysis (I)

4.1.1 Data collection

The guidelines of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group (Stroup *et al.* 2000) were followed in reporting within the systematic review and meta-analysis.

The literature was searched using a broad search term “communication deviance” from several databases (covering the period from 1960 to 31st Dec 2011). In addition to a literature search of databases, the references cited by accessed potentially relevant papers, together with citations in major review papers and book chapters, were scrutinised in order to locate additional potentially relevant papers.

4.1.2 Study selection

Based on predefined criteria, quantitative original studies in which the concept of Communication Deviance was explicitly based on Singer and Wynne’s definitions and scoring methods were included. No limits were set with regard to the language of the papers.

Studies exploring the association between parental Communication Deviance and either psychiatric disorders or formal thought disorders in offspring were included in the systematic review.

The meta-analysis included papers from which descriptive statistics for the frequency of parental Communication Deviance in schizophrenia spectrum versus control groups could be extracted.

4.1.3 Statistical methods

The random-effects method was used to pool overall estimates of effect sizes (ES) for group differences. ES is calculated by dividing the difference between the mean scores for the groups by the pooled standard deviation. The *d* values of Cohen (1992) were used as a measure of ES. A *d* value of 0.2 was taken to indicate a small effect, 0.5 a medium effect, and 0.8 a large effect. If the results

were presented using categorical variables, odds ratios were calculated and converted to standardised mean differences (Borenstein *et al.* 2009). Cochran's Q statistic and I^2 statistics (Higgins *et al.* 2003) were used to assess the heterogeneity of the studies. The data were analysed using Stata 11.1 (StataCorp LP, College Station, TX, USA).

4.2 Study design

The present study (II, III) is a part of the Finnish Adoptive Family Study which is a prospective longitudinal high-risk study in which adoptees' study method is applied. In the adoptees' study method the adoptive children of affected biological parents are examined. This method enables the evaluation of the interaction between biological and psychosocial risk factors, because the biological parents are not the rearing parents and thus genetic and rearing factors can be disentangled.

4.3 Study population (II and III)

4.3.1 The Finnish Adoptive Family Study

As a starting point for the Finnish Adoptive Family Study, hospital records for all women ($n=19\ 447$) admitted to Finnish psychiatric hospitals from 1 January 1960 to 31 December 1979 were reviewed, in order to identify those women who had at least once received a hospital diagnosis of a schizophrenic or paranoid psychosis. Subjects were excluded if they had received only a diagnosis of a manic-depressive, depressive, reactive, or psychogenic psychosis, or any other disorder. Next, the list of these women was checked through every census and parish register in the country to find the children who had been adopted away. Altogether, 264 index biological mothers who gave up for adoption 291 offspring were identified. After the exclusion of 94 mothers with 105 offspring for various reasons (e.g. adoption by a relative or adopted abroad), the total sample included 170 biological index mothers with 186 adopted-away index offspring in 185 adoptive families. The adoptive parents were eligible in the study with no exclusive diagnostic criteria.

Biological control mothers and their offspring were eligible in the Finnish Adoptive Family Study if the mother had not been hospitalised because of

psychosis. In other words, biological control mothers had a full array of psychiatric and physical illness, as found in the community; they were not a “supernormal” control group. At the beginning of the sampling phase of the study, there was an effort to demographically match the index offspring and their adoptive families with control adoptees and their adoptive families. This, however, appeared to be impossible, and matching was abandoned. Finally, a total of 203 offspring of biological control mothers and their adoptive families were included in the study. Of 384 biological fathers (five being the fathers of two offspring each), 220 (57.3%) were identified.

After diagnostic reassignment, the final study group consisted of 190 adoptees at genetic high-risk (HR) of schizophrenia-spectrum disorders (72% of biological mothers had a diagnosis of schizophrenia, the rest a diagnosis of other schizophrenia-spectrum disorders), and 192 adoptees at genetic low-risk (LR) and their adoptive families (Tienari *et al.* 2003). The full details of sample selection have been reported elsewhere (Tienari *et al.* 2000).

Details of the assessment procedure of the adoptive families are provided elsewhere (Tienari *et al.* 1987). The initial evaluations of the adoptees and adoptive parents were carried out beginning in 1977. The extensive evaluation was performed in families’ homes and usually took two days. Each adoptive parent and adoptee was given an individual 10-card Rorschach test (Klopfer & Davidson 1962). The parental couple and the adoptee and adoptive parents together were given spouse and family Rorschach tests (Loveland *et al.* 1963), respectively. The initial evaluations also included individual, spousal, and family interviews, and the Interpersonal Perception Method (Laing *et al.* 1966). Abbreviated versions of Wechsler’s Adult Intelligence Scale (WAIS) and Wechsler’s Intelligence Scale for Children (WISC) were also administered. The Minnesota Multiphasic Personality Inventory (MMPI, Dahlstrom *et al.* 1982) assessments were carried out for the adopted children. The adoptees and both adoptive parents were interviewed individually with a semi-structured diagnostic procedure. All interviews and test examinations were tape-recorded.

After a median interval of eleven years from the initial evaluations, 130 index and 148 control adoptees were individually re-interviewed and re-tested. The interview schedules included an expanded lifetime version of the Present State Examination (PSE, Wing *et al.* 1974), Structured Clinical Interview for DSM-III-R Personality Disorders (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.

Research diagnoses of the biological index mothers were made using the DSM-III-R criteria (APA 1987). They were obtained through review of initial and subsequent hospital and clinic records and personal research interviews. The psychiatric interviews included a modified Present State Examination (Wing *et al.* 1974) (with added items that facilitate making DSM-III and RDC diagnoses) and information about biological family psychiatric history. In as much detail as possible, data were also obtained on psychiatric hospitalisations and symptoms and personal characteristics of the biological relatives of the biological index and control parents. Biological control mothers were also interviewed.

Finnish national computerised registers were searched for all subjects in the study (not only for biological parents and adoptees, but also for the adoptive parents and adoptive siblings). A register giving reasons for death was searched through to 31 December 2005, and the hospital discharge register for all public and private inpatients was searched through to 31 December 2006. Other registers were searched through to October 1994 for records of diagnoses that justified disability pension; information on sick leave prescribed by a doctor; records of free medication prescribed for certain illnesses, including psychoses; and information about criminality.

4.3.2 Publication II: Association of parental Communication Deviance with the attributes of the adoptive child and adoptive parents

Starting out from the total sample of 382 adoptive families (with 190 HR and 192 LR offspring), a family was included in the study if, at first, all its members were alive and the parents were not divorced, or if a parent had always been missing. Based on this criterion, 140 families were excluded. The second inclusion criterion was that Rorschach records had been tape-recorded, and the third was that individual, spouse, and family Rorschach tests had been carried out with all ten cards belonging to the test. These criteria further led to the exclusion of 117 and 16 families, respectively. These inclusion criteria were applied in order to avoid unnecessary substitutions for missing Communication Deviance scores, since not enough information is available on the validity of different substitution methods. The eventual subsample included 109 adoptive families, 44 of which were families of genetically high-risk adoptees, and 65 were families of low-risk

adoptees. Of these families, three were single-parent families in which the father had never existed. In these three single-parent families, the mother's CD score was multiplied by two to compensate for that of the missing father.

Comparison of the baseline characteristics of the eventual sample with the total original sample showed that the percentage of information available in the total sample varied from 47% (mother tongue) to 100% (gender of the adoptee and genetic risk status). There was no statistically significant difference between the cases in the subsample used here ($n=109$) and the total original sample in terms of the gender or genetic risk status of the adoptee, the age of the adoptee at placement with the adoptive family, or the adoptive family's mother tongue. A statistically significant difference was observed in the age [in years (SD)] of the adoptee at the initial assessment [19.6(6.5) vs. 26.7(10.3), $p=0.000$], and the age [in years(SD)] of the adoptive mother [53.8(8.1) vs. 60.2(10.9), $p=0.000$] and the adoptive father [55.3(7.8) vs. 60.5(10.4), $p=0.000$]. The subjects in the original sample were older. A statistically significant difference between the subsample used in this study and the total original sample was also observed in the social class of the adoptive family, based on the main provider's occupation and education (Statistics Finland 1983) (classes I-IV, a low number indicating a high social class); I: 10.1% vs. 18.9%, II: 50.5% vs. 44.2%, III: 36.7% vs. 30.2%, IV: 2.8% vs. 7.7% ($p=0.041$).

The demographic characteristics of the families with genetically high-risk and low-risk adoptees are presented in Table 1.

4.3.3 Publication III: Association of adoptive children's thought disorders and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders and season of birth and parental Communication Deviance

Starting out from the total sample of 382 adoptive families (with 190 HR and 192 LR offspring), a family was included in the study if, at first, all its members were alive and parents were not divorced, or if a parent had always been missing. Based on this criterion, 140 families were excluded. The second inclusion criterion was that the Rorschach records had been tape recorded and the individual Rorschach tests on the adoptive parents and adoptee had been carried out with all cards belonging to the test. This led to the exclusion of another 117 families. The subsample finally included 125 adoptive families (53 HR and 72 LR), with 119 families consisting of both parents and six of the mother alone. In

single-parent families, the mother's CD score was multiplied by two to compensate for that of the missing father.

Table 1. Demographic characteristics of the families with genetically high-risk (HR) and low-risk (LR) adoptees in the study samples in original publications II and III.

Demographic characteristics	Study sample in original publication II			Study sample in original publication III		
	HR n=44	LR n=65	p- value ¹	HR n=53	LR n=72	p-value
Age of the adoptive mother, in years (SD)	54.3(8.5)	53.51(7.9)	0.630	54.8(8.2)	54.2(8.3)	0.704
Age of the adoptive father ² , in years (SD)	55.1(7.7)	55.34(8.0)	0.886	55.9(7.9)	56.0(8.5)	0.932
Age of the adoptive child, in years (SD)	19.1(6.0)	20.0(6.8)	0.473	19.9(6.6)	20.6(7.3)	0.588
Age of the adoptive child at placement in the adoptive family, in months (SD)	14.7(15.4)	14.0(11.9)	0.791	16.4(15.3)	15.1(13.0)	0.612
Gender of the adoptive child, n(%) males	19(43.2)	27(41.5)	0.510	25(47.2)	33(45.8)	1.000
Socioeconomic status of the adoptive family ³ n(%)			0.216			0.323
I	7(15.9)	4(6.2)		8(15.1)	4(5.6)	
II	22(50.0)	33(50.8)		25(47.2)	38(52.8)	
III	13(29.5)	27(41.5)		17(32.1)	27(37.5)	
IV	2(4.5)	1(1.5)		3(5.7)	3(4.2)	

¹ Student t-test in continuous variables, otherwise Pearson Chi square test or Fisher's exact test, two-tailed significance. The limit for statistical significance was 0.05, ² Study sample II n=106, study sample III n=119, ³ Classes I-IV, a lower number indicating a higher social class

There was no statistically significant difference between the cases in the subsample used here (n=125) and the total original sample, in terms of the gender or genetic risk status of the adoptee, the age of the adoptee at placement with the adoptive family, the adoptive family's mother tongue, or the social class of the adoptive family. There was also no statistically significant difference regarding the birth month between the individuals in the subsample and in the total sample. A statistically significant difference was observed in the age [in years (SD)] of the adoptee at the initial assessment [20.3(7.0) vs. 26.7(10.3), p=0.000], and the age [in years(SD)] of the adoptive mother [54.5(8.3) vs. 60.2(10.9), p=0.000] and the

adoptive father [56.0(8.2) vs. 60.5(10.4), $p=0.000$]. The subjects in the original sample were older.

The demographic characteristics of the families with genetically high-risk and low-risk adoptees are presented in Table 1.

4.4 Variables (II, III)

Variables used in the original studies are presented in Table 2.

Table 2. Variables in original publications II and III.

	Original study II	Original study III
Predictor variables	Adoptive child Gender (male, female) Genetic risk status (HR, LR) Thought Disorder Index (continuous) Communication Deviance (continuous) Adoptive parents Communication Deviance (continuous)	Adoptive child Genetic risk status (HR, LR) Season of birth (winter-spring, summer-autumn) Adoptive parents Communication Deviance (continuous)
Covariates	Age of the adoptee (continuous) Age of the adoptive mother and father (continuous)	Gender of the adoptee (male, female) Age of the adoptee (continuous)
Outcome variables	Parental Communication Deviance (continuous)	Adoptive child's Thought Disorder Index (continuous) TDI schizophrenia subscales (Fluid Thinking, Confusion and Idiosyncratic Verbalisation) (no scores, at least one score) Adoptive child's schizophrenia spectrum diagnosis (present, absent)

4.4.1 Communication Deviance

Communication Deviance was assessed from both individual (Klopfer & Davidson 1962) and consensus (Loveland *et al.* 1963) Rorschach tests. In the individual Rorschach test, all ten cards are shown to the subject. CD was assessed from these using 42 items adapted from the unpublished Rorschach scoring

manual (Singer & Wynne 1986). These items have been divided into six conceptually different groups (Table 3).

Validity and reliability of Singer and Wynne’s Communication Deviance scoring system for the Thematic Apperception Test (TAT, Murray 1943) has been extensively evaluated by Chapman (2008). The same scoring system was also designed to apply to speech produced in individual Rorschach (Klopfer & Davidson 1962) situations. Chapman concluded that concurrent validity studies suggest that CD scores correlate with offspring’s schizophrenia spectrum diagnosis. The evidence based on studies applying the Rorschach test or ten-minute speech sample further supports this finding (Wynne 1967, Wynne *et al.* 1977, Wynne *et al.* 1978, Docherty 1993). Interrater reliabilities for the total TDI scores based on agreements about the occurrences of TAT CD categories have ranged from 0.69 to 0.80 (Chapman 2008).

The creators of the Communication Deviance scale personally guided one of the raters (Karl-Erik Wahlberg), and he then guided the others. The raters were blind to each other and to all the characteristics of the subjects except for age, sex, and occupation. The interrater reliability of the CD scores derived from the individual Rorschach records was good, in that the two raters obtained an intra-class correlation (ICC) of 0.95 for the total Communication Deviance scores for 51 protocols.

Table 3. The items of scoring manual for individual Rorschach

Communication Deviance 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 behaviour
	Environmental task disruptions
	Disruptive humour
	Disruptive swearing
	Other conversation stoppers
II	Problems of commitment and sustaining task
	Abandoned, abruptly ceased, uncorrected remarks
	Responses in negative form
	Subjunctive, “if” responses
	Question responses
	Nihilistic remarks about life or task in general
	Inability or failure to verify one’s own responses

Communication Deviance categories

- Forgetting responses
 - Answering unasked questions
 - Hopping around among responses
 - Negativistic, temporary card rejection followed by a response
 - Concrete-set responses
 - Assigning to others responsibility for the percept
 - III Unclear and unstable references
 - Unintelligible remarks: a) brief, without context, or b) the total effect ending with a unintelligible reference
 - Unstable percepts
 - Inconsistent and ambiguous references
 - 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 labelling
 - Clang associations, rhymed phrases, and word play
 - Reiteration
 - V Reasoning problems and contradictions
 - Contradictory information
 - Retractions and denials
 - Odd, tangential, inappropriate responses to questions and 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
-

The consensus Rorschach test consists of two parts, spouse and family Rorschach. In the first part, a parental couple is asked to look at Rorschach cards I and III and try to reach a consensus as to what the ink blot represents. This part of the test is useful for examining relations and communication between spouses in the absence of their children. The second part family Rorschach then begins with the spouses instructing the child about the task. This gives an impression of how

parents transmit information to their child. Then the family as a unit looks at Rorschach cards I and III, and a new card, VIII.

Communication Deviance was assessed from the spouse and family Rorschach records using 40 categories adapted from several unpublished scoring manuals [Singer & Faunce 1975, Doane & Singer 1977 (revised 1985), Velligan 1985 (revised 1989)], including slight modification to fit the Finnish language and culture through collaboration between the Finnish team and Singer and Wynne. The items of the scoring manual for Communication Deviance from the consensus Rorschach are largely the same as in the manual for individual Rorschach, with a few exceptions: the items "Put-down of the tester of the task", "Interruptions of the examiner's speeches", "Environmental task disruptions", "Unstable percepts", and "Assigning meaning on the basis of nonessential attributes of the cards" are removed. The items "Odd, tangential, inappropriate responses to questions and remarks" and "Answering unasked questions" are combined, as well as the items "Private, contrived terms and labelling" and "Contaminations". Six new scores are added, among them variations on the items "Extraneous questions and remarks", "Hopping around among responses", and "Inability or failure to verify one's own responses". Completely new items are the three concerning mind-reading answers, incorrectly pronounced words, and using unfamiliar words.

The raters were blind to each other and to all the characteristics of the subjects. An intra-class correlation (ICC) of 0.92 was obtained by two raters for the total communication deviance scores in spouse and family Rorschach records for 37 protocols.

The amount of Communication Deviance in the individual, spouse, and family Rorschach records was obtained by summing the occurrences of CD on all the cards belonging to each protocol, and standardising the total number by dividing the number of instances of Communication Deviance by the number of transactions (in the individual Rorschach speeches produced for each response, and in the spouse and family Rorschach speeches produced to reach an agreement as to what the card represented). If the number of transactions was zero, the number one was substituted for it to avoid a zero divisor. The standardised amount of CD was therefore conditional on both the total amount of CD and the number of transactions.

4.4.2 Season of birth

The season of birth of the adoptive child was defined as winter if the date of birth was between 1 November and 31 January; as spring between 1 February and 30 April; as summer between 1 May and 31 July, and as autumn between 1 August and 31 October. Birth months were categorised based on the peak and trough periods in the number of sunshine hours, around equinoxes and solstices (<http://ilmatieteenlaitos.fi/tahtitieteelliset-vuodenajat>). The date of the winter solstice is around 21 December; the spring equinox around 21 March; the summer solstice 21 June, and the autumn equinox around 21 September. Finland is located in the north (between 60° and 70° latitude) and the climatic conditions, such as the number of sunshine hours, vary greatly between seasons. The number of daily sunshine hours varies in southern Finland, from almost 19 hours in June to about 6 hours in December, and in Lapland from 24 hours in June to zero minutes in December (<http://en.ilmatieteenlaitos.fi/seasons-in-finland>). This categorisation of birth months was selected based on the hypothesis that winter or spring birth is a proxy for prenatal vitamin D deficiency (Kinney *et al.* 2009), which in Finland is more probable in the winter and spring time due to the limited amount of daylight.

In the present study, the season of birth of the adoptive child was collapsed into two classes: winter-spring birth (1 Nov–30 Apr) and summer-autumn birth (1 May–31 Oct). This was based on the evidence that the heightened risk for schizophrenia spectrum disorders is associated with winter-spring birth between November and April (Torrey *et al.* 1997).

4.4.3 Thought Disorder Index

Thought disorders in the adoptees were assessed using the Thought Disorder Index (TDI) (Johnston & Holzman 1979). One of the raters (Karl-Erik Wahlberg) was personally guided in this by one of the creators of the TDI scale (Dr. Holzman), and he then guided the others. The TDI, which tags, classifies, and measures instances of disordered thinking both qualitatively and quantitatively, was used here as an indicator of both subclinical and clinical psychopathology in the adoptive child. In this case, the responses to the Rorschach cards were used as material, but any verbal sample will suffice. The revised version of the Thought Disorder Index (Solovay *et al.* 1986) includes 23 categories weighted along a continuum of severity (0.25, 0.50, 0.75, and 1.0), where 0.25 represents minor

idiosyncrasies; 0.50 indicates a loss of mooring, shaky reality contact, emotional overreaction, and distinct oddness; 0.75 is associated with psychotic disruption and characterised by instability of thinking and perception, absurdity, and an unrestrained combinatory tendency; and the 1.0 level represents responses completely divorced from reality (Solovay *et al.* 1986) (Table 4).

Several studies have shown that the TDI is a valid indicator of disordered thought in patients with a schizophrenia diagnosis and also a valid indicator of familial vulnerability to schizophrenia (Hurt *et al.* 1983, Arboleda & Holzman 1985, Holzman *et al.* 1986, Shenton *et al.* 1987, Hain *et al.* 1995). Schizophrenia patients have elevated levels of thought disorders in all categories and at all severity levels as compared to healthy controls. Furthermore, specific TDI subscales have proved to be useful in differential diagnosis of severe psychiatric disorders (Holzman *et al.* 1986, Shenton *et al.* 1987, Solovay *et al.* 1987). Interrater reliabilities for the total TDI scores have ranged from 0.82 to 0.93 (Johnston & Holzman 1979, Solovay *et al.* 1986, Coleman *et al.* 1993).

In the present study, thought disorder on the Rorschach (TD_R) was used as an index of disordered thought. TD_R is calculated by dividing the sum of weighted TDI scores by the number of Rorschach responses according to the following formula:

$$\frac{0.25(A)+0.50(B)+0.75(C)+1.0(D)}{\text{Total number of Rorschach responses}} \times 100 \quad (1)$$

where A = the number of responses scored at 0.25, B = the number of responses scored at 0.50, C = the number of responses scored at 0.75, and D = the number of responses scored at 1.00.

At the assessment stage, four psychologists scored the records pairwise without prior knowledge of the subjects' relatedness to their biological and adoptive families or their psychiatric disorder. The pairs of psychologists were blind to each other and to all the characteristics of the subjects except age, sex, and occupation. The intra-class correlation coefficient (ICC) between the pairs of psychologists was 0.94 for TD_R , 0.92 for the 0.25 level, 0.92 for the 0.50 level, 0.86 for the 0.75 level, and 0.66 for the 1.0 level.

Table 4. Thought Disorder Index categories at increasing level of severity.

0.25 level	0.50 level	0.75 level	1.0 level
1. Inappropriate distance	8d. External-internal response	17. Fluidity	21. Contamination
a. Increase of distance	9. Relationship verbalization	18. Absurd responses	22. Incoherence
b. Excessive qualification	10. Idiosyncratic symbolism	19. Confabulations	23. Neologisms
c. Concreteness	a. Color symbolism	a. Details in one area	
d. Overspecificity	b. Image symbolism	generalized to larger area	
e. Syncretistic responses	11. Queer responses	b. Extreme elaboration	
2. Flippant responses	a. Queer expressions	20. Autistic logic	
3. Vagueness	b. Queer imagery		
4. Peculiar verbalizations and responses	c. Queer word usage		
a. Peculiar expression	12. Confusion		
b. Stilted, inappropriate expression	13. Looseness		
c. Idiosyncratic word usage	14. Fabulized combinations, impossible or bizarre		
5. Word-finding difficulty	15. Playful combinations		
6. Clangs	16. Fragmentation		
7. Perseveration			
8. Incongruous combinations			
a. Composite response			
b. Arbitrary form-color response			
c. Inappropriate activity response			

4.4.4 Schizophrenia spectrum diagnosis

The psychiatric status of the adoptees was assessed using best-estimate, hierarchically most severe lifetime diagnoses. Only diagnoses at a definite or probable level of certainty were accepted. The diagnostic hierarchy of disorders was selected according to the suggestions of Kendler and colleagues (1996). The diagnoses were based on personal interviews with the adoptees (including PSE, SCID-II, and SIS) and using information on psychiatric hospital admissions from the Finnish Hospital Discharge registers. All adoptees were re-interviewed and retested at a median interval of 11 years from the initial evaluation. Personal interviews were carried out, either initially, at follow-up, or both, with 89% of the HR adoptees and 91% of the LR adoptees (Tienari *et al.* 2000). Finnish national computerised registers were searched for all subjects in the study, such as the hospital discharge register for all public and private in-patients, which was searched through to 31 December 2006. Diagnostic evaluation was conducted according to DSM-III-R criteria for Axis-I or Axis-II psychiatric disorders based on all available data for all adoptees. The kappa coefficient for interrater reliability was found to be good (kappa 0.71–0.80). A detailed description of the diagnostic procedure of the Finnish Adoptive Family Study is presented in an earlier publication (Tienari *et al.* 2000). The adoptees were categorised into two mutually exclusive groups based on their psychiatric diagnoses at follow-up assessment: 1) no psychiatric disorder or any psychiatric disorder other than the broad schizophrenia spectrum; and 2) broad schizophrenia spectrum disorder (i.e. schizophrenia, schizoaffective disorder, schizophreniform disorder, schizotypal personality disorder (later PD), paranoid PD, schizoid PD, avoidant PD, delusional disorder, psychosis not otherwise specified, and bipolar and depressive disorders with psychotic features). Among twelve subjects with a schizophrenia spectrum disorder, the diagnostic distribution was as follows: schizophrenia ($n=2$), bipolar psychosis ($n=3$), depressive psychosis ($n=1$), and paranoid ($n=2$), schizoid ($n=2$), and avoidant personality disorders ($n=2$).

4.5 Statistical methods (II, III)

The statistical significances of group differences were assessed with the Student's t-test or Mann-Whitney U test, while those in categorical variables were assessed with the Pearson chi-square and Fisher's exact test.

The Analysis of Covariance method (ANCOVA, Tabachnick & Fidell 1989) was used in both original publication II and publication III to assess group differences in continuous variables after controlling for several independent variables. ANCOVA allows the use of both continuous and categorical independent variables. Before modelling the distributions of CD and TDI, ratings were checked statistically, and as they appeared to follow an approximately normal pattern, meaning that skewness ≤ 2.0 or kurtosis ≤ 7.0 (Curran *et al.* 1996), parametric statistical methods were applicable. In *original publication II*, separate ANCOVA models were constructed for the adoptive mothers, adoptive fathers, and parents together. The dependent variables used in the models were the CD scores from the individual and family Rorschach tests performed by the adoptive parent(s). The final ANCOVAs included all the independent variables that showed a statistically significant association with the CD scores of the adoptive parent(s) in the preliminary analyses. In *original publication III*, ANCOVA was used to examine the potential effect of various predictors on the thought disorder of the adoptees.

The logistic regression analysis was used in *original publication III* to examine the association of the schizophrenia spectrum diagnosis (present or absent) with the predictors. The logistic regression analysis was also performed, in which TDI schizophrenia subscales (Fluid Thinking, Confusion, and Idiosyncratic Verbalisation) were considered as dependent variables.

In *original publication III*, the population adjusted seasonal pattern of births was analysed using the Edward's test for seasonality (Edwards 1961). The seasonal pattern of births of adoptees with schizophrenia spectrum disorder was compared with that of the entire study population. In the Edward's test, a circular normal distribution method for one-cycle seasonality is applied to estimate the seasonal pattern of events.

A two-tailed significance level of $p=0.05$ was used to determine statistical significance. All analyses were performed using SPSS for Windows, version 15.0 (II) or 18.0 (III).

5 Ethical considerations and personal involvement

The Ethics Committee of the Oulu University Hospital (formerly Ethical Committee of Oulu University, the Faculty of Medicine) approved the Finnish Adoptive Family Study on 2 May 1988. The study design was reviewed by the Ethics Committee of the Oulu University Hospital on 15 October 1991. The data used in the present study already existed and, thus, there was no need to contact the subjects of the study personally. No individual or family can be identified from the data. In the Finnish Adoptive Family Study, verbal informed consent has been obtained since 1977.

The author of this thesis has participated in the Finnish Adoptive Family Study as a researcher since 1996. The author has not participated in the collection of the data due to the longitudinal nature of the study. The author learned to score Communication Deviance from consensus Rorschach records and participated in the scoring of the records.

The author has participated in the design of all original studies. The author planned and carried out the literature search for systematised review and meta-analysis, and read the abstracts and articles. The data for meta-analysis was extracted by the author but the meta-analysis was performed by Professor Jouko Miettunen. Statistical analyses of the other two original publications have been made by the author, together with PhD Helinä Hakko.

The author has written the first and final versions of all the original articles (I-III). The author has also been the corresponding author in all the original studies and coordinated the correction and resubmission process for all the original studies.

6 Results

6.1 Systematized review and meta-analysis of the association between parental Communication Deviance and thought disorders and psychiatric disorders in offspring (I)

6.1.1 Search results

As the broad search term “Communication Deviance” was used, a total of 176 studies were found. After exclusions based on predefined criteria, 19 studies were eligible for the review. The majority of studies were excluded because they did not explore the relationship of parental Communication Deviance with psychiatric or thought disorders in their offspring. The number of duplications was small, only three. Seven potentially relevant unpublished dissertations were found and accessed, but four of them appeared to be not relevant to the subject of the review, and the results of the other three were later published in scientific papers. Two of these papers were finally included in the review, but neither of them was eligible for the meta-analysis.

6.1.2 Association of parental Communication Deviance with psychiatric disorders in offspring

Fifteen of the studies eligible in the review considered the association of parental CD and psychiatric disorders in offspring. Ten of them were cross-sectional studies and of five reports on longitudinal studies, four were based on the data of one project, with varying follow-up times. Two reports concerned adoptive families and the rest biological relatives of individuals with a schizophrenia or schizophrenia spectrum diagnosis. The definition of schizophrenia spectrum was not uniform across studies. The vast majority of offspring were adults.

Seven of the fifteen reports were included in the meta-analysis. Eight papers yielded by the systematic review had to be excluded. Two of them did not offer the relevant parameters and they turned out to be impossible to obtain. Four papers in the review reported the results of the UCLA High-Risk Study, and only one of them was included in the meta-analysis. In three papers, the presence or absence of schizophrenia spectrum diagnosis as related to parental Communication Deviance was not explored, but the association with other

aspects of psychiatric disorders was. In one of the papers, parental high CD was shown to be associated with schizophrenia relapse, and in another with schizophrenia severity. The third paper compared the amount of Communication Deviance among parents of schizophrenia and mania patients, which did not differ from each other. In the meta-analysis, a large overall effect size was found (Figure 1). There was evidence for moderate heterogeneity.

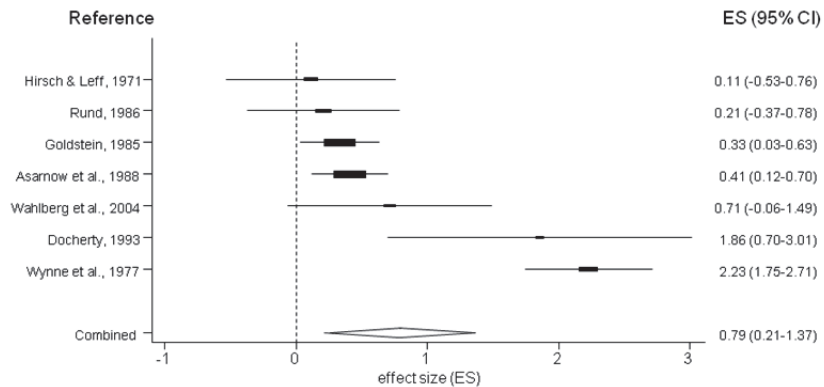


Fig. 1. Effect sizes ($\pm 95\%CI$) of the relationship between parental Communication Deviance and schizophrenia spectrum disorders in offspring (I Figure 2).

6.1.3 Association of parental Communication Deviance with thought disorders in offspring

Only four studies were identified that assessed the relationship between parental CD and thought disorders in the offspring. Three of them were derived from the data of the Finnish Adoptive Family Study, while one studied index subjects and their biological parents. All the subjects were adults. It was impossible to perform any meta-analysis of the association of parental Communication Deviance with thought disorders in offspring because three of four papers on this topic obtained in the review reported results from one project, and the fourth paper did not employ the relevant parameters. The results of studies on adoptive families suggest that the association between frequent parental CD and thought disorders

in the offspring is contingent on the genetic risk status of the child, meaning that the association exists only in the group of high-risk children. It is of interest that in the study concerning biological families, frequent parental Communication Deviance was associated specifically with thought disorders in the offspring, not a schizophrenia diagnosis as such.

6.2 Association of parental Communication Deviance with the attributes of the adoptive child and adoptive parents (II)

First, the amount of total Communication Deviance of adoptive parents in individual, spouse, and family Rorschach situations was compared between the families with an adoptive child at a high or low genetic risk. The only statistically significant difference between the groups was that the CD was greater among the mothers of high-risk children in the family Rorschach test situation.

The total CD among the adoptive mothers (II Table 3) in the individual Rorschach test was associated only with age ($p=0.000$), so that the older the mother, the higher the CD score. The characteristics of the adoptive child (gender, age, genetic risk status, TDI score, interaction of genetic risk and TDI, total CD of the adoptee in individual Rorschach) were not associated with the adoptive mother's CD scores in the individual Rorschach. As the variability in the adoptive mother's total CD in the family Rorschach test was examined, a statistically significant association with several independent factors was found: total CD of the adoptive mother in the individual Rorschach ($p=0.000$), age of the adoptee ($p=0.020$), TDI of the adoptee ($p=0.016$), interaction of genetic risk status and TDI of the adoptee ($p=0.010$), and total CD of the adoptee in family Rorschach ($p=0.000$).

Concerning the adoptive father (II Table 4), the total CD among them in the individual Rorschach test was not associated with any of the independent variables. The variability in the adoptive father's total CD in the family Rorschach test was closely associated ($p=0.000$) with total CD scores of the adoptive father in the individual Rorschach test, but also with the age of the adoptee ($p=0.007$) and the age of the adoptive father ($p=0.045$).

Table 5 shows the results concerning the relationship between total Communication Deviance in the adoptive parents together, and characteristics of the adoptive child and the adoptive parents themselves. Concerning parental CD in individual Rorschach, none of the characteristics was associated with it. Parental Communication Deviance in family Rorschach situations was closely

associated with total CD of the adoptive parents in individual Rorschach, but also with total CD in the adoptee in family Rorschach.

Table 5. Association between total Communication Deviance (CD) in adoptive parents in individual and family Rorschach tests, and characteristics of the adoptee and the parents themselves (II Table 5).

ANCOVA ¹ model	Adoptive parents					
	Individual Rorschach			Family Rorschach		
	B (95% CI for B)	<i>t</i>	<i>p</i> -value	B (95% CI for B)	<i>t</i>	<i>p</i> -value
Gender of the adoptee (female)	-0.445 (-1.108–0.219)	-1.329	0.187	0.703 (-4.002–5.408)	0.297	0.767
Age of the adoptee	-0.028 (-0.103–0.046)	-0.752	0.454	0.073 (-0.457–0.604)	0.274	0.784
Genetic low risk	-0.032 (-0.941–0.877)	-0.070	0.944	-0.169 (-6.765–6.427)	-0.051	0.959
TDI of the adoptee	0.042 (-0.011–0.095)	1.573	0.119	0.280 (-0.097–0.658)	1.473	0.144
Interaction genetic low risk x TDI of the adoptee	-0.029 (-0.091–0.033)	-0.937	0.351	-0.196 (-0.635–0.244)	-0.885	0.379
Total CD of the adoptee in individual Rorschach	0.202 (-0.176–0.579)	1.061	0.292	NA ²	NA	NA
Total CD of the adoptee in family Rorschach	NA	NA	NA	0.812 (0.463–1.161)	4.621	0.000
Age of the adoptive mother	0.055 (-0.020–0.129)	1.462	0.147	0.036 (-0.506–0.578)	0.132	0.895
Age of the adoptive father	0.042 (-0.039–0.124)	1.030	0.305	-0.096 (-0.678–0.487)	-0.327	0.744
Total CD of the adoptive parents in individual Rorschach	-- ³	--	--	2.278 (0.835–3.721)	3.134	0.002

¹Analysis of Covariance, ²NA: The independent variable was not applied to the analysis of covariance because of theoretical inappropriateness, ³--: The association was not analysed because the dependent variable is the same as the independent variable.

6.3 Association of adoptive children's thought disorders and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders and season of birth and parental Communication Deviance (III)

The pattern of births of adoptees with a schizophrenia spectrum diagnosis (adjusted to the pattern of births in the entire study population) followed a hypothesised seasonal pattern with a peak of births in April and a trough in October, with a peak/trough ratio of 12.92.

An adoptive child's schizophrenia spectrum diagnosis was not significantly associated with any of the predictors concerning the adoptive child (gender, age, genetic high risk for schizophrenia spectrum disorders, and season of birth), nor with the total Communication Deviance of the adoptive parents (III Table 3). Neither were interactions of risk indicators (genetic high risk, winter or spring birth, or parental CD) significantly associated with the diagnosis (III Table 3).

As for the association of the adoptive child's total TD_R scores with the aforementioned predictors and their interactions (III Table 2), the only significant association was found between TD_R and parental CD ($p=0.009$). No association was found between TDI schizophrenia subscale (Fluid Thinking, Confusion, and Idiosyncratic Verbalisation) scores and risk indicators or their interactions.

7 Discussion

7.1 Systematised review and meta-analysis (I)

7.1.1 Main findings

In the meta-analysis concerning the association of parental Communication Deviance and schizophrenia spectrum disorder in offspring, a large overall effect size was found. There was, however, a wide variation in findings, which was reflected in the confidence interval of the overall effect size (0.79, 95%CI 0.21–1.37). A meta-analysis concerning thought disorders in the offspring could not be performed.

7.1.2 Discussion of results

Thought disorders

In a few studies exploring the connection between parental CD and thought disorder in offspring, a statistically significant association was found. This is not surprising, since originally the Communication Deviance scale (Singer & Wynne 1966) was developed specifically to tap the interconnection between disordered thought in the offspring and difficulties in sharing and maintaining focus in a parent (or parents). Successful studies in which the form of thinking of the offspring was predicted on account of other family members' communication style (Wynne & Singer 1963 a, b, Morris & Wynne 1965, Singer & Wynne 1965 a, b, Wild *et al.* 1965) preceded the introduction of the Communication Deviance scale. The mechanisms of action by which parental Communication Deviance may affect a growing child's cognitive development have not yet been revealed. In the context of developmental psychology, the association between parental Communication Deviance and disordered thought in offspring is best explained by Vygotsky's assumptions of socially structured cognitive development (Vygotsky 1978). Parental Communication Deviance is presumed to impair especially the starting point, sharing and maintaining the focus of attention, of the process, which should eventually lead to consensually or visually validated meanings (Singer *et al.* 1978). This point is considered to be fundamental to cognitive development, according to Vygotsky's theories.

Schizophrenia spectrum disorders

In the meta-analysis, there was evidence of moderate heterogeneity between studies. There are many alternative explanations for this. Diagnostic criteria varied across studies, but in five of the studies a specific classification system was applied (RDC, DSM-III or DSM-III-R). A greater part of the heterogeneity may be explained by divergent index and control subject groups in the studies: the diagnoses of index patients varied from schizophrenia to schizophrenia spectrum, the latter of which was defined in numerous different ways. Control subjects were either psychiatrically healthy or had other than psychotic or schizophrenia spectrum diagnoses. As we included only studies in which the definition of Communication Deviance was based on Singer and Wynne's definitions and scoring methods, the variation in the methods of gathering speech samples and scoring them was limited, and may not explain heterogeneity significantly. However, in the seven studies included in the meta-analysis, four different types of standardisation of the amount of speech were used (number of Rorschach responses, number of words spoken, number of lines of speech produced in TAT test or ten-minute speech sample, and Story Length Index). The standardisation method is of importance because it crucially affects the amount of Communication Deviance. There has been debate especially on standardising by the number of Rorschach responses or the number of words spoken. The former is recommended on the following basis: CD scores are thought to represent the number of failures in sharing the focus of attention and meaning (Singer & Wynne 1966, Wynne *et al.* 1977). In a test situation like Rorschach, each response can be perceived as an attempt to share one meaning unit, and the CD score of one response reflects the failure to share the meaning in question. Therefore, a CD score standardised by dividing by the number of transactions (responses) would represent Communication Deviance in this sense more accurately. In addition, excessive verbosity is considered to reflect difficulties in sharing and maintaining the focus of attention, in other words to reflect Communication Deviance itself. Standardising the frequency of Communication Deviance by the number of words spoken will, thus, dissipate the whole phenomenon.

7.2 Association of parental Communication Deviance with the attributes of the adoptive child and adoptive parents (II)

7.2.1 Main findings

The variability of total CD of adoptive mothers in individual Rorschach was only explained by the age of the mother, while any feature of the adoptive child was not associated with maternal CD scores. None of the independent variables explained the variability in paternal or parental CD in the same situation. As regards the variability of total Communication Deviance in family Rorschach among mothers and fathers separately, several independent variables appeared to be associated with it. As the frequency of parental CD (parents together) in family Rorschach was observed, the closest relationship was that with parental CD in the individual Rorschach situation, but there was also a relationship with total CD of the adoptive child in the same situation.

7.2.2 Discussion of results

The amount of CD was statistically significantly higher in the group of mothers of high-risk children, but only when CD was scored from family Rorschach protocols. The difference between groups disappeared when the CD scores of the adoptive mother and father were summed. As genetic risk status was included in the models as one of many independent variables, it was not related to any Communication Deviance measures. This indicates that potential subtle deviances connected to the high-risk status of the child do not affect communication patterns of parents.

As the association between the amount of parental Communication Deviance (parents separately or together) in the individual Rorschach test and the characteristics of the adoptive child and parental age was modelled, the only statistically significant association found was that between maternal CD and her own age. The older the mother was, the more frequent CD was. However, as Communication Deviance was measured in the family Rorschach situation, the age of the adoptive mother was not associated with her CD scores, but the age of the adoptive father was inversely proportional to his CD scores. When the CD scores of adoptive mothers and fathers were summed, the association with the age of the mother or father did not reach statistical significance. Results of former studies concerning the association of age and amount of Communication

Deviance suggest that after adolescence, the amount of CD is stable and not dependent on age (Doane & Mintz 1987, Wahlberg *et al.* 2001). In both of these studies, the Communication Deviance data was derived from individual testing situations, and in the first study gender differences concerning the stability were observed, while in the second study there were no such differences.

Concerning the modelling of the association between the amount of parental Communication Deviance in the family Rorschach test and the characteristics of the adoptive child and parents themselves, the results were more complex. As both parents' CD was analysed separately, the age of the adoptee was inversely proportional to the amount of maternal CD but directly proportional to the amount of paternal CD. The relationship between the frequency of the adoptive child's Communication Deviance and parental CD was also different among the groups of adoptive mothers and fathers: it was statistically significantly associated to maternal CD but not to paternal CD. The above-mentioned findings may display different roles for the parents, depending on the gender of the parent and the age of the adoptee. The mothers may have a closer relationship with the children (at least at the times when the adoptive children of this series grew up) and the qualities of communication of the child (in this study, Communication Deviance) may affect the mother more than the father. In addition, the role of the mother may be different from that of the father, depending on the child's age: while trying to explain the family Rorschach task and cards more actively than the fathers to younger children, mothers may produce more CD than the fathers.

The Thought Disorder Index (TDI) of the adoptive child was positively associated with maternal Communication Deviance in the family Rorschach test, but not with paternal or parental CD. This may also reflect the more intensive relationship of the mother and child when compared to that of the father and child, so that frequent maternal CD has a stronger effect on the cognitive functioning of the child. The other possible explanation is that eccentricities in the adoptive child's thinking and speech affect the mother more than the father. The interaction of the TDI of the adoptive child with a low genetic risk of schizophrenia-spectrum disorders had a negative association with maternal CD in the family Rorschach test, in contrast to the positive association concerning the TDI alone. This may reflect the assumption that frequent maternal CD does not interfere with the cognitive development of a low-risk child as it does with a genetically vulnerable child. The result runs in parallel with the former finding from the Finnish Adoptive Family Study: a higher proportion of the high-risk children among the offspring of adoptive parents with higher levels of CD than

the controls had thought disorders. Among the offspring of adoptive parents with low levels of CD, a lower proportion of high-risk children than of control children showed evidence of thought disorders (Wahlberg *et al.* 1997). These findings are in line with the Differential Susceptibility to Environment theory (Ellis *et al.* 2011).

When both parents' Communication Deviance scores in the family Rorschach were summed, the variability in scores was closely associated with total CD of the adoptive parents in the individual Rorschach, but also with total CD of the adoptee in the family Rorschach. This indicates that parental Communication Deviance is a trait-like characteristic of an individual, but as presumed in a systems theory context, not completely independent of the characteristics of the child.

The association of attributes of the adoptive child with parental Communication Deviance differed between the groups of mothers, fathers, and parents together. This may indicate that maternal and paternal CD are not equally significant in the cognitive development of the child, and their mutual significance may change over time as a child grows up. In a majority of Communication Deviance studies, the CD of both parents or only mothers is used. In the studies in which CD of parents separately is used in analyses, the results have not been uniform: in some studies, the association between parental CD and outcome measures have been similar regardless of whether the CD of mothers, fathers, or parents together have been used (Wynne *et al.* 1977, Asarnow *et al.* 1988; studies on psychiatric disorders), while in other studies, there have been differences as regards CD of mothers and fathers (Doane *et al.* 1982, Velligan *et al.* 1988, Cole *et al.* 1993; studies on child's competence, family distress, and severity of schizophrenia, respectively).

7.3 Association of adoptive children's thought disorders and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders and season of birth and parental Communication Deviance (III)

7.3.1 Main findings

In original publication III, the relationship between the adoptive child's thought disorders and schizophrenia spectrum diagnosis and risk indicators (and their

interaction) was assessed. The risk indicators were the adoptive child's genetic risk status, season of birth, and parental CD. The only statistically significant association was found between thought disorder in the adoptee and parental CD.

7.3.2 Discussion of results

The finding that parental Communication Deviance is associated with thought disorders in offspring but not with schizophrenia spectrum disorders is consistent with the original assumption (Wynne & Singer 1963 a, b, Singer & Wynne 1965 a, b, Singer & Wynne 1966) that parental CD is associated specifically with thought disorders in offspring. Since thought disorders are common in schizophrenia spectrum disorders, the association between parental CD schizophrenia spectrum disorders may be explicable in terms of the accompanying thought disorder. In the only study in which the association of parental CD with both thought disorder and a diagnosis of schizophrenia in offspring was explored, only schizophrenia patients with severe thought disorders had parents with high CD (Sass *et al.* 1984). Contrary to previous findings of the Finnish Adoptive Family Study of Schizophrenia (Wahlberg *et al.* 2000), the presence of any TDI schizophrenia subscale (Fluid Thinking, Confusion, and Idiosyncratic Verbalisation) was not predicted by any of the risk indicators or their interactions, but only by total TD_R scores. This may be due to a different subsample. The absence of association between parental CD, genetic high risk status, or their interaction is in line with another paper on the Finnish Adoptive Family Study (Wahlberg *et al.* 2004), in which a subsample of 109 adoptees without any psychiatric disorder at initial assessment was used. In that subsample, neither parental CD nor genetic high risk status nor their interaction predicted the adoptive child's schizophrenia spectrum disorder at follow-up.

It is hypothesised that certain measures of thought disorders could serve as a schizophrenia endophenotype (Gooding *et al.* 2012, Gooding *et al.* 2013). The finding that neither total TDI scores nor TDI schizophrenia subscale (Fluid Thinking, Confusion, and Idiosyncratic Verbalisation) scores were associated with genetically high risk of schizophrenia spectrum disorders does not support the hypothesis. In addition, the total TDI scores were associated only with parental CD independent of genetic risk status, which further indicates that TDI may not reflect underlying genetic vulnerability.

There was an excess of winter or spring births among adoptive children with schizophrenia spectrum diagnosis. The season of birth was not, however,

associated with schizophrenia spectrum diagnosis, either separately or together with other risk indicators. There was also no association between season of birth (separately or together with other risk indicators) and thought disorders in the offspring. There are several possible explanations for the lack of association between season of birth and schizophrenia spectrum disorders. The peak of births among adoptive children with schizophrenia spectrum disorders was in April, which means the months with the least daily sunshine hours (from November to January), and presumed prenatal hypovitaminosis D following, is dated in the second and third trimesters of pregnancy. This may not be the most critical time in foetal development for the deleterious effects of hypovitaminosis D, which is not known (McGrath *et al.* 2010). It is also probable that altered brain development linked to vitamin D deficiency functions as a vulnerability factor that interacts with biological or psychosocial risk factors other than those concerned in the present study. The adoptive children's diagnostic distribution may also have affected the result. Only five of them had a diagnosis of schizophrenia or bipolar psychosis, which are the conditions most distinctly connected with winter or spring birth. The small number of cases did not allow us to perform analyses using only schizophrenia and bipolar psychosis as an independent variable. Among neuropsychiatric disorders, the most robust evidence is for the association between schizophrenia and prenatal vitamin D depletion, while the results concerning other disorders are more controversial (Eyles *et al.* 2013).

7.4 Theoretical discussion

Possible explanations for the association between parental Communication Deviance and thought disorders and schizophrenia spectrum disorders in offspring

Even though the association between frequent parental CD and schizophrenia spectrum disorder in offspring was observed, the assessment of the direction of the effect between these two phenomena has to be based on indirect evidence. In order to define a high level of communication deviance in the parents as a risk factor of offspring psychopathology, in contrast to being a mere reflection of that, CD should at a minimum precede the appearance of the disease and be demonstrably a stable trait and not a fluctuating state. The results of longitudinal prospective high-risk studies, including both biological and adoptive families

(Goldstein 1987a, Wahlberg *et al.* 2004, I Table1), indicate that elevated levels of parental Communication Deviance are present before any severe psychiatric disorder is diagnosable in the offspring. There is also plausible evidence that the amount of Communication Deviance is an enduring trait in the parents rather than a transient state, as it has been shown to be relatively stable over time and even resistant to change (Doane & Mintz 1987, Velligan *et al.* 1995, Nugter *et al.* 1997, Wahlberg *et al.* 2001). In addition, in original publication II of this thesis, the amount of parental CD was shown to be relatively independent of the attributes of other family members. This evidence supports the hypothesis that frequent CD is an environmental risk factor for psychiatric disorders. Based on the existing evidence, the possibility that heightened CD levels were simply the parent's reaction to subclinical vulnerability signs in the offspring cannot completely be ruled out. Since parent-child interaction is circular, a child may have an effect on the behaviour of a parent. The adult can be assumed to be mainly responsible for the clarity of the communication, however, as the adult presumably has more mature cognitive functions and social skills.

It has also been suggested that parental Communication Deviance is neither a psychosocial stress factor affecting the child nor a parental reaction to the child's disturbed behaviour or thinking, but a reflection of the parent's own psychopathology. From this point of view, Communication Deviance represents a mild, subclinical form of thought disorder that is connected with a parent's psychiatric disorder. If this were true, CD would become more frequent along a continuum from healthy persons to persons with psychotic disorders. Thus, in studies of adult offspring with schizophrenia and their non-schizophrenic parents, the patient-offspring should have more CD than the parents. There were only four studies included in this review in which parental psychopathology was somehow assessed and reported (Wynne *et al.* 1977, Docherty 1993, Goldstein 1987, Wynne *et al.* 1978), and their results indicate that parental CD is independent of the measures of parental psychopathology. There are also two studies not included in this review that have specifically surveyed this issue. In a study by Goldstein and colleagues (1992), groups of biological parents with schizophrenia and schizophrenia spectrum diagnoses, and with other psychiatric diagnoses or none at all, were studied. No significant association between the parent's diagnosis and an elevated Communication Deviance score were found. In a study by Hamilton and co-workers (1993) in which chronically physically ill biological mothers with affective disorders and healthy controls were studied, diagnostic group differences were not found to exist for CD. In the latter study, however, the

subjects lacked diagnoses of psychotic disorders to which thought disorders are most probably related. In addition, within the subject, thought disorders measured by the Thought Disorder Index have been shown to be independent of frequency of Communication Deviance (Johnston & Holzman 1979), even though there is overlap between items on the two scales. Based on the existing evidence, it is unlikely that the association of parental CD with offspring psychopathology could be only an artefact attributable to parental psychopathology.

One theory for explaining the linkage between parental Communication Deviance and offspring psychopathology is to conceive of CD as a parental marker of shared genetic vulnerability, which manifests itself in the offspring as a psychiatric disorder. The supposed vulnerability genes could, for instance, be linked to attention disturbances. A positive family history of psychiatric disorders in second-degree relatives could also be regarded as such a marker. Only two studies discussing shared genetic vulnerability issues were included in this review (Docherty 1993, Goldstein 1987b), and their results were contradictory. In addition, a study was found in which the statistical association between a family history of schizophrenia spectrum disorder and CD was observed among 60 mothers of schizophrenic or schizoaffective patients (Subotnik *et al.* 2002). Mothers with a family history of schizophrenia spectrum disorders had higher CD scores than mothers without such a history, but a personal history of some kind of lifetime psychiatric disorder, or only schizophrenia spectrum disorder, accounted for very little of the variance in the CD scores. In conclusion, the evidence for the shared genetic vulnerability theory is weak. In addition, the adoption studies (Wynne *et al.* 1978, Wahlberg *et al.* 1997, Wahlberg *et al.* 2000, Wahlberg *et al.* 2004) provide evidence to refute this theory, as they show that high parental CD is associated with psychopathology and thought disorders in the child, even in the absence of shared genetic vulnerability.

In the light of recent research into schizophrenia and other psychotic disorders, it is unlikely that any single cause, biological or psychosocial, can be found for it, but an interaction between genetic and environmental risk factors is likely to be essential for its onset (Kendler 2005, van Os *et al.* 2008). The studies on Communication Deviance unfortunately include mainly biological relatives of patients, which does not allow optimal assessment of the interaction between genetic and environmental risk factors, because the two factors cannot be separated. This is possible in adoption studies, however, and the results of the Finnish Adoptive Family Study have shown that only the interaction of genetic vulnerability to schizophrenia spectrum disorders with parental CD increases the

probability of thought disorders or psychiatric disorders in the child. The results of the UCLA High-Risk Project also showed that the combination of a positive family history and high parental CD was a much more powerful indicator of a risk of schizophrenia spectrum disorders than either of them separately. It is likely that high parental CD is not an independent risk factor for psychiatric and thought disorders, but interacts with genetic vulnerability in the offspring.

7.5 Strengths and limitations of the study

7.5.1 Systematised review and meta-analysis of the association between parental Communication Deviance and psychiatric and thought disorders in offspring (I)

Even though several reviews of Communication Deviance in families who have a member with schizophrenia or another schizophrenia spectrum disorder have been published (e.g. Wynne 1970, Doane 1978, Wynne 1981, Goldstein 1984, Miklowitz & Stackman 1992, McFarlane & Lukens 1994, Miklowitz 1994, Rund 1994, Kymalainen & Weisman de Mamani 2008), this was the first review that fulfilled the criteria for a systematic review. There are also no previous meta-analyses on this issue.

A thorough search for the relevant papers was performed. The broad search term “communication deviance” was used in several databases without placing limits on the language of the papers. In addition to electronic search, manual search was performed. The references cited by papers, together with citations in major review papers and book chapters, were scrutinised in order to locate additional potentially relevant papers. Unpublished dissertations were also accessed. Almost all of the papers found in electronic and manual searches were obtained (172/176 potential papers).

The strength and limitation of the study is a strict definition of Communication Deviance used as an inclusion criterion. This was considered to be essential based on the theoretical rationale of the concept of Communication Deviance, which connects specifically difficulties in sharing and maintaining a focus of attention in a parent with disordered thought in the offspring. The scoring methods, based on Singer and Wynne’s criteria, are supposed to grasp the same phenomenon and make comparisons across studies meaningful. In the studies included in the review, Rorschach or TAT CD scoring methods were mostly used.

The years of publication of the papers covered a wide time span, from 1967 to 2007. As a consequence of the wide time span, there was heterogeneity of the diagnostic criteria employed in the studies. However, specific classification systems (DSM-III, DSM-III-R, or RDC) were employed in eleven out of the fifteen papers included in the review. The quality requirements for the reporting of methods and results, and for statistical analyses, have also changed over time. Due to the lack of information, two studies had to be excluded from the meta-analysis. The number of subjects examined in the majority of studies was quite small, which increases the possibility that minor differences between the groups may not have been detected, or alternatively it is possible that the differences found were coincidental.

Five papers reporting the results of two studies pointed to an association between parental CD and a schizophrenia spectrum disorders in offspring, which is somewhat problematic in view of the varying and insufficiently established definition of the schizophrenia spectrum.

On a review level, the decision to exclude unpublished congress abstracts found in the electronic and manual searches may be criticised. Fortunately, only seven relevant congress abstracts were found, and their titles and authors' names suggested that the results had been published later in scientific papers and books. Even though we did not place limits on the language of the papers, only the English search term was used, without translations into any other languages. This excluded papers that lacked English language titles or abstracts.

It is always possible that the results of the review may have been skewed by publication bias. Positive results are more likely to be submitted and published, which leads to the possibility that the strength of the association between parental Communication Deviance and psychiatric and thought disorders in offspring may be overestimated.

7.5.2 Association of parental Communication Deviance with the attributes of the adoptive child and adoptive parents (II)

The main strength of the study is the adoption study method, which provides a possibility to investigate the genetic and environmental risk factors separately, because the genes of the child come from the biological parents and the psychosocial environment in the early years of life is shaped by the adoptive parents. The adoption study method also makes the investigation of gene-environment interactions possible.

In the Finnish Adoptive Family Study, biological mothers and adoptive children are carefully diagnostically assessed, and there was a good interrater reliability for the diagnoses (0.71-0.80). In the Finnish Adoptive Family Study, several procedures were used to establish and maintain interrater reliability for the diagnoses (Tienari *et al.* 2000). Operationalised instruments were used as a measure of environmental risk (Communication Deviance) and thought disorders (Thought Disorder Index). The interrater reliabilities were good for both CD and the TD_R (0.95 and 0.94, respectively). The study was the first to assess the interconnection between Communication Deviance in adoptive parents and the attributes of both the adoptive child and the parents themselves.

There are several limitations affecting this study. First, the subsample of families ($n=109$) differed from the total sample ($n= 382$). The adopted children were younger at the initial assessment, as were the adoptive mothers and fathers. There were relatively more families belonging to social classes II and III in the subsample, while there were more families belonging to classes I and IV among the total original sample. The age of the adoptive child and adoptive parents was used as a covariate in the analysis of covariance, in order to control for their effect statistically. The association of social class with CD in the adoptive parents was controlled by testing bivariate correlations (independent samples t test), and no statistically significant correlation was found between these two variables. That is why the social class of the family was not used as a covariate in the analyses.

Unfortunately, the majority of families had to be excluded from the study because of insufficient data. Since the sample size was relatively small, some possibility of chance findings exists (Type I error), and also a possibility of differences not being detected (Type II error).

This study was cross-sectional. Thus, the results concerning the direction of the effect of parental Communication Deviance on the offspring remain only suggestive.

7.5.3 Association of adoptive children's thought disorders and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders, season of birth, and parental Communication Deviance (III)

The strengths concerning the adoption study method, and diagnostics and instruments used in the Finnish Adoptive Family Study, are the same as in original publication II. This was the first study in which the association of a

schizophrenia spectrum diagnosis of the adoptive child with genetic high risk of schizophrenia spectrum disorders in the child and environmental risk factors (season of birth and parental CD) was investigated. A putative schizophrenia endophenotype measure, Thought Disorder Index, was also used as a dependent variable.

There are several limitations affecting this study. This subsample differed from the total sample as far as the ages of the adoptive child, mother, and father were concerned. The subjects in the subsample were younger than those in the total sample. The age of the adoptive child was used as a covariate in the logistic regression analysis and analysis of covariance. The ages of the adoptive parents were not used as a covariate, to avoid an unnecessary number of independent factors, and also to avoid problems with multicollinearity: the ages of the adoptive parents and the child are highly correlated.

The main limitation is its small sample size and the small number of adoptive children with schizophrenia spectrum diagnosis. There is a possibility that the lack of interactions may be a chance finding due to the small subgroups.

Vitamin D depletion was also only hypothetical and not based on maternal serum concentrations or umbilical cord blood samples. However, the depletion is very probable, since even in an era of vitamin D supplementation, the intake in Finland falls below that which is recommended (Prasad *et al.* 2010). There is also direct evidence of low vitamin D levels in maternal and cord serum samples from the time before vitamin D supplementation was recommended (Kuoppala *et al.* 1986). The season of birth effect may also be mediated by factors other than hypovitaminosis D, such as maternal influenza during pregnancy. Data on exposure to other factors that are hypothesised to be associated with the season of birth effect is not available in the Finnish Adoptive Family of Schizophrenia.

8 Conclusions

8.1 Main conclusions

The meta-analysis strongly suggests that there is an association between parental Communication Deviance and psychiatric disorders in offspring. Since the majority of the studies included in the meta-analysis were cross-sectional and concerned with biological families of patients with a schizophrenia spectrum diagnosis, they do not provide an explanation for the association found. The meta-analysis could not be performed for the association between parental CD and thought disorders in offspring. A few reports included in the systematised review indicate that there is an association between frequent parental CD and thought disorders in offspring.

In original publication II, it was shown that Communication Deviance in the individual Rorschach situation of adoptive mother, father, or parents together was not associated with any characteristics of the adoptive child. Concerning parental CD in the family Rorschach situation, the closest relationship found was with parental CD measured from individual Rorschach protocols. This finding further confirms the hypothesis that the amount of Communication Deviance is a trait-like feature of an individual and not a changing state. Together with the evidence that parental CD precedes the offspring's schizophrenia spectrum diagnosis and is associated with the offspring's psychopathology, also in the absence of shared genetic inheritance, the results of this thesis suggest that parental Communication Deviance is a risk factor for thought and schizophrenia spectrum disorders in offspring. It may, however, interact with genetic vulnerability.

Parental Communication Deviance, or an adoptive child's genetic vulnerability to schizophrenia spectrum disorders, or winter or spring birth separately, or their interactions were not associated with the adoptive child's schizophrenia spectrum diagnosis. As far as thought disorders in the offspring were concerned, only parental CD was associated with them. The results did not confirm the hypothesis on the significance of interaction of risk indicators.

8.2 Clinical implications

The results of this thesis indicate that parental Communication Deviance could be treated as a risk indicator for schizophrenia spectrum disorders and thought

disorders. As well as other known risk indicators, parental CD is neither a necessary nor a sufficient prerequisite for schizophrenia spectrum disorders. It is possible that parental Communication Deviance affects the cognitive development of a child only among those children who have inherited or acquired biological vulnerability to schizophrenia spectrum disorders. More research is needed to confirm (or refute) this hypothesis. Parental CD may, and is even likely to interact with other environmental risk factors, such as measures of family affective tone.

If we knew the contribution of parental high CD and other risk factors to the aetiology of schizophrenia spectrum disorders, a risk calculator for future schizophrenia spectrum disorders could be developed. If the high-risk individuals were identified more accurately than it is possible at present, primary preventive interventions, or at least careful monitoring of their development and health, could be provided.

Since the amount of Communication Deviance is considered to be a trait-like feature of an individual, changing it by means of psychotherapeutic interventions may be very hard. In addition, this kind of psychotherapeutic intervention should be timed very early in an infant's life in order to prevent the effect of frequent CD on the child's cognitive development. Like any primary preventive intervention, this could be ethically and also economically justified only if there was very strong evidence that the incidence of the outcome, schizophrenia spectrum disorder, could really be reduced by the intervention.

8.3 Future studies

Even though there is evidence that an interconnection between parental Communication Deviance and schizophrenia spectrum disorders in offspring exists, the explanations for the association are based on indirect evidence. To confirm the hypothesis that parental Communication Deviance is an independent risk factor for a quite a rare condition like schizophrenia spectrum disorder, a large prospective study would be needed. The study should be a cohort study, in which a group of children with a genetic liability to schizophrenia spectrum disorders was compared with a group of children without such a liability. The follow-up should begin in early childhood and be tens of years long. Optimally, the children should be adoptive children to disentangle genetic and environmental factors.

Taking into account the resources required by the above-mentioned study, it seems unlikely to emerge, or at least the results would only be accessible after tens of years from the start of the study. A more realistic approach may be to gather more indirect evidence concerning the direction of the effect between parental Communication Deviance and psychopathology in the offspring. The studies on temporal stability of Communication Deviance uniformly show that the amount of CD is stable in adulthood. However, the studies on situational stability of Communication Deviance are sparse, and more research is needed on this issue. Studies are also needed that explore the association of Communication Deviance of an individual with the individual's characteristics. Of specific interest would be studies that investigate the neurocognitive substrate of Communication Deviance, such as association with measures of attention and executive functioning, which are also connected to thought disorders. Studies of genetics underlying neurocognitive functioning and its impairments, and potential shared genetic vulnerability between parental CD and schizophrenia spectrum and thought disorders in offspring, would also be of interest.

An area of crucial importance, but neglected in Communication Deviance research, is revealing the mechanisms by which parental CD could affect the growing child's cognitive development and lead to impairment in cognitive functioning. The connection between Communication Deviance, thought disorders, and schizophrenia spectrum disorders should be clarified. It is possible that the link between parental CD and schizophrenia spectrum disorders in offspring is actually a link between CD and thought disorders.

The problem in Communication Deviance studies has been scoring of speech samples, which is so laborious that it has made research on large enough samples practically impossible. Efforts to overcome this obstacle have included developing a variety of shortened versions of the Communication Deviance scoring scale. Most of these scales, however, lack validity and reliability assessments, and it is not obvious that they really reflect the same phenomena as the original scale. So, instead of developing new scales, information technology could be harnessed for Communication Deviance studies, to enable automated analysis of communication.

The growing evidence of the significance of complex interaction between genetic and environmental factors in the aetiology of schizophrenia spectrum disorders should also be borne in mind in Communication Deviance research. Studying Communication Deviance in isolation from other risk factors is not meaningful; at least a genetic vulnerability to schizophrenia spectrum disorders

should be used as a covariate in studies assessing the connection between parental CD and psychiatric disorders in offspring.

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Original publications

- I Roisko R, Wahlberg K-E, Miettunen J & Tienari P (2014) Association of parental Communication Deviance with offspring's psychiatric and thought disorders. A systematic review and meta-analysis. *Eur Psychiatry* 29: 20-31.
- II Roisko R, Wahlberg K-E, Hakko H, Wynne L & Tienari P (2011) Communication Deviance in parents of families with adoptees at a high or low risk of schizophrenia spectrum disorders and its associations with attributes of the adoptee and the adoptive parents. *Psychiatry Res* 185: 66-71.
- III Roisko R, Wahlberg K-E, Hakko H & Tienari P (2014) Association of adoptive child's thought and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders, season of birth and parental Communication Deviance. Manuscript.

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