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Ville Tikkanen

ADOLESCENT SOCIAL FUNCTIONING AND LATER PSYCHIATRIC MORBIDITY IN GENETIC HIGH- AND LOW-RISK ADOPTEES

THE FINNISH ADOPTIVE FAMILY STUDY OF SCHIZOPHRENIA

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
FACULTY OF EDUCATION AND PSYCHOLOGY

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The Finnish Adoptive Family Study of Schizophrenia

Academic dissertation to be presented with the assent of the Doctoral Programme Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 1, Building PT1 of the Department of Psychiatry (Peltolantie 17), on 12 January 2024, at 12 noon

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Abstract

Both genetic and environmental factors are known to play a role in the etiology of schizophrenia and other psychiatric disorders. The vulnerability-stress model suggests that psychiatric disorders develop as a result of the interaction between genetic or biological vulnerability and environmental stress. Poor social functioning during adolescence has been identified as a plausible indicator of vulnerability to later psychiatric disorders.

This study utilized the data from the Finnish Adoptive Family Study of Schizophrenia. The data comprises adoptees at high (HR) and low (LR) genetic risk for schizophrenia spectrum disorders by their biological mother, and the adoptive families of the adoptees. The purpose of this doctoral dissertation was to analyze social functioning in adolescence between HR and LR adoptees. The adoptees were reared by the adoptive families instead of their biological parents, making the rearing environment comparable between HR and LR adoptees. Adoptees' social functioning at age 16-20 was assessed using the UCLA Social Attainment Survey (UCLA SAS). The impact of the adoptive rearing environment could be taken into consideration in the analyses by utilizing the Global Family Ratings (GFRs) which measured the level of family functioning.

The findings showed that poor social functioning was emphasized in HR adoptees even when the impact of the adoptive family functioning was taken into consideration in the analyses. Poor social functioning was particularly emphasized in HR adoptees reared in adoptive families with dysfunctional processes. Poor social functioning, specifically in peer relationships, was associated with later psychiatric morbidity in both HR and LR adoptees.

The findings suggest that, in terms of their adolescent social functioning, offspring who are at high genetic risk for schizophrenia spectrum disorders may be particularly vulnerable to dysfunctional family processes. Poor social functioning during adolescence may be an indicator of vulnerability to later psychiatric disorders not only in adoptees, but possibly in all offspring in general.

Keywords: adolescence, adoption study, genetic risk, family functioning, psychiatric disorders, schizophrenia, social functioning, vulnerability

Tikkanen, Ville, Nuoruusiän sosiaalinen toimintakyky ja myöhempi psykiatrinen sairastavuus riskilapsilla ja näiden verrokeilla. Suomalainen skitsofrenian adoptiolapsiperhetutkimus

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Tiivistelmä

Perimä- ja ympäristötekijöiden tiedetään olevan yhteydessä skitsofrenian ja muiden psykiatristen häiriöiden kehittymiseen. Haavoittuvuus-stressimallin mukaan psykiatriset häiriöt kehittyvät perinnöllisen tai biologisen haavoittuvuuden sekä ympäristön stressitekijöiden vuorovaikutuksen seurauksena. Nuoruusiän sosiaalisen toimintakyvyn ongelmat ovat mahdollisia haavoittuvuusindikaattoreita myöhemmille psykiatrisille häiriöille.

Tutkimus pohjautuu Suomalaisen skitsofrenian adoptiolapsiperhetutkimuksen aineistoon. Aineistoon sisältyivät perimänsä (biologisen äidin) kautta skitsofreniaspektrin häiriöön sairastumiseen altistuneet adoptiolapset (riskilapset) ja näiden verrokit sekä lasten adoptioperheet. Tämä väitöskirjatutkimus keskittyi selvittämään nuoruusiän sosiaalista toimintakykyä riski- ja verrokkilasten välillä. Tutkimuksen adoptiolapset olivat kasvaneet adoptioperheissä sen sijaan, että olisivat kasvaneet biologisten vanhempiensa kanssa, mikä mahdollistaa riski- ja verrokkilasten kasvuympäristön vertailukelpoisuuden. Sosiaalisen toimintakyvyn arviointi ikävuosina 16-20 pohjautui UCLA Social Attainment Survey (UCLA SAS) -asteikon tuloksiin. Kasvuympäristön vaikutus kontrolloitiin käyttämällä adoptioperheen toimivuutta tarkastelevaa Global Family Ratings (GFRs) -asteikkoa.

Tulosten mukaan nuoruusiän sosiaalisen toimintakyvyn ongelmat korostuivat riskilapsilla, myös silloin kun kasvuympäristön vaikutus kontrolloitiin analyyseissä. Sosiaalisen toimintakyvyn ongelmat korostuivat erityisesti heikommin toimivissa adoptioperheissä kasvaneilla riskilapsilla. Nuoruusiän toverisuhteisiin liittyvät sosiaalisen toimintakyvyn ongelmat olivat yhteydessä sekä riskilasten että verrokkilasten myöhempään psykiatriseen sairastavuuteen.

Tutkimustulokset viittaavat siihen, että skitsofreniaspektrin häiriöön liittyvän perimäalttiuden omaavat lapset ovat sosiaalisen toimintakykynsä näkökulmasta erityisen haavoittuvia perheen heikolle toimivuudelle. Nuoruusiän sosiaalisen toimintakyvyn ongelmat ovat mahdollisia haavoittuvuusindikaattoreita myöhemmille psykiatrisille häiriöille adoptiolapsilla, mutta mahdollisesti myös kaikilla lapsilla yleisesti.

Asiasanat: adoptiolapsiperhetutkimus, haavoittuvuus, kasvuympäristö, nuoruus, psykiatriset häiriöt, riskilapsitutkimus, skitsofrenia, sosiaalinen toimintakyky

To my father

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List of abbreviations and symbols

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CD	Communication Deviance
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
EE	Expressed Emotion
GxE	Gene-environment interaction
GFRs	Global Family Ratings
GWAS	Genome-Wide Association Study
GWEIS	Genome-Wide Environment Interaction Study
HPA	Hypothalamic-pituitary-adrenal
HR	High risk (for schizophrenia spectrum disorders)
ICD	International Classification of Diseases
KW	Kruskal-Wallis
LR	Low risk (for schizophrenia spectrum disorders)
MWU	Mann-Whitney U
PRS	Polygenic risk score
SES	Socioeconomic status
SPSS	Statistical Package for the Social Sciences
UCLA SAS	UCLA Social Attainment Survey

List of original publications

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

I Tikkanen, V., Siira, V., Wahlberg, K-E, Hakko, H., Läksy, L., Roisko R., Niemelä, M., & Räsänen, S. (2020). Adolescent social functioning in offspring at high risk for schizophrenia spectrum disorders in the Finnish Adoptive Family Study of Schizophrenia. *Schizophrenia Research, 215*, 293–299. https://doi.org/10.1016/j.schres.2019.10.013.

II Tikkanen, V., Siira, V., Wahlberg, K-E, Hakko, H., Myllyaho, T., Läksy, L., Roisko R., Niemelä, M., & Räsänen, S. (2022). Adolescent social functioning deficits in association with adoptive family functioning and genetic risk for schizophrenia spectrum disorders: The Finnish adoptive family study of schizophrenia. *Journal of Nervous and Mental Disease, 210(6),* 418–425. https://doi.org/10.1097/NMD.0000000000001483

III Tikkanen, V., Siira, V., Wahlberg, K.-E., Hakko, H., Myllyaho, T., Läksy, K., Roisko, R., Niemelä, M., & Räsänen, S. (2022). Deficits in adolescent social functioning, dysfunctional family processes and genetic risk for schizophrenia spectrum disorders as risk factors for later psychiatric morbidity of adoptees. *Psychiatry Research 316,* 114793. https://doi.org/10.1016/j.psychres.2022.114793

Contents

1 Introduction

It is well established that genetic factors play a significant role in the etiology of schizophrenia. Along with the development of molecular genetic technology, studies have continued to identify an increased number of genetic loci associated with the risk for the disorder (Ripke et al., 2014; Trubetskoy et al., 2022). It has become increasingly clearer that thousands of genetic variants with small effect sizes may contribute to the risk for schizophrenia (Sandstrom et al., 2020; Zwicker et al., 2018). Moreover, the same genetic variants may shape the risk for a range of psychiatric disorders, not only schizophrenia. Despite these advancements, various biological, social, and family environmental factors over the life course are known to play an important role in shaping the risk for schizophrenia and other psychiatric disorders (Buehler, 2020; Henssler et al., 2020; Robinson & Bergen, 2021; Salokangas et al., 2020).

It has been suggested that any genetic or environmental factor on its own is unlikely to cause a severe psychiatric disorder such as schizophrenia (Uher & Zwicker, 2017). A more likely explanation is that genetic and environmental factors jointly influence the development of schizophrenia (i.e., gene-environment interaction). Individuals at genetic risk for schizophrenia have been suggested to be oversensitive to environmental stressors, which may increase the likelihood of developing the disorder (Read et al., 2001). As demonstrated by the Finnish Adoptive Family Study of Schizophrenia, adoptees at high genetic risk for schizophrenia spectrum disorders have been found to be more sensitive to the unfavorable, but also to the favorable/protective aspects of the rearing environment compared to genetic low-risk adoptees (Tienari et al., 2004; Wahlberg et al., 1997, 2004; Wynne et al., 2006).

According to the vulnerability-stress model (Nuechterlein & Dawson, 1984; Rosenthal, 1970; Zubin & Spring, 1977), schizophrenia develops as a result of the interaction between genetic (and other biological) vulnerability and environmental stress. It is thought that certain characteristics of an individual may potentially serve as indicators of this vulnerability (Cheng et al., 2016; Nuechterlein & Dawson, 1984). Consequently, studies have sought to identify such indicators as they may be highly useful in identifying those who are potentially at increased risk for psychiatric disorders. Poor social functioning, particularly during adolescence, has been identified as a potentially important indicator of vulnerability to schizophrenia as well as to other psychiatric disorders (e.g., Cannon et al., 2002; Carrión et al., 2021; Tarbox & Pogue-Geile, 2008).

Findings suggest that compared to low-risk controls, offspring at high genetic risk for schizophrenia display poorer social functioning during adolescence: they show poorer relationships with peers and opposite sex and have fewer hobbies and interests (Christiani et al., 2019; Dworkin et al., 1994; Glatt et al., 2006; Hans et al., 2000). In addition, there are findings to suggest that social functioning deficits are found in high-risk adolescents who later developed schizophrenia (Olin et al., 1995; Tarbox & Pogue-Geile, 2008). Preceding the full onset of schizophrenia, such deficits (e.g., social withdrawal) also characterize the prodromal phase of the disorder (Cheng et al., 2016). It is known that the social functioning of an individual is shaped by both genetic and environmental factors, but the impact of the rearing environment of offspring is still not comprehensively considered in earlier studies of the topic. Indeed, high-risk studies have typically analyzed offspring who have a biological parent with schizophrenia, but the biological parents are also the rearing parents.

Adolescence is characterized by various changes in biological, physical, cognitive, and psychosocial development. Consequently, adolescence is a period of sensitivity to environmental stressors as well as heightened vulnerability to later psychopathology. On the other hand, this period represents a critical window of opportunity for prevention and intervention (Fuhrmann et al., 2015; Patel et al., 2021). Therefore, a deeper understanding of adolescent social functioning deficits in genetically vulnerable individuals could be utilized to inform the identification of potential at-risk groups and in recognizing targets for preventative strategies.

The present study from the nationwide Finnish Adoptive Family Study of Schizophrenia (Tienari et al., 2000, 2004) was focused to analyze social functioning in adolescence among adoptees at high (HR) and low (LR) genetic risk for schizophrenia spectrum disorders. Importantly, it was possible to take into consideration the impact of the rearing environment provided by the adoptive family in the analyses. The first aim of this study was to examine whether HR and LR adoptees (i.e., offspring at high and low genetic risk for schizophrenia spectrum disorders who have not been reared by their biological parents) differed in terms of social functioning during adolescence. Subsequently, it became necessary to get a deeper understanding of the subject, and the next step was to analyze whether the rearing environment provided by the adoptive family had an impact on the social functioning of the adoptees in adolescence. Thus, the second aim of the study was to examine adoptees' adolescent social functioning in association with adoptive family functioning and genetic risk of the adoptees. The final step was to study poor social functioning during adolescence as a plausible indicator of vulnerability to

later psychiatric disorders in adoptees. Thus, the third aim of the study was to examine whether adoptees' adolescent social functioning would associate with adoptees' later psychiatric morbidity after controlling for the genetic risk of the adoptees and adoptive family functioning.

2 Review of the literature

2.1 Adolescence

Adolescence is the period of transition between childhood and adulthood, and according to modern views, the age range of adolescence is approximately from 10 to 25 years (Sawyer et al., 2018). This period is characterized by various types of biological and psychological growth and development. For instance, the adolescent brain goes through a number of structural and functional changes, particularly in the limbic and cortical regions (Galván, 2021). Such changes, in turn, influence the cognitive and emotional processes and behavior (for a review, see Casey et al., 2008). Adolescence is also traditionally marked by significant changes in the social environment (e.g., increased need for independence, time spent with peers, increased complexity in interpersonal relationships). As such, adolescence is a pivotal period in terms of social development as it lays the foundation for later well-being and mental health (Cornblatt et al., 2012; Repetti et al., 2002; Troop-Gordon et al., 2021).

On the other hand, adolescence is known to be a period of heightened vulnerability during which the developing brain may be particularly sensitive to environmental stressors (Fuhrmann et al., 2015; Patel et al., 2021). Indeed, it is well known that a range of psychiatric disorders begin in adolescence, such as mood and anxiety disorders, and schizophrenia (Dalsgaard et al., 2020; Kessler et al., 2005). Regarding the latter, adolescence is also known to be the age when various types of premorbid deficits as well as prodromal symptoms of schizophrenia are first observed (e.g., Cheng et al., 2016). Given such observations, it has been suggested that disruptions in brain development during key developmental periods may underlie the later onset of schizophrenia (Schmitt et al., 2023). Such disruptions may result from the interaction of various environmental (e.g., prenatal and perinatal) and genetic factors, possibly inducing the symptoms of schizophrenia during vulnerable adolescent brain development (Keshavan et al., 2014; Rund, 2018).

2.2 Schizophrenia

2.2.1 Characteristics and epidemiology of schizophrenia

Schizophrenia is one of the most debilitating psychiatric disorders. The clinical picture of schizophrenia is heterogeneous, but certain features are considered the core features of the disorder. These include positive symptoms (e.g., delusions, hallucinations, disorganized speech, thinking and behavior) and negative symptoms (e.g., social withdrawal, affective flattening, avolition, and anhedonia) (American Psychiatric Association, 2013). Schizophrenia is also characterized by deficits in several areas of cognition, such as attention, thinking, verbal fluency, and executive function (Jauhar et al., 2022). Consequently, individuals with schizophrenia often show a decline in social and occupational functioning (Blackman & MacCabe, 2020). The outcome of schizophrenia is also heterogeneous. In a recent meta-analysis (Molstrom et al., 2022), 24.2% of the patients were found to recover, and 35.5% had a favorable outcome (e.g., showed intermediate or moderate symptoms). Of the patients, 40.3% were found to have a poor outcome (e.g., severe symptoms, chronic course).

The classification of psychiatric disorders and diagnostic criteria have developed over time according to increased research information and input from clinicians for use in both research and clinical practice. In this development, the goal has been good validity and reliability. DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised, American Psychiatric Association, 1987) was published in 1987, according to which the diagnoses of this study have been set. It is relatively similar to the ICD-10 classification (International Classification of Diseases, 10th edition, World Health Organization, 2011) currently used in Finland. The ICD-10 diagnostic criteria for schizophrenia are presented in Table 1.

Table 1. Diagnostic criteria for schizophrenia according to ICD-10 (International Classification of Diseases, 10th edition).

Criterion	Description
Duration of symptoms	Present for a significant portion of time during a one-month period
Characteristic symptoms	1. At least one of the following: a) Thought echo, thought insertion or withdrawal, or thought broadcasting b) Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations, or delusional perception c) Hallucinatory commentary, voices conversing or voices coming from some part of the body d) Persistent bizarre delusions 2. Or, at least two of the following: a) Persistent hallucinations in any modality accompanied by delusions b) Neologisms, thought disorder, incoherence, or irrelevant speech c) Catatonic behavior d) Negative symptoms
Exclusion criteria	Both of the following: a) Criteria for characteristic symptoms of schizophrenia (1 & 2) must be met before a manic episode or depressive state b) State is not caused by organic brain disorder, alcohol or drug intoxication, addiction, or withdrawal state

The finding that about 1 in 100 people (1%) worldwide will develop schizophrenia during their lifetime continues to be supported (Jauhar et al., 2022). In Finland, the incidence of schizophrenia is approximately 0.5–1.5% (Tuominen & Salokangas, 2017). It is known that schizophrenia often develops during adolescence and early adulthood, with findings suggesting a somewhat higher incidence among men compared to women (Jongsma et al., 2019). Men also tend to develop the disorder earlier than women, usually in late adolescence or early adulthood. Women usually develop the disorder in their late 20s or early 30s, and rarely during their mid and late 40s (Häfner, 2003).

2.2.2 Schizophrenia spectrum disorders

Over a hundred years ago, Kraepelin observed that some biological family members of a patient with schizophrenia displayed similar schizophrenia-like traits as the patient, although in a milder form. Over the years, it has become well established that schizophrenia and other psychiatric disorders tend to cluster in biological relatives of patients with schizophrenia (Lichtermann et al., 2000). This has led to the suggestion that certain disorders may share a common genetic susceptibility with schizophrenia. Such disorders have been posited under the term "schizophrenia spectrum", first introduced by Kety et al. (1968).

In their study, Kendler et al. (1996) formed three diagnostic categories of the putative schizophrenia spectrum: narrow, intermediate, and broad schizophrenia spectrum. The narrow spectrum, which was categorized to comprise "core schizophrenia phenotypes", included DSM-III-R (American Psychiatric Association, 1987) diagnoses of schizophrenia, schizoaffective disorder (poor-outcome), and simple schizophrenia. The intermediate spectrum included diagnoses on the narrow spectrum and diagnoses of schizotypal personality disorder, and nonaffective psychotic disorders (schizophreniform disorder, delusional disorder, atypical psychosis, and schizoaffective disorder (good outcome)). The broad spectrum included the diagnoses from the two previous categories, and also diagnoses of mood-incongruent and mood-congruent psychotic affective disorder and paranoid, avoidant and schizoid personality disorder.

Based on the categories by Kendler et al. (1996), the broad schizophrenia spectrum utilized in the present study includes the following DSM-III-R (American Psychiatric Association, 1987) diagnoses: schizophrenia; schizotypal, schizoid, paranoid, and avoidant personality disorders; schizoaffective, schizophreniform, and delusional disorders; bipolar disorder with psychosis; depressive disorder with psychosis; and psychotic disorder not otherwise specified (Tienari et al., 2003).

2.3 Etiology of schizophrenia

2.3.1 Genetics of schizophrenia

Schizophrenia is known to be a polygenic and multifactorial psychiatric disorder. It is well established that schizophrenia tends to run in families, suggesting a strong genetic component in the etiology of the disorder. Indeed, twin studies have demonstrated that the concordance rate for schizophrenia in monozygotic twins is

higher compared to dizygotic twins (approximately 45–75% vs. 4–15%) (Lichtermann et al., 2000). Similarly, family studies have shown that the rate of schizophrenia is higher in biological relatives of patients with the disorder compared to general population (Henriksen et al., 2017). The approximate risk for children with one parent with schizophrenia is 13%, being 46% for children with two parents with the disorder (for a review, see Hameed & Lewis, 2016). Although having a first-degree relative with schizophrenia is understood as the strongest risk factor for the disorder, the majority of the affected individuals do not have a biological relative with schizophrenia (Blackman & MacCabe, 2020). In addition, no single risk gene for the disorder has been identified. As such, these findings most likely reflect both genetic and environmental influences.

Early studies investigating genetic contributions to schizophrenia have used a hypothesis-driven candidate gene approach, which examines the association of a small number of pre-selected genes with a disorder. Although associations between several potential genes and schizophrenia have been found, subsequent research has often failed to replicate the initial reports (Farrell et al., 2015; Zwicker et al., 2018). With the development of molecular genetic technology, genome-wide association studies (GWAS) now allow for a hypothesis-free approach in which the entire human genome can be examined. GWAS have identified an increasing number of genomic loci associated with the risk for schizophrenia (Lam et al., 2019; Ripke et al., 2014), with a recent GWAS identifying 287 genomic loci (Trubetskoy et al., 2022). In GWAS, a large number of weakly associated genetic variants can be combined into polygenic risk scores (PRS). When more weakly associated genetic variants are included in PRS analyses, genes seem to explain a larger proportion of variance in the schizophrenia risk (Sandstrom et al., 2020; Zwicker et al., 2018). Thus, thousands of genetic variants with small effect sizes may contribute to the risk for schizophrenia. Findings also suggest that there is a considerable overlap in the genetic variants associated with psychiatric disorders such as schizophrenia, bipolar disorder, and depression (Uher & Zwicker, 2017). In other words, the same genetic variants may shape the risk for a range of psychiatric disorders, not only schizophrenia.

2.3.2 Environmental factors

Biological environment

Studies have shown that a variety of environmental factors associate with the development of schizophrenia (for a review, see Robinson & Bergen, 2021). Some of the most studied pre- and perinatal exposures include prenatal maternal stress, poor maternal nutrition, abnormal fetal growth and development, and obstetric complications (e.g., hypoxia) (Paquin et al., 2021; Robinson & Bergen, 2021). Findings also support the role of the immune system in the development of the disorder, with viral and bacterial infections associating with later schizophrenia (Khandaker et al., 2012). The effects of viral infections may be particularly deleterious during early stages of development, such as the first trimester of pregnancy (Brown et al., 2004). In addition, season of birth seems to be associated with an increased risk for schizophrenia, which is assumed to be related to the seasonal variation in viral infections (Robinson & Bergen, 2021). Physical factors such as air pollution and vitamin deficiencies have also been suggested to play a mediating role between urbanicity and the risk for schizophrenia, although the existing research evidence is generally weak or inconclusive (Zwicker et al., 2018). Cannabis use, in turn, has been consistently associated with an increased risk for the disorder (for a review, see Godin & Shehata, 2022).

Social environment

Several aspects of the social environment have been linked to the development of schizophrenia. There are findings to suggest that lower educational status of the parents, lower paternal occupational status, and poorer residential area socioeconomic status (SES) associate with the disorder (Werner et al., 2007). Urbanicity and migration are also known to associate with the risk of schizophrenia (Henssler et al., 2020). For a long time, the association between socioeconomic factors and schizophrenia was primarily explained by *social drift* (rather than *causation),* in which psychopathology leads to a downward drift in social class (Heinz et al., 2013). However, more recent findings suggest that social drift does not fully account for this association, and that socioeconomic factors may contribute to the liability to schizophrenia via increased socioenvironmental (and/or physical) exposures (Blackman & MacCabe, 2020; Radua et al., 2018; Saxena & Dodell-Feder, 2022). Such plausible socioenvironmental exposures

include social fragmentation, deprivation, social defeat, exclusion, and discrimination (Heinz et al., 2013; Selten et al., 2013).

Family environment

Earlier studies have demonstrated that several characteristics of the family environment are important determinants of offspring mental health. For instance, childhood adversity (e.g., childhood trauma, physical/emotional abuse, neglect, parental loss) has been studied extensively. A number of studies suggest an association between childhood adversity and psychotic, mood, anxiety, substance, and externalizing disorders (Benjet et al., 2010; Rosenfield et al., 2022; Salokangas et al., 2020).

Another important family environment variable is Communication Deviance (CD) (Singer & Wynne, 1966), which was conceptualized to assess the degree to which the family members are unable to share and maintain a focus of attention during communication. In general, findings suggest an association between parental CD and the development of schizophrenia as well as schizophrenia spectrum disorders more broadly (De Sousa et al., 2014; Roisko et al., 2014; Wahlberg et al., 2004). Moreover, findings from the Finnish Adoptive Family Study of Schizophrenia suggest an interaction between parental CD and high genetic risk for schizophrenia spectrum disorders in predicting later psychiatric morbidity in adoptees (Wahlberg et al., 2004). Based on such findings, it is plausible that parental CD influences the cognitive development of genetically vulnerable adoptees in particular, thus increasing the likelihood of the development of psychiatric disorders (Wahlberg et al., 1997; 2004). Furthermore, the concept of Expressed Emotion (EE) has also received considerable attention in psychiatric research. EE refers to emotional characteristics expressed by relatives towards a family member with schizophrenia. EE is not considered a risk factor for the development of schizophrenia, but high EE (i.e., critical, hostile and/or overprotective attitudes) have been shown to be a strong predictor of relapse (O'Driscoll et al., 2019).

Furthermore, family functioning is a concept which refers to the multifaceted interactions and relationships within the family unit (Buehler, 2020). Some of the central aspects of family functioning include expressed trust, warmth and affection, problem-solving, boundaries between family members and with the outside world, and the presence of anxiety and conflicts (Beavers & Hampson, 2003; Buehler, 2020; Wynne et al., 2006). Findings suggest that dysfunctional processes of the

family associate with a broad range of mental health difficulties in offspring (e.g., Freed et al., 2015; Repetti et al., 2002). Moreover, findings from the Finnish Adoptive Family Study of Schizophrenia suggest that dysfunctional processes of the adoptive family associate with later schizophrenia spectrum disorders and other psychiatric disorders, particularly in genetic high-risk adoptees (Myllyaho et al., 2019; Tienari et al., 2004; Wahlberg et al., 2004; Wynne et al., 2006). On the other hand, these studies also reported that well-functioning rearing may be protective against the development of psychiatric disorders.

It has been suggested that any single environmental exposure on its own is unlikely to cause a severe psychiatric disorder such as schizophrenia (Uher & Zwicker, 2017). Instead, it is more plausible that the risk of developing schizophrenia is shaped by several different environmental factors and their interplay at different stages of life. The same environmental factors may also increase the risk of a variety of psychiatric disorders, and at the same time, not all individuals develop psychiatric disorders under certain environmental exposures (Uher, 2014).

2.3.3 Gene-environment interaction

Twin studies have typically estimated that a large proportion of the heritability of schizophrenia is attributable to genetic factors, and that the shared environment plays little to no role in the etiology of the disorder. On the other hand, epidemiological studies have repeatedly demonstrated associations between different environmental exposures and schizophrenia (Robinson & Bergen, 2021). In addition, heritability estimates from molecular genetic research have been considerably lower compared to twin study estimates (Uher, 2014). A likely explanation to this "heritability gap" is that the twin study estimates reflect gene-environment interactions (GxE) in which genetic and environmental factors jointly influence the development of schizophrenia.

From a theoretical perspective, three basic models have been formulated to describe how GxE may occur (Kendler & Eaves, 1986). The first model is *additive genetic and environmental effects.* The idea of the model is simple: the liability to develop schizophrenia stems from additive effects of genetic and environmental factors (Boomsma & Martin, 2003; Robinson & Bergen, 2021). As an example, an individual with a genetic predisposition to schizophrenia can be assumed to be more likely to develop the disorder compared to an individual without such predisposition. In addition to this predisposition, living in an unfavorable family

environment is an environmental risk factor for schizophrenia. Furthermore, the model assumes that the impact of the environment is the same regardless of an individual's genotype. It also assumes that the likelihood of being exposed to a certain environment is not influenced by an individual's genotype. Thus, the impact of living in any given family environment is the same whether or not an individual has a genetic predisposition to schizophrenia. In addition, an individual's genetic predisposition has no influence on the likelihood of being exposed to an unfavorable family environment.

The second model, *genetic control of sensitivity to the environment*, suggests that genetic factors do not directly influence the likelihood of developing the disorder. Instead, they influence the degree to which an individual is sensitive to their environment. Thus, GxE occur when environmental influences on a trait differ depending on the genetic predispositions of an individual, or when an individual's genetic predispositions are expressed differently depending on the environment (Boomsma & Martin, 2003; Tienari et al., 2004; Tsuang et al., 2004; Van Os et al., 2008). For instance, in an unfavorable family environment, an individual with a genetic predisposition to schizophrenia may be more sensitive to the risk-increasing aspects of the family environment compared to an individual without such predisposition. Thus, an individual with genetic predisposition may be more likely to develop schizophrenia. On the other hand, in a favorable family environment, an individual with genetic disposition may be at very low risk for developing the disorder. For the individual without such predisposition, however, the risk of developing the disorder is only mildly decreased. Thus, an individual's genotype may make them more sensitive to the risk-increasing, but also to the risk-reducing aspects of the environment. The hypothesis that genetic factors explain why individuals respond to the same environment differently has gained support in psychiatric research. Findings from the Finnish Adoptive Family Study of Schizophrenia suggest that, compared to genetic low-risk adoptees, adoptees at high genetic risk for schizophrenia are more sensitive to the unfavorable, but also to the favorable/protective aspects of the rearing environment (Tienari et al., 2004; Wahlberg et al., 1997, 2004). Several findings from molecular genetic research on GxE also support this hypothesis (Uher & Zwicker, 2017).

The third model is *genetic control of exposure to the environment (or gene-environment correlation).* In contrast to previous models, this model assumes that the exposure to certain environments is not random but is driven by differences in individual genotypes (for a review, see Jaffee & Price, 2007; Kendler & Eaves, 1986). Thus, an individual's genotype influences the probability of being exposed

to a certain environment, but the likelihood of developing a disorder such as schizophrenia does not differ between genotypes. As an example, an individual with a genetic predisposition to schizophrenia is at increased risk of being exposed to an unfavorable family environment, therefore increasing the risk of developing schizophrenia. However, the impact of being exposed to an unfavorable family environment does not differ between individuals with and without genetic predisposition to schizophrenia.

Initial examinations of GxE have relied on a method in which a family history of schizophrenia is used as a proxy for genetic risk, and it has been an important step towards understanding how genes and environment may interact. This method has also been criticized, particularly because the information on the individual's full family history of psychiatric disorders may be lacking (Uher, 2014). On the other hand, the strength of this method is that it includes the complete genetic load of an individual (Van Os et al., 2008). Genome-wide environment interaction studies (GWEIS) will likely reveal new information on GxE, although such analyses require substantial statistical power, and thus far, no single GxE identified explains a large proportion of cases (Uher & Zwicker, 2017). Thus, it is likely that several environmental and genetic factors interact at different stages of life to develop a severe psychiatric disorder such as schizophrenia.

2.3.4 Adoption studies of the etiology of schizophrenia

Adoption studies have been a highly valuable method for understanding the significance of genetic and environmental factors in schizophrenia and schizophrenia spectrum disorders (Ingraham & Kety, 2000; Tienari & Wynne, 1994). The major strength of adoption studies is the possibility to separate genetic and environmental factors, given that the biological parents are not the rearing parents (Tienari et al., 2004).

Two major adoption study designs have been utilized. The *adoptees study method,* which is also utilized in this study*,* examines the adopted-away offspring of biological parents with schizophrenia (Heston, 1966; Rosenthal et al., 1971; Tienari et al., 2000). If these offspring show elevated rates of the disorder compared to offspring of non-affected parents, the genetic component of schizophrenia is supported. By assessing the adoptive families, this method allows for an examination of environmental factors and their interaction with the genetic risk of the offspring (Tienari & Wynne, 1994). In addition, the psychiatric status of the offspring may be studied longitudinally and possible vulnerability indicators may

be identified. The second major approach is called the *adoptee's relatives study* (Kety et al., 1976; Kety & Ingraham, 1992), in which biological relatives of adoptees with and without schizophrenia are compared. Elevated rates of the disorder among biological relatives of affected adoptees support the genetic component of schizophrenia.

Wender et al. (1974) utilized a *cross-fostering* approach, in which adoptees born to biological parents with psychiatric disorders of interest are compared with adoptees born to biological parents without such disorders (similar to the *adoptees study method*). In addition, adoptees born to healthy parents are reared by adoptive parents with psychiatric disorders such as schizophrenia. In a fourth approach called the *adoptive parents' method* (Wender et al., 1968), adoptive parents of adoptees with schizophrenia are compared with adoptive parents of healthy control adoptees and with biological parents who have reared their offspring with schizophrenia.

In addition to the strengths of the adoption studies, they are also faced with certain limitations. For instance, it is possible that the adoptees and the adoptive parents may not be representative of the general population (Tienari & Wynne, 1994). In addition, it has been suggested that the potential early environmental influences of the parental psychiatric illness may be difficult to rule out (Ingraham & Kety, 2000).

2.3.5 Vulnerability to schizophrenia

The vulnerability-stress model (Nuechterlein & Dawson, 1984; Rosenthal, 1970; Zubin & Spring, 1977) has been widely used in understanding why some individuals develop schizophrenia under certain conditions while others do not. According to this model, the vulnerability (or diathesis) stems from inherited as well as acquired (e.g., prenatal events) factors, thus originating from the individual. Stress, in turn, is considered external and encompasses a multitude of biological and psychosocial facets (e.g., significant life events) (Cheng et al., 2016). It has also been noted that although stress is considered primarily external, individual vulnerability might influence how stress is perceived and experienced (Kestler et al., 2012). A person who is vulnerable to psychopathology or is already symptomatic might also evoke negative reactions from others, thus playing a role in creating stressful situations (Ingram et al., 1998).

The model presents that when the stress level exceeds the vulnerability of an individual, they may be more likely to develop schizophrenia (Cheng et al., 2016).

In other words, schizophrenia develops as a result of the interaction between the vulnerability and environmental stress (Hankin & Abela, 2005; Monroe & Simons, 1991; Nuechterlein, 1987). On the other hand, protective factors such as positive family and peer relationships and individual resilience may buffer against the development of schizophrenia (Van Orden et al., 2005).

It has been suggested that certain characteristics of an individual may potentially serve as vulnerability indicators, factors, markers, or traits, which in turn make the individual vulnerable to environmental stressors (Nuechterlein & Dawson, 1984). Moreover, vulnerability indicators are thought to be shaped throughout an individual's physiological and psychosocial development and expressed at biological and behavioral levels (Hankin & Abela, 2005; Wynne, 1978). Consequently, studies have sought to identify such indicators as they may be highly useful in identifying those who are potentially at increased risk of developing schizophrenia. Findings suggest that reduced grey matter volume (Fusar-Poli et al., 2011), increased striatal dopamine synthesis (Huttunen et al., 2008), and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Aiello et al., 2012) may reflect biological vulnerability to schizophrenia. Similarly, individuals who have developed schizophrenia have been found to show delays and abnormalities in motor development during early childhood (Filatova et al., 2017). Regarding neurocognition, findings suggest that deficits in the speed of processing, memory, attention, and reasoning may be potential vulnerability indicators (Asarnow et al., 1991; Donati et al., 2020; Keshavan et al., 2010). Studies have also identified deficits in several areas of social cognition (e.g., facial emotion recognition, theory of mind), which is considered separate from, yet related to neurocognition (Eack et al., 2010; Lavoie et al., 2013). Finally, deficits in social functioning have been recognized as potentially important indicators of vulnerability to schizophrenia (e.g., Shim et al., 2008).

2.4 Social functioning

2.4.1 Definition of social functioning

Social functioning has received a lot of attention in psychiatric research and it is considered an important dimension of broader functioning (Nevarez-Flores et al., 2019). The definition of the term "social functioning", however, varies greatly. According to the Handbook of Social Functioning in Schizophrenia (Mueser &

Tarrier, 1998), social functioning refers to the ability to meet societally defined roles (e.g., homemaker, worker, family member, friend) and to individuals' satisfaction with their ability to do so. Similarly, Hooley (2010) defines social functioning as the ability to interact appropriately and effectively in the social world. According to more recent definitions, social functioning refers to the ability to initiate, form and maintain social relationships (Campbell et al., 2015; Wagner et al., 2017), or to the involvement in social interactions and social activities (Velthorst et al., 2017). Similarly, Fulford et al. (2018) define the term as the quantity and quality of interpersonal relationships.

Over time, social functioning has been used interchangeably with several other terms. These related and overlapping terms include, for example, *social adjustment* (the way an individual conforms to social expectations), *social adaptation* (the ability to live in accordance with social and cultural norms), and *social competence* (the appropriate social skills and knowledge needed in everyday social interactions) (Burns & Patrick, 2007; Hooley, 2010). This overlap is mostly related to the broad nature of the term and to the considerable number of scales that measure social behavior.

2.4.2 Social functioning in patients with schizophrenia and other psychiatric disorders

For a long time, impaired social functioning has been recognized as a core feature of schizophrenia (Carrión et al., 2021; Kraepelin, 1919). It is well established that patients with schizophrenia display a variety of social difficulties, including problems in establishing, initiating, and maintaining stable social relationships, maintaining employment, and achieving important social milestones such as marriage (Harvey et al., 2012). Findings suggest that social functioning deficits are highly stable and predictive of the functional outcome (Tarbox & Pogue-Geile, 2008; Velthorst et al., 2017). That is, patients who initially display poor social functioning often show worse functioning throughout the course of the disorder compared to patients with better initial social functioning. Moreover, early social functioning deficits associate with symptom severity, rate of relapse, and the use of mental health services (Bellido-Zanin et al., 2015; Pinkham et al., 2003; Tarbox & Pogue-Geile, 2008).

Given that social functioning deficits are often observed in schizophrenia, studies have also begun to examine the more specific components of social functioning in patients. At least three main components of social functioning have

been recognized (for a review, see Fulford et al. 2018). First, patients with schizophrenia display deficits in their social skills, which refer to the learnable verbal and nonverbal behaviors and abilities essential for successful social interactions (Hooley, 2010). Social skills include behaviors such as active listening, body posture, voice tone, reciprocity, problem-solving and eye contact. As noted by Hooley (2010), poor social skills are likely to evoke negative reactions from others during social interactions, thus contributing to the rejection and avoidance that patients might experience.

Second, studies have documented deficits in patients' social cognition, which is the combination of emotional and cognitive facets that underlie and support social behavior (Fulford et al., 2018). Social cognition includes the domains of emotion recognition and regulation, facial affect recognition, theory of mind, and social perception, for instance (Green et al., 2015; Tikka et al., 2020). It is also noteworthy that while neurocognitive deficits are central symptoms of schizophrenia, social cognitive deficits seem to be more strongly associated with social functioning compared to neurocognition (Fett et al., 2011). Third, patients with schizophrenia have been shown to display deficits in social motivation (Fulford et al., 2018; Moe et al., 2021). Social motivation deficits are reflected as a lack of drive and effort required in forming, initiating, and maintaining social relationships. Although social functioning deficits are emphasized in schizophrenia, similar deficits are also observed in other psychiatric disorders (e.g., depression, bipolar disorder) (Kupferberg et al., 2016; Velthorst et al., 2017). Thus, social functioning deficits are not specific to schizophrenia.

2.4.3 Deficits in social functioning as indicators of vulnerability to schizophrenia and other psychiatric disorders

Findings indicate that social functioning deficits are relatively independent of the clinical state (Cornblatt et al., 2007, 2012; Hooley, 2010). In other words, social functioning deficits are not solely explained by clinical factors such as positive and negative symptoms, or the effects of medication or hospitalizations. Furthermore, social functioning deficits have been observed years before the onset of schizophrenia, even as early as in childhood or early adolescence (Parellada et al., 2017; Tarbox & Pogue-Geile, 2008). As highlighted by Cheng et al. (2016), difficulties in adolescent peer relationships are particularly emphasized in individuals who develop schizophrenia. Moreover, studies have observed longitudinal associations between social functioning and later schizophrenia (e.g.,

Carrión et al., 2021). Such findings support the hypothesis that deficits in social functioning may serve as plausible vulnerability indicators to schizophrenia (Nuechterlein & Dawson, 1984), and as indicated by existing literature, to other psychiatric disorders as well (Cannon et al., 2002).

Social functioning in offspring of parents with schizophrenia and their controls

It is well established that social functioning deficits are observed in children and adolescents who have a first-degree relative (e.g., a parent) with a schizophrenia spectrum disorder. Such findings are primarily based on high-risk studies, which attempt to study the etiology of schizophrenia spectrum disorders by examining individuals who are at an increased risk for developing the disorder (usually based on their family history) (for a review, see Niemi et al., 2003). Findings suggest that high-risk individuals display poorer social functioning relative to low-risk controls: they show poorer relationships with peers and opposite sex and have fewer hobbies and interests (Christiani et al., 2019; Dworkin et al., 1994; Glatt et al., 2006; Hans et al., 2000).

More recent studies have also reported deficits in social cognition, social skills, and social motivation in high-risk individuals (Gibson et al., 2010; Horton et al., 2014, 2017; Lavoie et al., 2013). Furthermore, in a study by Olin et al. (1995) high-risk males who later developed schizophrenia were reported to be more lonely, anxious, rejected and having more disciplinary problems in school during adolescence compared to their low-risk controls. High-risk females were found to be quiet, passive, withdrawn and nervous. In a more recent prospective high-risk study (Tsuji et al., 2013), social functioning deficits during adolescence and genetic risk for schizophrenia spectrum disorders were found to be independent risk factors for later schizophrenia spectrum disorders. No association or interaction between genetic risk and social functioning was found. Overall, these studies did not include measures of the family environment in their analyses.

Social functioning and adoption studies

The number of studies that have utilized an adoptive study design or a similar setting to examine social functioning in high-risk individuals is highly limited. In the Danish Adoption study (Kendler et al., 1981), which utilized the *adoptee's relatives study* approach (see section 2.3.4), the biological relatives of adoptees

with schizophrenia were found to display more social withdrawal and antisocial behavior compared to biological relatives of control adoptees. In addition, biological relatives of adoptees with schizophrenia who displayed childhood social withdrawal were at high risk for developing schizophrenia spectrum disorders in adulthood. The authors emphasized the role of genetic factors in their findings, but no family environmental variables were included in the analyses. In a study by MacCrimmon et al. (1980), offspring of parents with schizophrenia who were placed in foster homes at early age were compared with foster children with no parental psychopathology, and with non-foster children. The high-risk offspring were found to show increased social isolation relative to controls during adolescence. The authors concluded that social isolation may be an important aspect of the etiology of schizophrenia. The rearing environment of the offspring was not assessed.

Considering that the social functioning of an individual is shaped by both genetic and environmental factors, it is noteworthy that the impact of the rearing environment of genetic high-risk offspring is still not comprehensively considered in earlier studies of the topic. Moreover, high-risk studies have typically analyzed offspring who have a biological parent with schizophrenia, but the biological parents are also the rearing parents. The present study from the Finnish Adoptive Family Study of Schizophrenia was focused on analyzing social functioning in adolescence among adoptees at high (HR) and low (LR) genetic risk for schizophrenia spectrum disorders. In the analyses, it was possible to take into consideration the impact of the rearing environment provided by the adoptive family by utilizing the Global Family Ratings, which were assessed for each adoptive family and which measured the level of family functioning.

3 Aims of the study

The aim of the present study was to analyze social functioning in adolescence among adoptees at high and low genetic risk for schizophrenia spectrum disorders. The adoption study design made it possible to take into consideration the impact of the rearing environment provided by the adoptive family. The specific aims of the study were:

1. to examine the differences in adolescent social functioning between adoptees at high and low genetic risk for schizophrenia spectrum disorders (I).
2. to examine the association of adoptees' adolescent social functioning with adoptive family functioning and adoptees' high or low genetic risk for schizophrenia spectrum disorders (II).
3. to examine the association of adoptees' adolescent social functioning with adoptees' later psychiatric morbidity after controlling for the genetic risk of the adoptees and adoptive family functioning (III).

4 Materials and methods

4.1 Study population and data collection

The present study utilizes the nationwide data from the Finnish Adoptive Family Study of Schizophrenia (Figure 1). In the first phase of sample definition, the hospital records of all women (N = 19,447) who had been admitted to Finnish psychiatric hospitals between the years 1960 and 1979 and diagnosed with schizophrenia or paranoid psychosis at least once were identified. Excluded were those women who had received a hospital diagnosis of reactive (psychogenic), manic-depressive or depressive psychosis, or any other disorder (Tienari et al., 2000, 2003). Next, every census and parish register in Finland was searched to identify all women with schizophrenia/paranoid psychosis who had given up a child or children for adoption (HR adoptees), yielding a sample of 291 children of 264 biological mothers (some biological mothers had given up two offspring for adoption). Those children who had been adopted after the age of four, adopted by a relative, or adopted abroad were excluded. After the exclusion, the total sample included 186 HR adoptees of 170 biological mothers. After the HR adoptees were identified, their adoptive families were included in the study population with no diagnostic exclusion criteria applied (Tienari et al., 2000, 2003). This yielded a sample of 185 adoptive families with 186 HR adoptees.

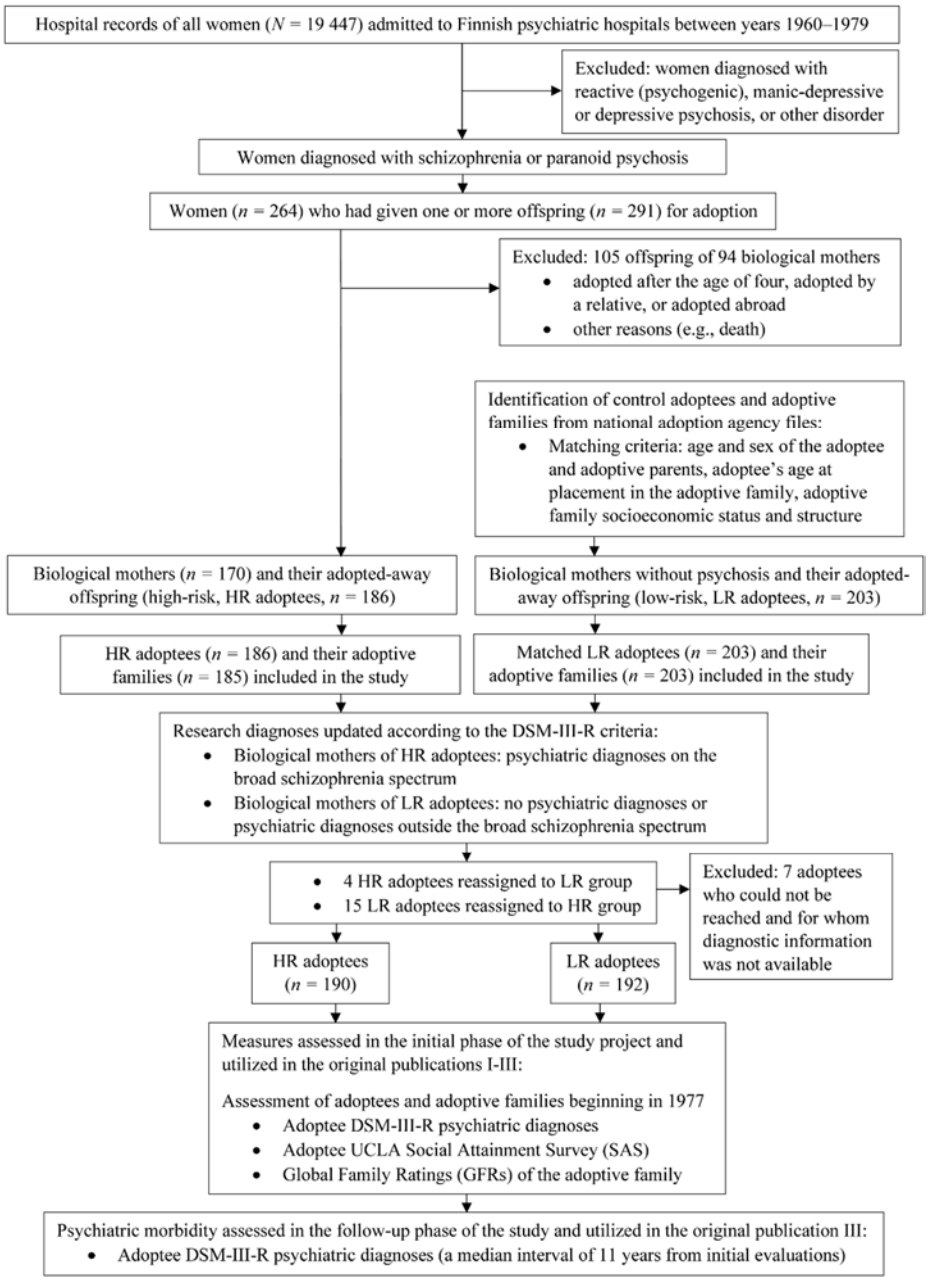

Fig. 1. Flowchart of the study sample selection in the Finnish Adoptive Family Study of Schizophrenia.

Subsequently, the files of a national adoption agency were scrutinized to identify the adoptees and adoptive families that matched with each HR adoptee and adoptive family. The matching criteria included the age and sex of the adoptee and adoptive parents, age of the adoptee at placement in the adoptive family, and socioeconomic status and family structure of the adoptive family. The biological mothers of the LR adoptees were included in the study if they had not been hospitalized for a psychotic disorder. After the matching process, the total control sample comprised 203 LR adoptees reared in 203 adoptive families.

The original screening of the hospital records of high-risk and control biological mothers was based on the classification of ICD-8 or ICD-9 (World Health Organization, 1967, 1978). Later, the research diagnoses of the biological mothers were updated according to the DSM-III-R criteria (American Psychiatric Association, 1987). Consequently, three biological mothers originally assigned to the HR group were assigned to the control group as they were found to have non-schizophrenia spectrum diagnoses. Their four offspring were assigned to the LR group. Also, fourteen biological control mothers were found to have diagnoses on the broad schizophrenia spectrum. Therefore, their 15 offspring were assigned to the HR group. Seven adoptees who could not be reached and for whom diagnostic information was not available were excluded. After the diagnostic reassignment, the two study groups of the Finnish Adoptive Family Study of Schizophrenia included 190 adoptees at high genetic risk for schizophrenia spectrum disorders and 192 genetic low-risk adoptees (Tienari et al., 2000, 2003).

4.1.1 Diagnostic procedure of biological mothers

The final research diagnoses of the biological mothers were obtained by reviewing the initial and subsequent hospital and clinical records and by conducting personal research interviews. In addition, the following Finnish national registers were scrutinized: Cause of Death Register (Statistics Finland), Care Register for Health Care (previously Hospital Discharge Register, THL, 2021), and Pensions Register (the Social Insurance Institution of Finland) (Tienari et al., 2000, 2003). Regarding the biological mothers of HR adoptees, 120 of 170 were personally interviewed. The diagnoses of the non-interviewed mothers (39 had died and 11 refused an interview) were made based on hospital and clinical records and registers. Of the 201 biological mothers of LR adoptees, 121 were diagnosed with DSM-III-R criteria to have psychiatric diagnoses outside the broad schizophrenia spectrum. Of them, 114 mothers were personally interviewed, and seven mothers were diagnosed

based on medical records and phone interviews. For the remaining 80 mothers, registers were checked to confirm that they had not been hospitalized due to a psychiatric disorder. All the diagnosticians were blinded to the genetic risk status of the adoptees.

Based on definitions by Kendler et al. (1996), biological mothers of HR adoptees were classified into broad schizophrenia spectrum group if, according to the DSM-III-R (American Psychiatric Association, 1987), they were diagnosed as follows: schizophrenia, schizotypal, schizoid, paranoid and avoidant personality disorder, schizoaffective, schizophreniform, delusional disorder, and psychotic disorder not otherwise specified, and bipolar and depressive disorders with psychotic features. Biological mothers of LR adoptees had no psychiatric diagnoses or were diagnosed with a psychiatric disorder outside the broad schizophrenia spectrum (Tienari et al., 2000, 2003).

4.1.2 Diagnostic procedure of adoptees

The research diagnoses of the adoptees were made according to the DSM-III-R criteria (American Psychiatric Association, 1987) and were based on all available information from personal interviews, hospital records, and national computerized registers. The initial evaluation of the adoptees was conducted during extensive visits to the adoptive family homes, beginning in 1977. After a median interval of 11 years from the first evaluations, 130 HR adoptees and 148 LR adoptees were individually re-interviewed and re-tested by new experienced research psychiatrists. 89.1% of the HR adoptees and 91.5% of the LR adoptees were personally interviewed either initially or at follow-up, or both. In the initial and follow-up phase, the interviewing psychiatrists were blinded to the genetic risk status of the adoptees (Tienari et al., 2000, 2003). Register information for diagnoses for disability pension, sick leaves, free medication prescriptions, and information about criminality was checked up to the end of 1994. Information for reasons of death and hospital discharges were checked up to the end of 2000 and 2001, respectively (Tienari et al., 2004).

Adoptees' psychiatric status was defined using best-estimate, hierarchically most severe lifetime diagnosis. The diagnostic hierarchy was selected based on the suggestions of Kendler et al. (1996). The hierarchy of the DSM-III-R (American Psychiatric Association, 1987) diagnoses was as follows: 1) schizophrenia and schizoaffective disorder; 2) cluster A of personality disorders; 3) schizophreniform disorder, delusional disorder and psychosis not otherwise specified; 4) affective

psychoses; 5) cluster B personality disorders; 6) non-psychotic affective disorders; 7) cluster C of personality disorders, alcohol disorders and other psychiatric disorders; and 8) no disorder (Tienari et al., 2000). In order to reassess the diagnostic status of the adoptees after the follow-up, the Finnish national Care Register for Health Care (previously referred as Hospital Discharge Register) (THL, 2021) was searched through to 31 December 2006 (Roisko, 2014; Tienari et al., 2003).

4.1.3 Diagnostic reliability

The interrater reliability of the research diagnoses was carefully assessed in the Finnish Adoptive Family Study of Schizophrenia (Tienari et al., 2000). During the initial phase of the study, a sample of 40 subjects was randomly selected and enriched by a subgroup with mental health ratings at a serious level. The kappa coefficient between the Finnish and American (Dr Kenneth Kendler and Dr Lyman Wynne) raters was 0.80. The same process was repeated for the new raters in the follow-up phase, resulting in a kappa coefficient of 0.71. In addition, an additional rater was assigned to independently review every 30th randomly selected subject. This procedure was carried out to prevent possible rater drift, leading to a kappa of 0.77. Possible diagnostic 'problem cases' (e.g., cases producing disagreements between raters) were also carefully reviewed.

4.1.4 Assessment of adoptive families

During the initial phase of the study, starting in 1977, the adoptees and their adoptive families were comprehensively interviewed and observed during visits to their homes. The interviewers were experienced psychiatrists who were blinded to the genetic risk status of the adoptees. The extensive interview procedure of a family usually lasted two days. The duration of the visits together with the familiar environment for the family allowed for a wide range of observations, including aspects of non-verbal communication and emotional atmosphere among family members and other habitual patterns of interaction (Wynne et al., 2006). The semi-structured interview procedure consisted of an interview with the whole family, followed by an interview with the parental couple. Next, the parents and the adoptees were interviewed individually. In addition to the interviews and observations, the evaluation methods included diagnostic personality tests, intelligence tests, and interactional spouse and family tests (Tienari et al., 1987;

Tienari et al., 2005). A psychiatric assessment of the adoptive parents was also carried out. All the interviews and test procedures were tape-recorded.

4.2 Study samples in original publications (I-III)

Figure 2 shows the sample selection process for the original publications I-III. *Original publications I, II:* the studies comprised those adoptees for whom information on the UCLA Social Attainment Survey (UCLA SAS) was available for at least four of seven items of the survey. The subsample consists of 171 adoptees (88 HR and 83 LR) with a minimum age of 16 years.

Original publication III: the study comprised those adoptees for whom information on the UCLA SAS was available for all seven items. Thus, the subsample consists of 117 adoptees (57 HR and 60 LR) with a minimum age of 16 years.

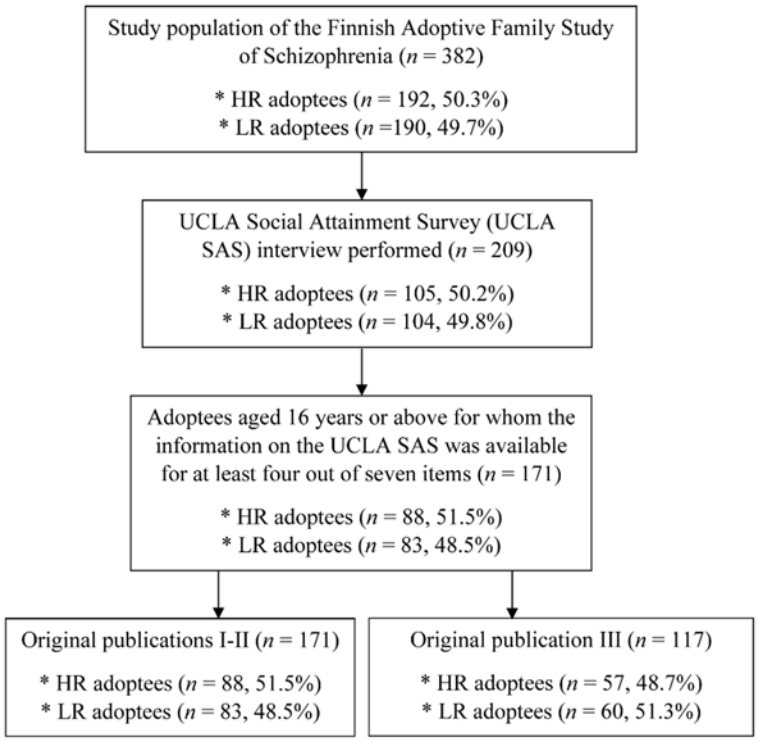

Fig. 2. Flowchart of the selection of study samples in the original publications I-III.

Characteristics of the adoptees with complete data on UCLA SAS interview (n = 117) are presented in Table 2. There were no statistically significant differences in the characteristics between male and female adoptees. When gender differences in these characteristics were assessed using the subsample of 171 adoptees analyzed in the original publications I and II, the results remained unchanged.

Table 2. Characteristics of the adoptees in relation to gender.

Demographics	Total (n = 117)	Male (n = 53)	Female (n = 64)	p
Main variables				
UCLA SAS scores, Mean (SD) [a]				
Overall Social Functioning	23.93 (6.12)	23.21 (6.26)	24.53 (5.99)	0.246
Peer Relationships	6.44 (2.05)	6.43 (2.06)	6.45 (2.05)	0.960
Romantic Relationships	11.0 (3.53)	10.62 (3.73)	11.31 (3.36)	0.295
Involvement in Activities	6.49 (2.23)	6.15 (2.12)	6.77 (2.23)	0.139
Genetic risk (%) [b]				
LR	60	27 (45)	33 (55)	0.947
HR	57	26 (45.6)	31 (54.4)	
Global Family Ratings (%) [b]				
Families with functional processes	48	21 (43.8)	27 (56.3)	0.540
Families with mildly dysfunctional processes	37	18 (48.6)	19 (51.4)	
Families with dysfunctional processes	26	9 (34.6)	17 (65.4)	
Psychiatric status at follow-up (%) [b]				
No	54	25 (46.3)	29 (53.7)	0.841
Yes	63	28 (44.4)	35 (55.6)	
Covariates				
Social class (%) [b]				
I-II	76	37 (48.7)	39 (51.3)	0.317
III-IV	41	16 (39)	25 (61)	
Initial psychiatric status (%) [b]				
No	77	36 (46.8)	41 (53.2)	0.661
Yes	40	17 (42.5)	23 (57.5)	
Age at UCLA SAS assessment, years, Mean (SD) [c]	24.56 (8.45)	25.08 (9.37)	24.14 (7.67)	0.554
Age at placement in adoptive family, months, Mean (SD) [c]	16.20 (13.26)	14.92 (10.78)	17.25 (14.97)	0.346

[a] One-way analysis of variance (ANOVA) was used for UCLA Social Attainment Survey (SAS) score differences.

Demographics	Total (n = 117)	Male (n = 53)	Female (n = 64)	p

[b] The chi-square analyses were used for HR (genetic high risk for schizophrenia spectrum disorders) and LR (genetic low risk for schizophrenia spectrum disorders), Global Family Ratings (GFRs), psychiatric status at initial study phase and at follow-up, and social class group differences.

[c] *T*-test analyses were used for mean age differences.

Social class of the adoptive family was determined according to the four-level Finnish socioeconomic classification, a low number indicating a high social class (Statistics Finland, 17, 1983).

Adoptees' psychiatric status at initial study phase and at follow-up was determined according to the DSM-III-R criteria (American Psychiatric Association 1987).

Global Family Ratings (GFRs): Families with functional processes (GFR categories 1–2), families with mildly dysfunctional processes (GFR category 3), families with dysfunctional processes (GFR categories 4–5). The total *n* on which the percentages are based varies because of missing data for some variables.

4.2.1 Attrition analyses

Attrition analyses were conducted to evaluate the representativeness of the subsamples utilized in the original publications I-III.

Original publications I, II. Given that UCLA SAS is directed to study subjects who have turned 16, the total sample of adoptees was 306. Among them, the information of the UCLA SAS was lacking for 135 adoptees. Thus, original publications I and II analyzed a subsample of 171 adoptees. A comparison of the baseline characteristics was made between this subsample of adoptees (n = 171) and the rest of the adoptees (n = 135) with a minimum age of 16 years during the initial assessment, but on whom the information on the UCLA SAS was lacking. A statistically significant difference between the present subsample and the excluded adoptees was found in the age (in years; mean, SD) of the adoptee during the initial assessment (24.91, SD 8.92 vs. 32.93, SD 8.78, $p < 0.001$). The adoptees in the present subsample were younger compared with the excluded adoptees. A statistically significant difference was also found in the family functioning categories (families with functional processes, 47.1% vs. 33.1%; families with mildly dysfunctional processes, 34% vs. 24.6%; families with dysfunctional processes, 19% vs. 42.4%; $p < 0.001$). The proportion of adoptees belonging to adoptive families with dysfunctional processes was lower in the present subsample. There were no statistically significant differences between these two samples in terms of the age of the adoptee at placement in the adoptive family, sex, genetic risk status or the initial psychiatric status of the adoptee, or the socioeconomic status of the adoptive family.

Original publication III. From the total sample of adoptees with a minimum age of 16 years (n = 306), 117 adoptees had complete information on the UCLA SAS items. Thus, original publication III analyzed the subsample of 117 adoptees. A comparison of the baseline characteristics was made between this subsample of adoptees (n = 117) and the rest of the adoptees (n = 189) with a minimum age of 16 years during the initial assessment, but on whom the information on the UCLA SAS was lacking. A statistically significant difference between the present subsample and the excluded adoptees was found in the age (in years; mean, SD) of the adoptee during the initial assessment (24.56, SD 8.45 vs. 30.85, SD 9.67, $p <$ 0.001). The adoptees in the present subsample were younger compared with the excluded adoptees. There were no statistically significant differences between these two samples in terms of the age of the adoptee at placement in the adoptive family, sex, genetic risk status, initial psychiatric status of the adoptee, follow-up psychiatric status of the adoptee, adoptive family functioning, or the socioeconomic status of the adoptive family.

4.3 Main variables

Figure 3 illustrates the flow of the research design with the main research variables on which the analyses were based on.

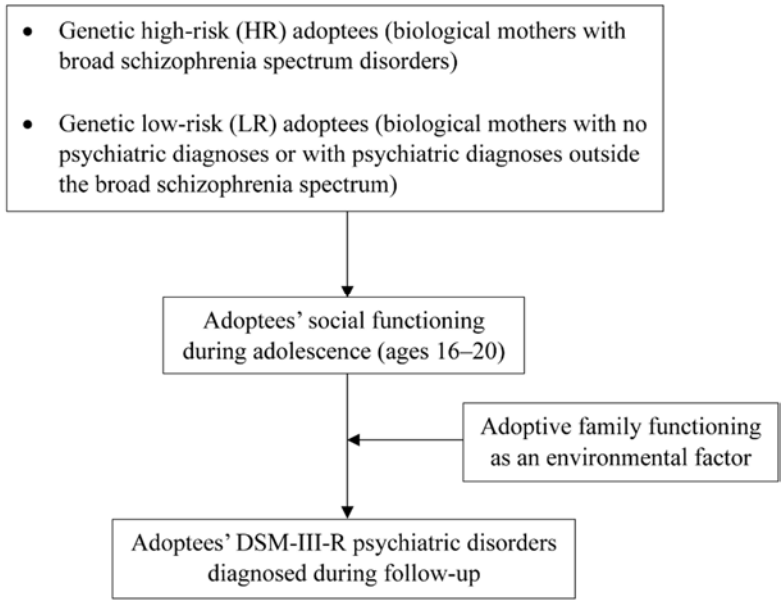

Fig. 3. The research design and the main research variables.

4.3.1 Social functioning during adolescence (I-III)

During the initial phase of the study, adoptees' social functioning during adolescence (ages 16–20) was assessed using the UCLA Social Attainment Survey (UCLA SAS, Goldstein, 1978). The assessment was based on semi-structured interviews conducted by experienced psychiatrists during the visits to the adoptive family homes.

UCLA SAS is a seven-item scale evaluating adolescent social functioning in the areas of peer relationships, romantic relationships, and involvement in activities. It comprises the following items: 1. Same-sex peer relationships, 2. Leadership in same-sex peer relationships, 3. Opposite-sex relations, 4. Dating history, 5. Sexual experience, 6. Outside activities and 7. Participation in organizations. Each item is scored on a scale from 1 (low functioning) to 5 (high functioning), with total scores ranging from 7 to 35. Similar to earlier studies using the UCLA SAS (e.g., (Horan et al., 2006; Subotnik et al., 2000), the following three categories were formed: Peer Relationships (items 1–2), Romantic Relationships (items 3–5), and Involvement in Activities (items 6–7). In addition, the total scores were used to

indicate Overall Social Functioning in this study. See Table 3 for the distribution of adoptees' UCLA SAS scores in original publications I-III.

Table 3. Distribution of adoptees' UCLA Social Attainment Survey (SAS) scores in original publications I-III.

UCLA Social Attainment Survey (SAS) scores, mean (SD)	Original publications I, II (*n* = 171)	Original publication III (*n* = 117)
Overall Social Functioning	23.93 (6.12)	23.93 (6.12)
Peer Relationships	6.78 (2.04)	6.44 (2.05)
Romantic Relationships	11.33 (3.53)	11.0 (3.53)
Involvement in Activities	6.81 (2.24)	6.49 (2.23)

Original publications I, II: the study sample comprised those adoptees for whom information on the UCLA Social Attainment Survey (SAS) was available for at least four of seven items of the survey. Original publication III: the study sample comprised those adoptees for whom information on the UCLA SAS was available for all seven items.

4.3.2 Adoptive family functioning (II, III)

Global Family Ratings (GFRs; Wynne et al., 2006) were used as a measure of adoptive family functioning in the present study. GFRs were assessed during the visits to the adoptive family homes during the initial study phase. The ratings are based on semi-structured family, couple, and individual interviews, as well as on comprehensive and objective observations made by the interviewers.

GFRs were used to evaluate the following family characteristics: 1. Anxiety and its levels, 2. Boundaries between the individual family members, generations, and between the family and the outside world, 3. Parental coalition, 4. Quality of interaction, 5. Flexibility of homeostasis, 6. Transactional defenses, 7. Conflicts, 8. Empathy, 9. Power relations, 10. Reality testing, and 11. Basic trust within the family. Based on these domains, five family functioning categories were formed: 1. Healthy, 2. Mildly dysfunctional, 3. Neurotic, moderately dysfunctional, 4. Rigid, syntonic, and 5. Severely dysfunctional, chaotic families. A detailed description of the five GFRs categories is reported elsewhere (Wynne et al., 2006).

After the adoptive family assessments, each of the interviewers immediately rated the adoptive families they had interviewed. A year later, the interviewers listened and checked the consistency of their ratings. In addition, based on the tape-recorded interviews with the whole families and parental couples, a random sample of 40 families was rated by a core group of interviewers. The reliability assessment

(intraclass correlation coefficient) for the interviewers was 0.72. The reliability assessment was considered satisfactory, especially since each of the families was also observed by one of the interviewers of the core group.

Similar to (Wynne et al., 2006), the five GFRs categories were combined and relabeled into three categories in the present study. Categories 1–2 were combined as "Families with functional processes", given that they can both be considered within the range of healthy and functional family processes in terms of anxiety, boundaries within the family and between outside world and interaction, for instance. "Families with mildly dysfunctional processes" was formed to include category 3 of GFRs, as there were moderate and unresolved conflicts, clear yet mildly angry, restricted, and repetitive interpersonal patterns within the family. Categories 4–5, in which dysfunctional decision-making, unclear boundaries and communication, lack of warmth and open conflicts within the family were often observed, were combined as "Families with dysfunctional processes".

4.3.3 Later psychiatric morbidity of the adoptees (III)

Based on DSM-III-R criteria (American Psychiatric Association, 1987), adoptees' psychiatric morbidity at follow-up was assessed with personal interviews, reviews of hospital records and nationwide social and health care registers, and interviews with family members and other available informants (Tienari et al., 2000, 2003). In the present study, adoptees were divided into two categories based on their psychiatric status: 1) adoptees diagnosed with any psychiatric disorder, and 2) adoptees with no diagnosed psychiatric disorder.

4.4 Background characteristics

The following background characteristics were included in the present study: age of the adoptee at initial study phase (in years) (I-III), and at placement in the adoptive family (in months) (I-III), and sex of the adoptee (female, male). Initial psychiatric status of the adoptees (I-III) was based on DSM-III-criteria (American Psychiatric Association, 1987). The diagnostic procedure of the adoptees is described in section 4.1.2. The adoptees were divided into two categories based on their psychiatric status at the initial study phase: 1) adoptees diagnosed with any psychiatric disorder, and 2) adoptees with no diagnosed psychiatric disorder. Social class of the adoptive family (I-III) was based on a four-level Finnish socioeconomic classification (Statistics Finland 17, 1983), a low number indicating a high social

class. The adoptive families were further dichotomized into two groups as high (groups I-II) and low social class (groups III-IV). The present variables and their status as outcome variables, exposure variables, and covariates in original publications I-III are summarized in Table 4.

Table 4. Outcome variables, exposure variables, and covariates used in original publications I-III.

Variables and their categorization	Outcome variable	Exposure variable	Covariate
Social functioning during adolescence (ages 16–20)	I, II	III	
High or low genetic risk for schizophrenia spectrum disorders (HR, LR)		I-III	
Adoptive family functioning (Families with functional, mildly dysfunctional, and dysfunctional processes)		II, III	
Diagnosed psychiatric disorder at follow-up (yes, no)	III		
Diagnosed psychiatric disorder at initial study phase (yes, no)			I-III
Age at initial study phase (years)			I-III
Age at placement in adoptive family (months)			I-III
Gender (female, male)			I-III
Social class (I-II, III-IV, from high to low)			I-III

4.5 Statistical methods (I-III)

IBM SPSS (Statistical Package for the Social Sciences) version 25 was used in the original publication I, version 26 in the original publication II, and version 27 in the original publication III. In these studies, all tests were two-tailed and the limit for statistical significance was set at $p < 0.05$. Statistical significance of group differences in categorical variables was assessed with Pearson's Chi-square test or Fisher's Exact test. Statistical significance of group differences in continuous variables was assessed with Student's t-test, one-way analysis of variance (ANOVA), Mann-Whitney U test or Kruskal-Wallis test. If the assumptions required by the parametric statistical techniques were not met satisfactorily or if sample size was considered to be too small for parametric analyses, non-parametric tests were applied (Kitchen, 2009). The violation of statistical assumptions was evaluated, for example, by using graphical investigation of the data and homogeneity of variance test.

Original publication I. The differences in adolescent social functioning between adoptees at high and low genetic risk for schizophrenia spectrum disorders were examined using the one-way analysis of variance (ANOVA).

Original publication II. The association of adoptees' adolescent social functioning with adoptive family functioning and adoptees' genetic risk for schizophrenia spectrum disorders (as main effects) was examined using the analysis of covariance (ANCOVA).

Original publication III. The association of adoptees' adolescent social functioning, adoptive family functioning and genetic risk for schizophrenia spectrum disorders to adoptees' psychiatric morbidity at follow-up was examined using a logistic regression analysis.

4.6 Ethical considerations

The study design of the Finnish Adoptive Family Study of Schizophrenia was approved by the Ethics Committee of Oulu University Hospital on May 2, 1988. The study design was reviewed and reapproved on October 15, 1991 by the Ethics Committee of Oulu University Hospital. The study design was evaluated to have followed the ethical practices of the time.

4.7 Personal involvement

The present study is based on an already existing data set, and the author of this thesis has not participated in its collection. Thus, the study subjects were not contacted, met, or interviewed personally.

I, the author, am the first and corresponding author in all original publications (I-III) and contributed substantially to the planning of their study designs. The statistical analyses for the original publications were performed under the supervision of Helinä Hakko, PhD. The results of these analyses were discussed and interpreted together with all the authors. I am responsible for writing the first drafts of the manuscripts and submitting the final drafts to the selected journals.

5 Results

5.1 Adolescent social functioning in genetic high- and low-risk adoptees (I)

When assessing the difference in adolescent social functioning between HR and LR adoptees (see Table 5 and Figure 4), HR adoptees were shown to have lower scores (i.e., poorer social functioning) in all the domains when compared to LR adoptees. HR adoptees scored significantly lower in Overall Social Functioning, Peer Relationships, and Involvement in Activities compared to LR adoptees.

Table 5. HR & LR adoptees' UCLA Social Attainment Scale scores (Modified from paper I: Table 2 © 2020 Elsevier).

	Mean (SD)	min-max	Mean (SD)	min-max	F (df)	*p*
All adoptees	HR (*n* = 88)		LR (*n* = 83)			
Overall Social Functioning	22.4 (6.1)	8–33	25.4 (5.8)	7–35	7.5 (1,115)	0.007
Peer Relationships	6.4 (2.1)	2–10	7.2 (1.9)	2–10	5.7 (1,151)	0.019
Romantic Relationships	11.0 (3.6)	3–15	11.6 (3.4)	3–15	1.0 (1,127)	0.317
Involvement in Activities	6.4 (2.3)	2–10	7.2 (2.1)	2–10	5.3 (1,156)	0.022
Male	HR (*n* = 40)		LR (*n* = 37)			
Overall Social Functioning	21.4 (6.6)	8–33	25.0 (5.5)	11–35	4.6 (1,51)	0.036
Peer Relationships	6.6 (2.1)	2–10	7.3 (2.0)	2–10	2.2 (1,70)	0.141
Romantic Relationships	9.9 (3.9)	3–15	11.5 (3.4)	4–15	2.7 (1,53)	0.109
Involvement in Activities	6.1 (2.5)	2–10	6.9 (2.0)	3–10	2.2 (1,71)	0.145
Female	HR (*n* = 48)		LR (*n* = 46)			
Overall Social Functioning	23.2 (5.6)	12–33	25.8 (6.2)	7–34	2.9 (1,62)	0.091
Peer Relationships	6.2 (2.1)	3–10	7.1 (1.8)	2–10	3.5 (1,79)	0.065
Romantic Relationships	11.8 (3.3)	4–15	11.7 (3.5)	3–15	0.01 (1,72)	0.932
Involvement in Activities	6.7 (2.1)	3–10	7.5 (2.2)	2–10	2.9 (1,83)	0.093

Note: HR = high genetic risk; LR = low genetic risk. One-way analysis of variance (ANOVA) was used for mean differences between UCLA SAS scores.

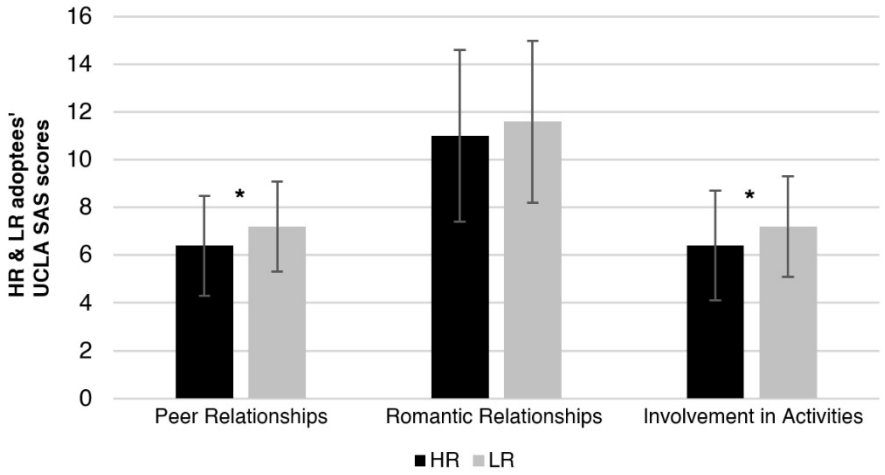

Fig. 4. Mean differences and standard deviations in Peer Relationships, Romantic Relationships, and Involvement in Activities scores between adoptees at high risk (HR) and low genetic risk (LR) for schizophrenia spectrum disorders. *$p < 0.05$ (Reprinted, with permission, from paper I © Elsevier 2020).

5.2 Association of adoptees' adolescent social functioning with adoptive family functioning and adoptees' genetic risk (II)

The impact of adoptive family functioning on adoptees' adolescent social functioning was also evaluated. Table 6 shows that statistically significantly lower scores in Overall Social Functioning, Peer Relationships and Involvement in Activities were observed in adoptees reared in families with dysfunctional processes. Statistically significantly lower scores in Overall Social Functioning, Peer Relationships and Involvement in Activities were observed in female adoptees reared in families with dysfunctional processes. No differences were found between the three family functioning categories in male adoptees.

Table 6. Adoptees' UCLA Social Attainment Survey (SAS) scores according to their adoptive family functioning (Modified from Paper II: Table 2 © 2022 Wolters Kluwer).

UCLA SAS	Families with functional processes	Families with mildly dysfunctional processes	Families with dysfunctional processes	
	Mean (SD)	Mean (SD)	Mean (SD)	*p*
All adoptees				
Overall Social Functioning	25.73 (5.92)	23.22 (5.96)	21.65 (6.05)	0.015
Peer Relationships	7.29 (1.96)	6.44 (1.81)	5.79 (2.33)	0.003
Romantic Relationships	11.90 (3.16)	10.93 (3.59)	10.59 (3.84)	0.220
Involvement in Activities	7.16 (2.08)	6.63 (2.07)	5.79 (2.41)	0.017
Male				
Overall Social Functioning	23.57 (6.77)	22.72 (6.54)	23.78 (5.52)	0.892
Peer Relationships	7.03 (2.30)	6.45 (2.06)	7.36 (1.75)	0.456
Romantic Relationships	11.14 (3.78)	10.33 (3.73)	10.56 (3.32)	0.781
Involvement in Activities	6.48 (2.45)	6.05 (2.04)	6.64 (1.91)	0.705
Female				
Overall Social Functioning	27.41 (4.62)	23.68 (5.49)	20.53 (6.18)	< 0.001
Peer Relationships	7.53 (1.58)	6.42 (1.60)	4.76 (2.11)	< 0.001
Romantic Relationships	12.50 (2.49)	11.38 (3.50)	10.61 (4.16)	0.162
Involvement in Activities	7.71 (1.54)	7.17 (1.99)	5.28 (2.59)	< 0.001

One-way analysis of variance (ANOVA) was used for UCLA Social Attainment Survey (SAS) score differences. Global Family Ratings (GFRs): Families with functional processes (GFR categories 1–2), families with mildly dysfunctional processes (GFR category 3), families with dysfunctional processes (GFR categories 4–5).

The association of adoptive family functioning and adoptees' genetic risk for schizophrenia spectrum disorders with adoptees' adolescent social functioning was analyzed after controlling for the covariates (adoptee's gender and initial psychiatric status, social class of the adoptive family, adoptee's age at placement in the adoptive family, and adoptee's age at UCLA SAS assessment) (Table 7). The variation of Overall Social Functioning and Peer Relationships scores was statistically significantly associated with family functioning (as main effect). Adoptees reared in families with dysfunctional and mildly dysfunctional processes received poorer UCLA SAS scores compared to adoptees reared in families with functional processes. The variation of UCLA SAS Overall Social Functioning, Peer Relationships, Romantic Relationships, and Involvement in Activities scores was

statistically significantly associated with genetic risk (as main effect). HR adoptees scored lower than LR adoptees.

The analyses were verified by excluding the adoptees with initial psychiatric diagnoses, and the major results did not change. In an additional ANCOVA analysis, the interaction between family functioning and genetic risk was tested but no significant interaction effect was found.

Table 7. Adoptees' UCLA Social Attainment Survey (SAS) scores in association to their genetic risk for schizophrenia spectrum disorders and adoptive family functioning (Reprinted, with permission, from paper II © 2022 Wolters Kluwer).

UCLA SAS		Overall Social Functioning			Peer Relationships			Romantic Relationships			Involvement in Activities		
	n	Adj. means (SE)	F	*p*	Adj. means (SE)	F	*p*	Adj. means (SE)	F	*p*	Adj. means (SE)	F	*p*
Main exposures													
Environmental risk													
Families with functional processes	72	25.30 (0.94)	3.64	0.030	6.87 (0.28)	3.30	0.040	11.75 (0.54)	1.61	0.205	6.87 (0.31)	2.33	0.101
Families with mildly dysfunctional processes	52	21.99 (0.98)			5.98 (0.28)			10.48 (0.56)			6.18 (0.32)		
Families with dysfunctional processes	29	22.62 (1.14)			6.09 (0.35)			10.94 (0.67)			5.92 (0.38)		
Genetic risk													
LR	83	25.13 (0.82)	10.87	0.001	6.63 (0.25)	3.95	0.049	11.74 (0.47)	4.59	0.034	6.71 (0.27)	4.97	0.028
HR	88	21.47 (0.81)			5.99 (0.24)			10.37 (0.47)			5.93 (0.26)		
Covariates													
Gender													
Female	94	23.96 (0.73)	1.47	0.228	6.25 (0.22)	0.17	0.681	11.42 (0.42)	1.38	0.243	6.69 (0.25)	4.85	0.029
Male	77	22.65 (0.86)			6.38 (0.25)			10.69 (0.51)			5.95 (0.28)		
Social class													
I-II	114	22.51 (0.68)	2.01	0.159	6.37 (0.20)	0.13	0.721	10.48 (0.40)	3.19	0.077	6.34 (0.23)	0.01	0.910
III-IV	57	24.10 (0.93)			6.25 (0.28)			11.63 (0.54)			6.30 (0.31)		
Initial psychiatric status													
No	125	24.93 (0.78)	6.2	0.014	6.97 (0.22)	11.16	0.001	11.83 (0.44)	4.39	0.039	6.83 (0.24)	5.67	0.019
Yes	46	21.68 (0.97)			5.66 (0.31)			10.28 (0.57)			5.81 (0.33)		
Age at placement			1.45	0.231		7.98	0.005		0.65	0.421		4.84	0.029

UCLA SAS		Overall Social Functioning			Peer Relationships			Romantic Relationships			Involvement in Activities		
	n	Adj. means (SE)	F	*p*	Adj. means (SE)	F	*p*	Adj. means (SE)	F	*p*	Adj. means (SE)	F	*p*
Age at UCLA SAS assessment			1.88	0.173		0.53	0.468		6.88	0.010		0.07	0.795

Analysis of covariance (ANCOVA) was used to assess the statistical significance of the mean differences in UCLA Social Attainment Survey (SAS) scores between the main exposure groups (genetic risk and environmental risk) and covariates (gender and psychiatric status of the adoptee, social class of the adoptive family, and adoptee's age at placement in the adoptive family and at UCLA SAS assessment).

Social class of the adoptive family was determined according to the four-level Finnish socioeconomic classification, a low number indicating a high social class (Statistics Finland, 17, 1983).

Adoptees' initial psychiatric status was determined according to the DSM-III-R criteria (American Psychiatric Association 1987). HR = genetic high risk for schizophrenia spectrum disorder; LR = genetic low risk for schizophrenia spectrum disorder; Global Family Ratings (GFRs): Families with functional processes (GFR categories 1–2), families with mildly dysfunctional processes (GFR category 3), families with dysfunctional processes (GFR categories 4–5). The total *n* varies because of missing data for some variables.

As visualized in Figure 5, adoptees reared in families with dysfunctional and mildly dysfunctional processes had lower Overall Social Functioning scores than adoptees reared in families with functional processes. HR adoptees had lower Overall Social Functioning scores in all three family functioning categories compared to LR adoptees, with a statistically significant difference found in families with functional processes (p = 0.035). Additional analysis showed that after combining the two categories of more dysfunctional family processes (families with dysfunctional and mildly dysfunctional processes) the difference between LR and HR adoptees was statistically significant (p = 0.023). In addition, there was a statistically significant difference (p = 0.043) between LR adoptees in families with functional processes and LR adoptees in the two dysfunctional family processes categories. The difference between their corresponding HR adoptees was marginally significant (p = 0.082).

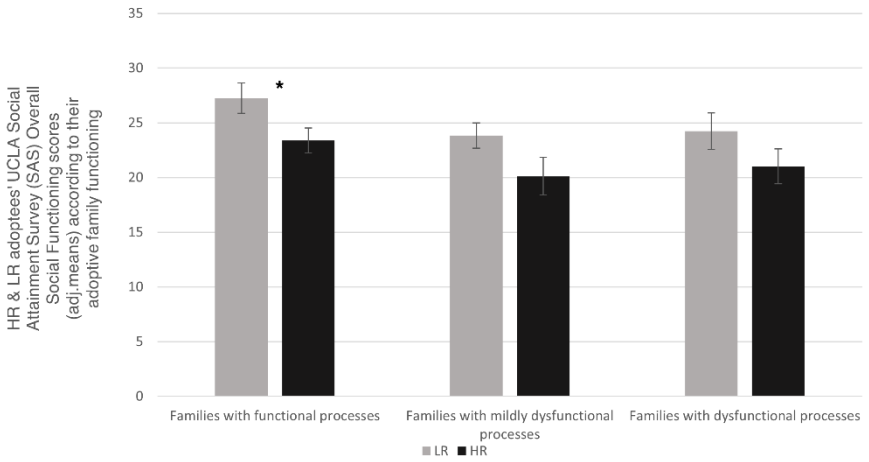

Fig. 5. Genetic high (HR) and low-risk (LR) adoptees' UCLA Social Attainment Survey (SAS) Overall Social Functioning and standard errors according to their adoptive family functioning based on ANCOVAs and adjusted for the covariates (gender and initial psychiatric status of the adoptee, social class of the adoptive family, adoptee's age at placement in the adoptive family, and adoptee's age at UCLA SAS assessment). Note: *p < 0.05. Lower UCLA SAS scores indicate poorer social functioning (Reprinted, with permission, from paper II © 2022 Wolters Kluwer).

5.3 Association of adoptees' adolescent social functioning with later psychiatric morbidity (III)

Adoptees' later psychiatric morbidity was associated with adoptees' adolescent social functioning in relation to adoptees' genetic risk status and levels of adoptive family functioning. Among adoptees without psychiatric disorders, Overall Social functioning scores differed marginally significantly between those reared in adoptive families with functional (Median = 28, Q1-Q3 = 25–31), mildly dysfunctional (Median = 26, Q1-Q3 = 18–28.75) and dysfunctional processes (Median = 24, Q1-Q3 = 19–28) (Kruskal-Wallis, KW-test, p = 0.086 (Figure 6).

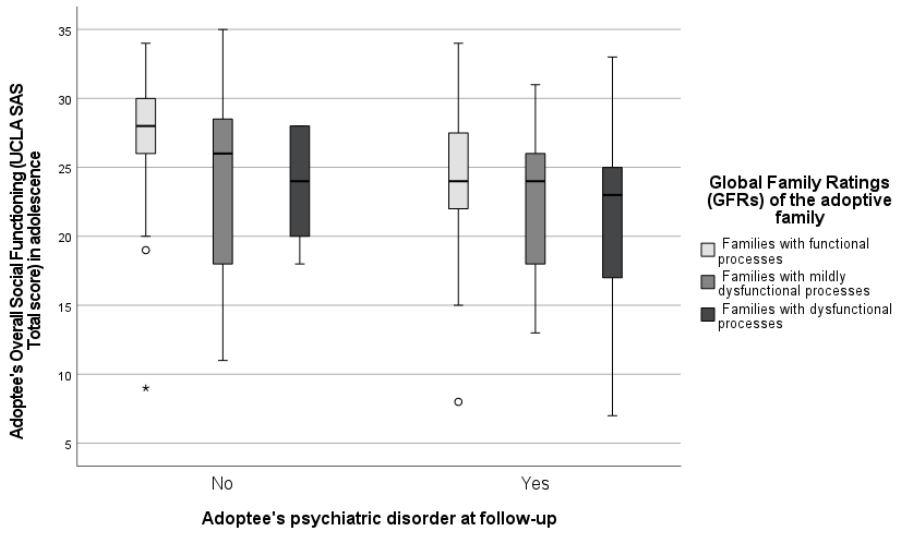

Fig. 6. Box plot of distribution of UCLA Social Attainment Survey (SAS) scores among adoptees with and without psychiatric disorders according to their adoptive family functioning. Global Family Ratings (GFRs): Families with functional processes (GFR categories 1–2), families with mildly dysfunctional processes (GFR category 3), families with dysfunctional processes (GFR categories 4–5). The horizontal lines indicate the median and the box boundaries indicate the quartiles 1 and 3. The whiskers represent the minimum and maximum values. The circles indicate outliers and stars indicate extreme outliers (Reprinted, with permission, from paper III © 2022 Elsevier).

There was also a marginally significant difference in Romantic Relationships between adoptees without psychiatric disorders reared in adoptive families with functional (Median = 13, Q1-Q3 = 12.5–14.5), mildly dysfunctional (Median = 11.5, Q1-Q3 = 6.25–13.75) and dysfunctional processes (Median = 12, Q1-Q3 = 6.5–14.5) (KW-test, $p = 0.091$). Among adoptees with psychiatric disorders, no statistically significant differences were found in any of the UCLA SAS scores between the three family functioning categories.

As Figure 7 illustrates, within HR adoptees the Overall Social Functioning scores in adolescence were significantly lower among adoptees with psychiatric disorders (Median = 22, Q1-Q3 = 17–25) compared to those without psychiatric disorders (Median = 26, Q1-Q3 = 20–30) (Mann-Whitney U test, MWU, $p = 0.025$).

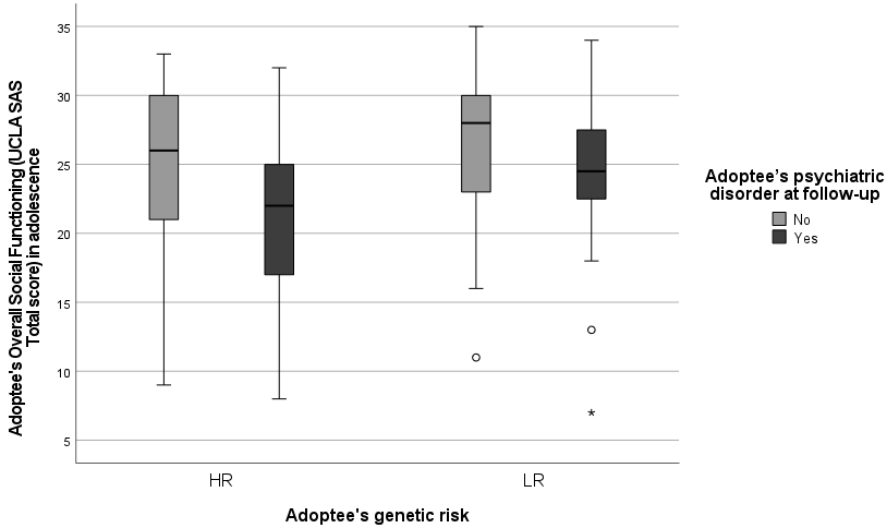

Fig. 7. Box plot of distribution of UCLA Social Attainment Survey (SAS) scores among adoptees with and without psychiatric disorders according to their genetic risk status. HR = high genetic risk for schizophrenia spectrum disorders; LR = low genetic risk for schizophrenia spectrum disorders. The horizontal lines indicate the median and the box boundaries indicate the quartiles 1 and 3. The whiskers represent the minimum and maximum values. The circles indicate outliers and stars indicate extreme outliers (Reprinted, with permission, from paper III © 2022 Elsevier).

In addition, in Peer Relationships and Involvement in Activities, HR adoptees with psychiatric disorders (Median = 5, Q1-Q3 = 3–7) (Median = 6, Q1-Q3 = 3–7) scored significantly lower compared to HR adoptees without psychiatric disorders (Median = 7, Q1-Q3 = 6–8.25, MWU, p = 0.012) (Median = 7, Q1-Q3 = 5–8, MWU, p = 0.017). In LR adoptees, there were no statistically significant differences between those with and without psychiatric disorders in terms of their UCLA SAS scores.

When examining adoptees' later psychiatric morbidity, the likelihood of a psychiatric disorder at follow-up was increased in adoptees who scored lower in Peer Relationships, in adoptees who were reared in adoptive families with dysfunctional processes, and in HR adoptees (Table 8, Model 2). Additional analysis (Model 5) showed that the results regarding the association of the Peer Relationship with the likelihood for psychiatric disorder of the adoptees remained statistically significant even after controlling for the impact of two other domains (Romantic Relationships, Involvement in Activities).

Table 8. The likelihood for psychiatric disorder of the adoptees (Reprinted, with permission, from paper III © 2022 Elsevier).

Characteristics	**Likelihood for any psychiatric disorder at follow-up**		
	Adj. OR*	95% CI	*p*
Overall Social Functioning (total UCLA SAS score) Model 1			
Social functioning, Total score	0.94	0.88–1.02	0.133
Family functioning (ref. families with functional processes)			
Families with mildly dysfunctional processes	1.1	0.41–2.96	0.856
Families with dysfunctional processes	4.52	1.33–15.38	0.016
HR adoptees (ref. LR adoptees)	2.77	1.13–6.78	0.026
Peer Relationships, Model 2			
Score for Peer Relationships - domain	0.77	0.61–0.96	0.02
Family functioning (ref. families with functional processes)			
Families with mildly dysfunctional processes	1.1	0.42–2.93	0.843
Families with dysfunctional processes	4.57	1.32–15.82	0.017
HR adoptees (ref. LR adoptees)	2.91	1.2–7.06	0.018
Romantic Relationships, Model 3			
Score for Romantic Relationships - domain	0.97	0.86–1.1	0.668
Family functioning (ref. families with functional processes)			
Families with mildly dysfunctional processes	1.29	0.49–3.41	0.609
Families with dysfunctional processes	5.41	1.64–17.9	0.006
HR adoptees (ref. LR adoptees)	3.21	1.33–7.72	0.009
Involvement in Activities, Model 4			
Score for Involvement in Activities - domain	0.87	0.71–1.07	0.187

Characteristics	**Likelihood for any psychiatric disorder at follow-up**		
	Adj. OR*	95% CI	*p*
Family functioning (ref. families with functional processes)			
Families with mildly dysfunctional processes	1.19	0.45–3.14	0.726
Families with dysfunctional processes	4.55	1.34–15.46	0.015
HR adoptees (ref. LR adoptees)	2.83	1.16–6.91	0.023
All UCLA SAS domains, Model 5 (combination of Model 2-Model 4)			
Score for Peer Relationships - domain	0.74	0.56–0.99	0.042
Score for Romantic Relationships - domain	1.04	0.9–1.2	0.602
Score for Involvement in Activities - domain	1.01	0.78–1.31	0.935
Family functioning (ref. families with functional processes)			
Families with mildly dysfunctional processes	1.18	0.43–3.25	0.745
Families with dysfunctional processes	4.84	1.34–17.48	0.016
HR adoptees (ref. LR adoptees)	3.1	1.22–7.89	0.018

UCLA SAS = UCLA Social Attainment Survey

Global Family Ratings (GFRs): Families with functional processes (GFR categories 1–2), families with mildly dysfunctional processes (GFR category 3), families with dysfunctional processes (GFR categories 4–5).HR = genetic high risk for schizophrenia spectrum disorders; LR = genetic low risk for schizophrenia spectrum disorders. *Odds Ratios (ORs) with 95% Confidence Intervals (CI) are based on the logistic regression model, in which the likelihood for psychiatric disorder is predicted with the variable(s) for social functioning, genetic risk and family functioning (method = enter) after adjusting (method = stepwise, forward LR) for gender of the adoptee, social class of the adoptive family, adoptee's age at placement in the adoptive family, and adoptee's age at UCLA SAS assessment). Lower UCLA SAS scores indicate poorer social functioning.

6 Discussion

6.1 Overview of the main findings

The aim of original publication I was to examine whether HR and LR adoptees differed in terms of social functioning at ages from 16 to 20 years. The findings showed that HR adoptees displayed poorer social functioning during adolescence compared to LR adoptees. In the light of these findings, it became necessary to get a deeper understanding of the subject; the further step was to analyze whether the rearing environment provided by the adoptive family had an impact on the social functioning of the adoptees in adolescence. Therefore, original publication II aimed to examine adoptees' adolescent social functioning in association to adoptive family functioning and genetic risk of the adoptees. The findings showed that poorer social functioning during adolescence was associated with both dysfunctional processes of the adoptive family and high genetic risk for schizophrenia spectrum disorders. Finally, in original publication III, the aim was to examine whether adoptees' adolescent social functioning would associate with adoptees' later psychiatric morbidity after controlling for the genetic risk of the adoptees and adoptive family functioning. The findings showed that poorer social functioning during adolescence, specifically in peer relationships, was associated with increased likelihood of psychiatric morbidity of adoptees but was independent of the genetic risk status of the adoptees.

6.2 Discussion of the findings

6.2.1 Adolescent social functioning in genetic high- and low-risk adoptees (I)

Poorer social functioning during adolescence was emphasized in HR adoptees compared to LR adoptees, particularly in overall social functioning, peer relationships and involvement in activities. More specifically, HR adoptees reported less initiative-taking in their peer relationships, fewer close peer relations, and less self-initiated participation in social activities outside the home.

These findings are in concordance with previous findings indicating that adolescents at high genetic risk for schizophrenia show poorer peer relationships, reduced engagement in hobbies and interests, and poorer overall social functioning

compared to low-risk controls (Christiani et al., 2019; Dworkin et al., 1994; Glatt et al., 2006). The finding of HR adoptees' lower initiative-taking in peer relationships and self-initiated participation in social activities is also supported by a study in which deficits in social motivation and initiative were observed in high-risk adolescents (Horton et al., 2014). Social motivation, which encompasses the effort and drive required to establish and maintain social relationships, is a key aspect of social functioning (Fulford et al., 2018). Interestingly, in the present study, HR adoptees did not have poorer romantic relationships with the opposite sex than LR adoptees, which differs from findings from previous high-risk studies (Glatt et al., 2006; Hans et al., 2000).

Altogether, the findings from original publication I show that among offspring at high and low genetic risk for schizophrenia spectrum disorders who have not been reared by their biological parents, poor social functioning is emphasized in genetic high-risk offspring. Thus, these findings add weight to findings from earlier high-risk studies in psychiatric populations. The present findings suggest that poor social functioning during adolescence may be linked to high genetic risk for schizophrenia spectrum disorders of offspring, and that poor social functioning during adolescence may be a plausible vulnerability indicator in high-risk individuals.

6.2.2 Association of adoptees' adolescent social functioning with adoptive family functioning and adoptees' genetic risk (II)

In both HR and LR adoptees, poorer overall social functioning and peer relationships were associated with dysfunctional processes of the adoptive family. Moreover, poorer scores in overall social functioning and in all social functioning domains (peer relationships, romantic relationships, involvement in activities) were associated with high genetic risk for schizophrenia spectrum disorders. In addition, HR adoptees were found to display poorer overall social functioning compared with LR adoptees in all family functioning categories (families with functional, mildly dysfunctional, and dysfunctional processes). Poor social functioning was emphasized particularly in HR adoptees reared in adoptive families with dysfunctional processes.

The association between adoptees' social functioning and adoptive family functioning is concordant with previous findings that offspring in general population show poorer friendships and decreased participation in social interactions and increased loneliness when the family environment is characterized

by dysfunctional interpersonal patterns, lack of expressed warmth and empathy, and conflicts (e.g., Mak et al., 2018; Repetti et al., 2002). In the present study, these family characteristics were also included in the definition of adoptive families with dysfunctional family processes. Furthermore, the association between adoptees' social functioning and genetic risk is concordant with findings from several earlier studies, in which poor social functioning was emphasized in offspring at high genetic risk for schizophrenia (Christiani et al., 2019; Dworkin et al., 1994; Glatt et al., 2006; Hans et al., 2000). However, the present adoption study design made it possible to control the impact of the adoptive family functioning when studying this association, thus verifying the findings from earlier high-risk studies from psychiatric populations.

The finding of the present study that HR adoptees showed poorer adolescent social functioning in all family functioning categories may reflect a variety of mechanisms, and one plausible link may be found in social cognition (emotional and cognitive factors underlying and supporting social behaviour; Fulford et al., 2018). First, it has been suggested that deficits in social cognition, such as difficulties in interpreting and attributing intentions and emotions of others, may result from genetically influenced disruptions to certain neural mechanisms (Dodell-Feder et al., 2014). Accumulating evidence suggests that social cognition deficits are potential endophenotypes for schizophrenia (Tikka et al., 2020). In other words, social cognition deficits may serve as trait-like deficits that are found in patients with the disorder and that are present independent of its state. In addition, such deficits are found in unaffected family members at higher rates than in general population, and they are considered heritable (Gottesman & Gould, 2003; Green et al., 2015). Second, family functioning also influences and shapes social cognition, such as emotion regulation abilities, which are essential for positive social interactions. For instance, family conflicts may have a negative influence on adolescents' ability to cope with negative emotions in social situations, leading to poorer social relationships and interactions (Schwarz et al., 2012). Therefore, the finding of the current study that poor social functioning was emphasized in HR adoptees reared in adoptive families with dysfunctional processes may possibly reflect a gene-environment interaction, in which genetic and family environmental factors jointly shape an individual's social cognition.

Altogether, the findings of the original publication II suggest that poor social functioning during adolescence may be emphasized in high-risk psychiatric populations even after controlling for the impact of family functioning, thus strengthening the link between genetic risk for schizophrenia spectrum disorders

and poor social functioning of offspring. In addition, the present findings suggest that poor social functioning may be emphasized particularly in high-risk individuals reared in families with dysfunctional processes. Therefore, in terms of their social functioning, genetically vulnerable individuals might be particularly sensitive to the negative influences of dysfunctional family processes.

6.2.3 Association of adoptees' adolescent social functioning with later psychiatric morbidity (III)

Of all social functioning domains in adolescence, poor peer relationships were shown to be an independent risk factor for later psychiatric morbidity in both HR and LR adoptees. This finding is in concordance with earlier literature suggesting that poor peer relationships during adolescence associate with a wide range of later psychiatric disorders (Cheng et al., 2016; Troop-Gordon et al., 2021). It is also in concordance with findings suggesting that poor social functioning during adolescence may be an indicator of vulnerability to psychiatric disorders in high- and low-risk offspring (Tsuji et al., 2013). Importantly, in the present study, the impacts of both genetic risk and adoptive family functioning on the association of social functioning in adolescence with later psychiatric morbidity were controlled for. Thus, the present findings verify the findings reported in earlier studies in which controlling the impacts of offspring's genetic risk and the rearing environment factors was not possible.

The present finding is of particular importance given that forming, maintaining, and initiating positive peer relationships is considered as one of the central developmental tasks of adolescence (Masten & Coatsworth, 1998). During this period, the role and time spent with peers becomes emphasized, and peers typically become an important source of social support. On the other hand, problematic adolescent peer relationships may also act as a significant source of stress, with such difficulties associating with a range of future negative outcomes including psychopathology (Rubin et al., 2013).

This association, in turn, may reflect a variety of mechanisms. From the perspective of the vulnerability-stress model (Nuechterlein & Dawson, 1984; Rosenthal, 1970; Zubin & Spring, 1977), individuals who lack appropriate social skills needed in positive social interactions (e.g., problem-solving, sensitivity to others, and appropriate verbal and nonverbal behaviors) may be particularly vulnerable to psychosocial distress (Segrin & Flora, 2000). As the demands of the social world increase in adolescence, during which social skills are still being

developed, individuals who display poor social skills may be more likely to face difficulties in their peer relationships (e.g., negative peer interactions, rejection) (Van Orden et al., 2005). This, in turn, may lead to social withdrawal and lack of close and supportive friendships, possibly further hindering the possibilities of the development of intact social skills. It has been suggested that when facing stress, individuals with poor social skills may lack an existing and well-developed social network and the skills needed to access social support (Segrin et al., 2016). Therefore, such individuals might be particularly vulnerable to the negative effects of stress and may be at increased risk for later psychiatric morbidity. Supporting this hypothesis, poor social skills during adolescence associate with psychiatric disorders and various psychosocial problems later in life, while good social skills associate with better later mental health (Hankin & Abela, 2005; Romppanen et al., 2021; Segrin et al., 2016). Moreover, social skills have been shown to be relatively stable traits (Mueser et al., 1991; Obradović et al., 2010). Thus, the role of social skills may provide one possible explanation for the present association between poor adolescent peer relationships and later psychiatric morbidity of adoptees.

It is worth mentioning that in the descriptive analyses, HR adoptees who developed psychiatric disorders displayed significantly poorer overall social functioning, peer relationships and involvement in activities in adolescence compared to HR adoptees who did not develop psychiatric disorders. Thus, it seems that the influences of poor social relationships may be particularly harmful to high-risk individuals, whereas positive social relationships may be highly beneficial. In addition, a noteworthy finding, albeit relating to a small subgroup of HR adoptees, indicated that psychiatric disorders were less prevalent in HR adoptees who were reared in adoptive families with functional family processes and who also displayed good overall social functioning in adolescence. While conclusions should be drawn cautiously, it seems plausible that functional family processes and positive social relationships during adolescence may be protective against psychiatric morbidity in genetic high-risk offspring, which is also supported by earlier studies (Collishaw et al., 2016; Myllyaho et al., 2019; Tienari et al., 2004; Wahlberg et al., 2004).

Altogether, the findings of original publication III highlight poor social functioning during adolescence, particularly in peer relationships, as a plausible risk factor for later psychiatric morbidity in high- and low-risk populations. The present findings also suggest that poor social functioning in adolescence may represent an indicator of vulnerability to later psychiatric disorders.

6.2.4 Strengths of the study

The subsamples analyzed in this study were derived from the nationwide and globally well-known Finnish Adoptive Family Study of Schizophrenia. The major strength of the present study is the adoption study design, in which the genetic risk for schizophrenia spectrum disorders is transmitted from biological mothers to the offspring. The rearing environment of the offspring is shaped by the adoptive family and is therefore comparable between HR and LR adoptees. This enables the examination of both genetic and family environmental factors and their interaction.

Furthermore, the adoption study design made it possible to study the social functioning of adoptees who were not reared by their biological parent with a schizophrenia spectrum disorder. The rearing environment of the adoptees was provided by adoptive families, which made it possible to control the impact of the adoptive family functioning on adoptees' social functioning in statistical analyses. In addition, the longitudinal study design made it possible to study the association of social functioning at ages 16 to 20 years with later psychiatric morbidity in HR and LR adoptees. Adoptees' social functioning during adolescence was assessed using the UCLA Social Attainment Survey (SAS) (Goldstein, 1978), a measure consistently used in research for evaluating social functioning in patients with schizophrenia and other psychiatric disorders.

The strength of the present study is also related to the assessment of the adoptive family functioning (using the Global Family Ratings (GFRs) (Wynne et al., 2006)), which was based on comprehensive interviews and objective observations during visits to the adoptive family homes. In other words, the researchers personally met all the adoptive families at their homes. The extensive procedure of the interviews was conducted using semi-structured questionnaires and was performed by trained researchers. This also made it possible to observe the verbal and non-verbal communication and emotional atmosphere of the adoptive family in great detail. Other considerable strengths include the reliable diagnostics and diverse methodological procedures accomplished by trained and experienced researchers. The psychiatric diagnoses of the study participants were ascertained, in addition to semi-structured interviews, with information obtained from other diagnostically relevant sources (e.g., hospital discharges and national registers). The psychiatric diagnoses of the biological mothers were ascertained so that no HR adoptees were assigned to the LR group, and vice versa. The control biological mothers in this study can be considered to be a control group representative of the nationwide population, given that they had psychiatric diagnoses outside the broad

schizophrenia spectrum or had no psychiatric diagnoses. The researchers who assessed the study participants during the initial study phase and follow-up were blinded to the genetic risk status of the adoptees. HR adoptees and their adoptive families were carefully demographically matched with LR control adoptees, and their adoptive families based on the age and sex of the adoptee and adoptive parents, age of the adoptee at placement in the adoptive family, and socioeconomic status and family structure of the adoptive family. In addition, the adoptive parents were included as a diagnostically unscreened sample in this study.

6.2.5 Limitations of the study

During the initial study phase, some of the adoptees had already passed the age range regarding the assessment of adolescent social functioning with the UCLA SAS (16–20 years). For this reason, the possibility of recall bias cannot be ruled out. It is noteworthy, however, that the adoptees were relatively young during the assessment (mean age approximately 25 years). It may therefore be assumed that the adoptees were able to recall the aspects of their social relationships quite well. On the other hand, this may have raised the possibility of recency bias, in which the most recent life events are emphasized. However, the level of social functioning during adolescence has been found to be relatively stable over time (Cornblatt et al., 2007, 2012; Velthorst et al., 2017). It is also noteworthy that UCLA SAS does not acknowledge romantic relationships with the same sex.

It should be noted that while the majority of adoptees did not meet the diagnostic criteria for any psychiatric disorder during the initial assessment, some adoptees in the original publication III already had a psychiatric diagnosis at this time. Thus, while deficits in adolescent social functioning may raise the likelihood of the development of a psychiatric disorder, it is also possible that individuals' psychiatric disorder causes difficulties in their social relationships and interactions (Romppanen et al., 2021). Indeed, it is well-known that many psychiatric disorders negatively affect the social functioning of an individual (Saris et al., 2017; Velthorst et al., 2017). However, a substantial body of evidence indicates that social functioning deficits may be independent of the clinical state of the manifested disorder (e.g., positive, or negative symptoms) and that they are not explained by the effects of medications and hospitalization, for instance (e.g., Addington et al., 2019; Cornblatt et al., 2012; Hooley, 2010). It has been suggested that social functioning deficits in adolescence may be indicators of relatively stable underlying vulnerability (Cornblatt et al., 2007, 2012; Shim et al., 2008), and that these deficits

may be present before, during and after the onset of illness in vulnerable individuals (Nuechterlein & Dawson, 1984). In addition, considering the time of data collection, it is noteworthy that this study does not take into account possible neurodevelopmental disorders in adoptees. According to current understanding, there is a genetic and phenotypic overlap between autism spectrum disorders and schizophrenia (e.g., poor social functioning) as well as considerable comorbidity between such disorders (Hossain et al., 2020; St Pourcain et al., 2018; Uher & Zwicker, 2017). In fact, over the recent decades, such disorders have been posited under a hypothetical genetic neurodevelopmental continuum (Morris-Rosendahl & Crocq, 2020). Rather than being discrete entities, these disorders may represent a wide range of outcomes resulting from disrupted brain development.

Given the cross-sectional nature of the assessment of Global Family Ratings (GRFs), it was not possible to evaluate the impact of changes which may have occurred in adoptive family functioning over time. However, many studies have shown stability in family functioning-related factors, including communication (e.g., Nugter et al., 1997; Roisko, 2014; Wahlberg et al., 2001). A limitation is that the information on biological fathers was limited, unknown, or based on unreliable sources, and thus was not included in the analyses. It is also noteworthy that the present adoption study design does not make it possible to control the prenatal environment due to lack of such information.

The subsample utilized in original publications I and II covered 56% of the original sample aged 16 years or older. The subsample of adoptees was significantly younger and the proportion of those belonging to adoptive family with dysfunctional processes was lower compared with the sample of excluded adoptees. The potential impact of these variables on the UCLA SAS scores and other variables (the age at placement in the adoptive family, sex, genetic risk and the initial psychiatric status of the adoptees, the socioeconomic status of the adoptive family) was statistically controlled in the covariance analyses in original publication II. The subsample utilized in original publication III covered 38% of the original sample aged 16 years or older. In this study, the subsample of adoptees was younger compared to the adoptees in the excluded sample. The potential impact of adoptees' age at initial assessment was controlled for in the regression analyses in original publication III together with other covariates (the age at placement in the adoptive family, sex and genetic risk of the adoptees, and the socioeconomic status of the adoptive family). Furthermore, given the moderate sample sizes in original publications I-III and the limited number of cases in some subgroup analyses, it is possible that some findings were due to chance (type I error)

and that some findings could not be detected due to lack of statistical power (type II error).

7 Conclusions

7.1.1 Main conclusions

The present study is a part of the nationwide Finnish Adoptive Family Study of Schizophrenia and was focused to analyze social functioning in adolescence among adoptees at high (HR) and low (LR) genetic risk for schizophrenia spectrum disorders. The impact of the adoptive rearing environment could be taken into consideration in analyses by utilizing the Global Family Ratings (GFRs), which measured the level of family functioning.

The current study findings contribute to the earlier literature by showing that poor social functioning during adolescence may be emphasized in HR adoptees, even when the impact of the rearing environment is taken into consideration. Thus, the present findings suggest a plausible link between poor social functioning during adolescence and high genetic risk for schizophrenia spectrum disorders. Moreover, poor social functioning during adolescence was emphasized in HR adoptees who were reared in adoptive families whose family processes were considered dysfunctional. This indicates that, in terms of their social functioning, offspring who are at genetic risk for schizophrenia spectrum disorders might be particularly sensitive to the negative influences of dysfunctional family processes. In the present study, poor social functioning during adolescence, specifically in peer relationships, was found to be an independent risk factor for later psychiatric morbidity in both HR and LR adoptees. This finding suggests that poor social functioning during adolescence may be an indicator of vulnerability to later psychiatric disorders in offspring regardless of their genetic risk status.

7.1.2 Clinical implications

The present study offers a number of viewpoints that can be utilized in identifying individuals who may be at increased risk for psychiatric disorders and in recognizing targets for preventive strategies. First, the present findings underscore the importance of functional family processes in adolescent social functioning, particularly in offspring at high genetic risk for schizophrenia spectrum disorders. Thus, families with a severe parental psychiatric disorder represent potentially important targets for family-based interventive approaches with a focus on enhancing the quality of intra-familial relationships and atmosphere. On the other

hand, in the present study, poor social functioning was not limited to genetic high-risk adoptees reared in families with dysfunctional processes but was also observed in genetic low-risk adoptees reared in such families. The present findings emphasize that although adolescence is traditionally associated with increased independence, the family environment also continues to play an important role in offspring's social well-being during this developmentally sensitive period. Thus, the information gained from this study may be universally utilized in informing and developing services aimed to support the family system and social development of adolescents.

The current findings also showed that adoptees who displayed poor peer relationships during adolescence were at increased risk for later psychiatric disorders regardless of their genetic risk status. Therefore, interventions aimed at supporting and enhancing the familial psychosocial environment could have long-lasting implications for the social relationships of adolescents, and together, they may potentially function as protective factors against later psychiatric morbidity in offspring.

Attention should be directed to not only to families, but also to other key social environments (e.g., schools) and their fundamental role in promoting the social development and functioning of children and adolescents. As indicated by earlier research, teachers may be particularly valuable in identifying early social functioning deficits in vulnerable individuals (Tsuji et al., 2013). Moreover, enhancing and developing community-based leisure activities may be highly beneficial from the perspective of experienced social support and development of social skills in children and adolescents. Supporting this notion, earlier study findings suggest that high participation in social leisure activities at a young age may be protective against later psychiatric morbidity (Timonen et al., 2021). The potential benefits of individual psychosocial interventions, such as social skills training, should also be considered (e.g., Browne et al., 2020).

7.1.3 Research implications

There are several implications for future research. First, the measure of adolescent social functioning used in the present study (UCLA SAS, Goldstein, 1978) assesses social functioning in key areas of adolescence (peer relationships, romantic relationships, involvement in activities). However, future studies should also aim to collect information regarding the more specific components of social functioning (e.g., social cognition, social skills). In general, existing high-risk studies from

psychiatric populations have mostly focused on either the key areas of social functioning (e.g., Dworkin et al., 1994; Glatt et al., 2006; Hans et al., 2000) or its components (e.g., Gibson et al., 2010; Horton et al., 2014, 2017). For a more comprehensive understanding of the topic, future studies should consider both viewpoints when assessing the social functioning in offspring at high and low risk for schizophrenia spectrum disorders and in vulnerable children and adolescents in general (e.g., those experiencing childhood adversity; Felitti et al., 1998),

Furthermore, the present findings showed that poor peer relationships during adolescence were associated with later psychiatric morbidity in adoptees at high and low genetic risk for schizophrenia spectrum disorders. As highlighted by Troop-Gordon et al. (2021), the process in which poor peer relationships lead to psychopathology is likely to be complex and cyclical, and the stress related to peer difficulties and psychopathology may reinforce each other over time. Therefore, future research should aim to better understand the possible mechanisms that may explain the association between poor adolescent peer relationships and later psychiatric morbidity. Such studies should also consider the impact of the family rearing environment and its role as a potentially protective factor against later psychiatric morbidity in adolescents.

The present study analyzed the later psychiatric morbidity of adoptees based on the presence or absence of any DSM-III-R (American Psychiatric Association, 1987) psychiatric disorder during the follow-up phase of the study. To date, most earlier studies examining the social functioning in offspring at high genetic risk for schizophrenia have focused on the development of schizophrenia, or schizophrenia spectrum disorders more broadly. For future research, it would be highly informative to study the association between high-risk offspring's adolescent social functioning and later psychiatric morbidity on a general level (i.e., not only on a diagnosis-specific level).

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Original publications

I Tikkanen, V., Siira, V., Wahlberg, K-E, Hakko, H., Läksy, L., Roisko R., Niemelä, M., & Räsänen, S. (2020). Adolescent social functioning in offspring at high risk for schizophrenia spectrum disorders in the Finnish Adoptive Family Study of Schizophrenia. *Schizophrenia Research, 215*, 293–299. https://doi.org/10.1016/j.schres.2019.10.013.

II Tikkanen, V., Siira, V., Wahlberg, K-E, Hakko, H., Myllyaho, T., Läksy, L., Roisko R., Niemelä, M., & Räsänen, S. (2022). Adolescent social functioning deficits in association with adoptive family functioning and genetic risk for schizophrenia spectrum disorders: The Finnish adoptive family study of schizophrenia. *Journal of Nervous and Mental Disease, 210(6),* 418-425. https://doi.org/10.1097/NMD.0000000000001483

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