



Interaction of genetic vulnerability to schizophrenia and family functioning in adopted-away offspring of mothers with schizophrenia

Toni Myllyaho^{a,*}, Virva Siira^{b,*}, Karl-Erik Wahlberg^a, Helinä Hakko^c, Kristian Läksy^d, Riikka Roisko^c, Mika Niemelä^{c,e}, Sami Räsänen^c

^a Faculty of Medicine, Department of Psychiatry, University of Oulu, P.O. Box 5000, Oulu 90014, Finland

^b Faculty of Education, University of Oulu, P.O. Box 2000, Oulu 90014, Finland

^c Department of Psychiatry, Oulu University Hospital, P.O. Box 26, Oulu 90029, Finland

^d Social Security Institute of Finland (SSI), Helsinki, Finland

^e Department of Medicine, Center for Life Course Health Research, University of Oulu, P.O. Box 5000, Oulu 90014, Finland

ARTICLE INFO

Keywords:

Adoption study
Gene-environment interaction
Psychiatric morbidity
Adverse childhood experience

ABSTRACT

Objective: The aim of this study was to examine the association of family functioning to psychiatric disorders of adoptees with and without genetic vulnerability to schizophrenia.

Methods: The data is based on the Finnish Adoptive Family Study of Schizophrenia. The study sample consisted of 346 adoptive families, of which 175 adoptees had high (HR) and 171 low (LR) genetic risk for schizophrenia. DSM-III-R was used for diagnostic criteria. Family functioning was assessed using the Global Family Ratings. Childhood adversities covered early parental divorce and death occurring before 18 years of age of the adoptees. **Results:** Approximately two thirds of the adoptees had lived in families with mildly dysfunctional processes (30%) or dysfunctional processes (28.4%). An increased likelihood for psychiatric disorders of the adoptees was related to dysfunctional family processes both in HR (OR = 4.8, 95% CI 2–11.4) and LR (OR = 2.6, 95% CI 1.1–6.3) adoptees, but not to early parental death or divorce.

Conclusions: The risk for psychiatric disorders was increased for adoptees in families with dysfunctional processes, especially for those adoptees with genetic vulnerability to schizophrenia. These results emphasize the importance of policies and practices that aim to strengthen and support family functioning.

1. Introduction

Dysfunctional family and disturbed family environment are adversities related to the development of schizophrenia and other psychiatric disorders (Nickerson et al., 2013; Rubino et al., 2009; Schroeder et al., 2016; Wynne et al., 2006a). Previous research has widely documented that family environment risk factors, such as emotional and psychological abuse (Pietrek et al., 2013; Rubino et al., 2009; Varese et al., 2012), family discord (Pirkola et al., 2005; Rubino et al., 2009) and adverse rearing experiences (Helgeland and Torgersen, 2005; Wynne et al., 2006a, 2006b) increase the risk for the development of psychiatric disorders.

The stress-vulnerability model suggests that latent individual vulnerability, in interaction with stressful environmental circumstances, may develop into schizophrenia or other psychosis. The severity of the stressors, in combination with individual vulnerability, largely determines how the environmental stressors influence the psychological

development of an individual (Hankin and Abela, 2005; Nuechterlein, 1987; Rosenthal, 1970; Zubin and Spring, 1977). In addition to inherited vulnerability, environmental factors, such as the interactions between peers or other family members, are thought to have the potential to both reduce and enhance the risk of individuals developing psychiatric disorders (Nuechterlein, 1987; Zubin and Spring, 1977).

Individuals who are genetically vulnerable to schizophrenia are suggested to be oversensitive to environmental stressors and adverse life events, which may increase the risk of developing schizophrenia or other psychotic disorders (Read et al., 2001). However, accumulating evidence from several studies have strongly suggested that the genetically vulnerable offspring of schizophrenic parents are at increased risk, not only of schizophrenia spectrum disorders (Erlenmeyer-Kimling et al., 1997; Gottesman et al., 2010; Hans et al., 2004; Parnas et al., 1993; Tienari et al., 2000; Sørensen et al., 2009), but also of non-psychotic disorders, such as anxiety disorders and avoidant personality disorder (Parnas et al., 1993; Schubert and McNeil, 2003; Tienari et al.,

* Corresponding authors.

E-mail addresses: tmyllyah@student.oulu.fi (T. Myllyaho), virva.siira@oulu.fi (V. Siira).

<https://doi.org/10.1016/j.psychres.2019.06.017>

Received 25 February 2019; Received in revised form 12 June 2019; Accepted 13 June 2019

Available online 13 June 2019

0165-1781/ © 2019 Elsevier B.V. All rights reserved.

2000).

Family dysfunctions are caused by conflictual and disturbed behavior within the family environment. These family disruptions can be caused by structural changes such as parental death or divorce (Gilman et al., 2003). Previous research findings have documented that early parental divorce may have a stronger association to the offspring's health and psychosocial well-being than exposure to early parental death (see Lang and Zagorsky, 2001; Larson and Halfon, 2013; Mack, 2001; Tennant, 1988). For example, the study by Larson and Halfon (2013) showed that offspring with early parental divorce had lower educational level, were more socially isolated and more prone to depression than the offspring with no parental divorce or with parental death.

The studies examining associations between early parental death and schizophrenia spectrum disorders and other psychiatric disorders in the children, have reported inconclusive results. The study by Ragan and McGlashan (1986) showed that early parental death was not associated to the development of schizophrenia in the offspring. This finding has been replicated in several other studies of schizophrenia spectrum disorders and psychiatric disorders in general (Cuijpers et al., 2011; Furukawa et al., 1998; Rubino et al., 2009; Schroeder et al., 2016; Varese et al., 2012). However, some studies have found early parental death to positively associate with psychiatric morbidity (Agid et al., 1999; Mack, 2001). Parental death during the early years of childhood is suggested to be a more prominent risk factor for schizophrenia spectrum outcomes in the offspring than parental death in adolescence (Agid et al., 1999).

Parental divorce is often associated to psychiatric disorders in the offspring, including major depression (Barrett and Turner, 2005; Shafer et al., 2017), schizophrenia and psychiatric morbidity in general (Hansagi et al., 2000). Hansagi and colleagues (2000) consider parental divorce as a severe risk factor for vulnerable individuals. Amato and Cheadle (2008) showed that the impact of parental divorce was comparable between biological and adopted children. In the Northern Finland 1966 birth cohort study by Mäkiyö et al. (1998) schizophrenia developed by the age of 28 years was not associated to living in single-parent families during childhood and adolescence.

Disadvantageous and stressful rearing environments in childhood and adolescence are reported to interact with genetic liability for the development of schizophrenia (Marcus et al., 1987; Mäki et al., 2005; Roisko et al., 2011; Tienari et al., 2004; Wahlberg et al., 2004; Wynne et al., 2006a). The results of earlier studies from the Finnish Adoptive Family Study of Schizophrenia have demonstrated that the adoptees at high genetic risk of schizophrenia are more sensitive to rearing environment adversities compared to the adoptees at low genetic risk (Siira et al., 2007; Tienari et al., 2004; Wahlberg et al., 2004; Wynne et al., 2006a). Accordingly, healthy rearing practices or low genetic risk, are shown to be protective factors against the development of offspring developing schizophrenia spectrum disorders (Tienari et al., 2004; Wahlberg et al., 1997; Wynne et al., 2006a).

The current study utilizes the gene-environment interaction (GxE) model, which includes both genetic and environmental hypotheses (Tienari et al., 2003, 2004; Wahlberg et al., 1997, 2004). In the *genetic control of sensitivity to the environment* model, it is hypothesized that genetic inheritance regulates individual responses to environmental stressors, and makes some individuals oversensitive to these stressors (Kendler et al., 1996). The adoptee study design provides a method for investigating environmental factors, disentangled from genetic factors, aiming to increase research-based evidence and understanding on the development of schizophrenic psychopathology and other psychiatric disorders (Tienari et al., 2000).

The focus of the present study was to pursue further research-based evidence of gene-environment interactions in the development of psychiatric disorder in the adoptees. We examine the association of adverse family processes to psychiatric morbidity in the adoptees with and without genetic vulnerability to schizophrenia. We hypothesize that adoptees at high genetic risk for schizophrenia, compared to adoptees

at low risk, are more vulnerable to adversities in family functioning, leading to an increased risk of developing a psychiatric disorder. Furthermore, we hypothesize that low genetic risk for schizophrenia, as well as functional family processes, are protective factors against psychiatric morbidity developing in the adoptees.

2. Methods

2.1. Participants

This study uses national data from the Finnish Adoptive Family Study of Schizophrenia. The study population was based on the hospital records of all women ($n = 19447$) who were admitted to Finnish psychiatric hospitals between the years 1960–1979. These records were scrutinized, with the objective of identifying all women (Tienari et al., 2000, 2003) who had been diagnosed with schizophrenia or paranoid psychosis (Kendler et al., 1993; Asarnow et al., 2001). The exclusion criteria included diagnoses of reactive (psychogenic) psychosis, manic-depression, depression, or any other disorder. The research diagnoses of biological parents were obtained by applying the DSM-III-R criteria (American Psychiatric Association, 1987) to their hospital records.

All biological mothers were further reviewed through national census and parish registers, to identify those who had given at least one child to adoption. No psychiatric diagnostic exclusion criteria were applied to the adoptive parents (see Tienari et al., 2000, 2003, 2004, for further details of the exclusion and selection criteria, study design and diagnostic procedures).

The psychiatric status of the adoptees was assigned using their hierarchically most severe lifetime diagnosis. The arrangement of the psychiatric disorders and schizophrenia spectrum disorders was based on the suggestions of Kendler et al. (1996), Tienari et al. (2003), Wynne et al. (2006a). The diagnoses were based on psychiatric hospital records, national registers, semi-structured initial interviews and structured follow-up interviews with the adoptees. The kappa coefficient for interrater reliability of the diagnostic evaluation of the adoptees was 0.71–0.80 (see Tienari et al., 2000 for more details).

The adoptees were defined as being at high risk (HR) of schizophrenia spectrum disorder, if their biological mother was verified as having a schizophrenia spectrum disorder, while low risk (LR) adoptees were those having been given up for an adoption by biological mothers with a non-spectrum diagnosis or without any psychiatric disorder (Tienari et al., 1987a, 2000). The adoptees excluded included those adopted by a relative or adopted after the age of four (Tienari et al., 2000). The final study population of the Finnish Adoptive Family Study of Schizophrenia consisted of 382 adoptees. Of them, 190 adoptees were at high-risk (HR) and 192 adoptees at low risk (LR) for schizophrenia spectrum disorders. (Tienari et al., 2003, 2004). The research protocol included an evaluation of the adoptive families in their homes, with comprehensive and intensive procedures performed by experienced psychiatrists (Tienari et al., 1987a). The procedures included family observations, whole family interviews, parent and individual interviews and individual, couple and family tests (Tienari et al., 1987a, 2005). The refusal rate of family interviews was 6.8% (Tienari et al., 2005).

In the present study, we examine a subsample of 346 adoptees (175 HR adoptees, 171 LR adoptees) and their adoptive families, for whom the information on early parental death, early parental divorce and the data of family functioning measured by the Global Family Ratings (GFRs; Tienari et al., 1987a, 1987b; Wynne et al., 2006a) was available for statistical analyses.

2.2. Measures

2.2.1. Psychiatric disorders of the adoptees

The major psychiatric disorders of the adoptees were based on DSM-III-R criteria (American Psychiatric Association, 1987). These disorders

were categorized into three groups as follows: schizophrenia spectrum disorders ($n = 45$), psychiatric disorder other than schizophrenia spectrum disorder ($n = 112$) and no psychiatric disorder ($n = 189$). The category of schizophrenia spectrum disorders (HR, $n = 37$; LR, $n = 8$) included diagnoses for schizophrenia, the odd-cluster personality disorders (schizotypal, schizoid and paranoid personality disorders plus avoidant personality disorder), non-schizophrenic non-affective psychoses (schizoaffective, schizophreniform, and delusional disorders and psychotic disorder not otherwise specified), and affective psychoses (bipolar and depressive disorders with psychotic features) (Kendler et al., 1996; Tienari et al., 2003).

The psychiatric disorders other than a schizophrenia spectrum disorder (HR, $n = 61$; LR, $n = 51$) included alcohol abuse, eating disorders, anxiety disorders, major depression disorder, dysthymic disorder, depressive disorder not otherwise specified, obsessive-compulsive disorder, somatoform disorder, antisocial personality disorder, borderline personality disorder, narcissistic personality disorder, histrionic personality disorder, dependent personality disorder and personality disorder not otherwise specified (Tienari et al., 2003). The third group, adoptees with no psychiatric disorder, included the adoptees without a history of any psychiatric disorder (HR, $n = 77$; LR, $n = 112$).

For the purposes of this study, the adoptees were dichotomized to the adoptees with ($n = 157$; HR $n = 98$, LR $n = 59$) and without ($n = 189$; HR $n = 77$, LR $n = 112$) a psychiatric diagnosis. This was based on the earlier research findings, indicating that genetic vulnerability to schizophrenia implies an elevated risk for any psychiatric disorder (Parnas et al., 1993; Schubert and McNeil, 2003; Tienari et al., 2000).

2.2.2. The assessment of family functioning

The Global Family Ratings (GFRs, see Tienari et al., 1987a, 1987b; Wynne et al., 2006a) were used as a measure of adoptive family functions, patterns and relationships during visits to the adoptive families. The GFRs are evaluations based on open-ended and holistic semi-structured interviews, accompanied with broad and pervasive observations by the researchers during the interview sessions. It is a convenient method for rating family functioning in a non-clinical environment (Tienari et al., 1987a, 1987b, 2005; Wynne et al., 2006a).

Each interviewer conducted an independent rating of the family, immediately after completion of the interview. After a few months, the interviewers listened to their tape-recorded interviews and re-evaluated their initial ratings. A random sample of 40 recorded interviews were also evaluated, and rated, by a group of three research interviewers, to clarify the reliability of the initial ratings. The reliability assessment of ratings between the interviewers was deemed reasonable (0.72) on the scale from 0 = poor to 1 = high concordance of ratings (Wynne et al., 2006a).

The GFRs reflect family functioning in the following terms: 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 defences, such as projective identification and splitting, 7) Conflicts, 8) Empathy, 9) Power relations, 10) Reality testing, and 11) Basic trust (see Tienari et al., 1985; Wynne et al., 2006a for further information about categorical procedures). The classifications of the GFRs followed the Global Assessment of Relational Functioning (GARF) scale that was published in DSM-IV (Tienari et al., 2004).

Based on the GFRs used in the earlier studies of the Finnish Adoptive Family Study of Schizophrenia, the families were classified into five categories (Tienari et al., 1985; Wynne et al., 2006a). Healthy family (category 1) contained families evaluated as healthy in terms of the GFRs-criteria such as anxiety and its levels; boundaries between the individual family members, generations, and between the family and the outside world; and parental coalition. Mildly disturbed families (category 2) consisted of families in which, for example, the levels of

anxiety, primitive defences and conflict were mild, and in which the interaction was healthy. In moderately dysfunctional, neurotic families (category 3), there were, for example, mildly angry and dysfunctional relationships and interpersonal patterns in the family and these conflicts were unresolved and moderate. The rigid, syntonetic families (category 4) were, for example, maladaptive and dysfunctional in boundaries, interpersonal patterns, conflict solving and emotional expressions. Severely disturbed, chaotic families (category 5) consisted of families in which, for example, anxiety was at a high level, the boundaries were unclear, interpersonal family patterns were unstable and disorganized, the conflict was open and disturbed and the emotional climate was deemed to be severe (see Tienari et al., 1987b; Wynne et al., 2006a for further information about the categories).

In this study, the GFRs categories 1 and 2 were combined and re-labeled as “families with functional processes”. Categories 4 and 5 were also combined and re-labeled as “families with dysfunctional processes”. The reason for these combinations was the significant similarities between the categories (Tienari et al., 1987b; Wynne et al., 2006a). As Tienari and colleagues (1987b) have proposed, categories 1 and 2 are within the scope of a healthy and functional family processes, whereas categories 4 and 5 show increased levels of disturbance and dysfunction that are assumed to be serious risk factors to family members. The GFRs category 3 formed the category of “families with mildly dysfunctional processes”.

2.2.3. Early parental death and divorce

Early parental death was defined as death of a parent occurring before their offspring reached the age of 18. Likewise, parental divorce indicates that the divorce took place while their offspring were aged under 18. In the present study, early parental death and early parental divorce were considered to describe the disruptions of the adoptive family. These were analyzed as separated variables, because they may have different effects on the development of the children (Lang and Zagorsky, 2001; Larson and Halfon, 2013; Mack, 2001; Tennant, 1988).

2.2.4. Statistical analyses

Statistical significance of group differences in categorical variables were assessed with Pearson's Chi-Square test or Fisher's Exact Test. A logistic regression model was used to examine the association of gender, early parental death, early parental divorce, GFRs and genetic risk to psychiatric disorder of the adoptees. All tests were two-tailed and the limit for statistical significance was set at $p = 0.05$. The statistical software used in analyses was IBM SPSS Statistic Version 24.

3. Results

Table 1 shows the bivariate associations between characteristics and genetic status of the adoptees. Nearly half of the adoptees were females, regardless of the genetic status. Nearly a quarter of the adoptees belonged to families with dysfunctional processes, but no significant difference between HR and LR adoptees was observed. A significantly higher proportion of HR adoptees, compared to LR adoptees, had experienced early parental death, while no difference between HR- and LR-adoptees was found in early parental divorce.

Table 2 presents the bivariate associations between characteristics and psychiatric disorder status, for HR- and LR- adoptees, separately. In the HR group, psychiatric disorder of the adoptees, compared to HR-adoptees without psychiatric disorder, was statistically significantly associated to families with dysfunctional processes, but not with gender and early parental death or divorce. In the LR group, none of the characteristics were associated to a psychiatric disorder in the adoptees. The Fig. 1 illustrates the prevalence of psychiatric disorders among HR- and LR-adoptees in the family functioning categories.

Table 3 shows the results of logistic regression analysis, separately for HR- and LR- adoptees. An increased likelihood for psychiatric disorder was associated with dysfunctional family processes both in the

Table 1

The characteristics of the adoptees with a high (HR) and low (LR) risk for schizophrenia spectrum disorders.

	Total (n = 346)	HR (n = 175)	LR (n = 171)	χ^2	Df	P-value
Gender, female	185 (53.5%)	93 (53.1%)	92 (53.8%)	0.015	1	0.902
Global Family Ratings				4.914	2	0.086
Families with functional processes	126 (41.6%)	70 (46.1%)	56 (37.1%)			
Families with mildly dysfunctional processes	91 (30%)	37 (24.3%)	54 (35.8%)			
Families with dysfunctional processes	86 (28.4%)	45 (29.6%)	41 (27.2%)			
Early parental death	41 (11.8%)	30 (17.1%)	11 (6.4%)	9.498	1	0.002
Early parental divorce	10 (2.9%)	8 (4.6%)	2 (1.2%)	3.566	1	0.105

The total *n* on which the percentages are based varies because of data missing for some variables.

HR = high-risk for schizophrenia spectrum disorder.

LR = 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).

HR- (OR 4.78, *p* = <0.001) and LR- (OR 2.62, *p* = 0.032) group of the adoptees.

4. Discussion

Genetic and environmental factors are known to play a major role in the development of schizophrenia and schizophrenia spectrum disorders (Löhrs and Hasan, 2019; Nimgaonkar et al., 2017; Read et al., 2005). However, further studies of the gene-environment interactions in psychiatric disorders are required, to improve our understanding and guide future preventive intervention strategies for the vulnerable populations affected (European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI, 2014); Gianfrancesco et al., 2019). Our objective was to clarify this complex gene-environment interaction and find further evidence of the risk and protective factors for psychiatric disorders. The current study focused on family functioning of adoptive families, as an environmental risk factor in the development of psychiatric disorders, among adopted-away offspring of mothers, with and without schizophrenia spectrum disorder.

The main finding of the current study was that dysfunctional adoptive family processes were significantly associated to an increased likelihood for the development of psychiatric disorders in adoptees, with or without a genetic risk for schizophrenia spectrum disorder. In our study, dysfunctional family functioning was deemed to include, maladaptive conflict solving, disturbed emotional expressions, unclear boundaries and unstable family patterns. Our finding is in line with numerous studies, using various types of study designs and populations

(Benjet et al., 2010; Fergusson and Horwood, 2001; Whitfield et al., 2005).

We were also able to show that the impact of dysfunctional family processes on the development of psychiatric disorders of the adoptees was more prominent in high-risk adoptees, compared to low-risk adoptees. This finding was in line with our hypothesis, that a genetic liability to schizophrenia spectrum disorders increases the sensitivity to family adversities. Our finding is also in concordance with previous studies of the environmental impacts on vulnerable populations (Marcus et al., 1987; Mäki et al., 2005; Roisko et al., 2011; Schiffman et al., 2002; Tienari et al., 2004; Wahlberg et al., 2004; Wynne et al., 2006a). In families with functional processes, psychiatric disorders of the adoptees were not as common as they were in families with dysfunctional processes. Consequently, it is also justifiable to conclude that our study provides further evidence of the protective effect of functional family processes (Wahlberg et al., 2004; Wynne et al., 2006a).

The impact of dysfunctional family processes on a child's likelihood of developing psychiatric disorders can be explained from various viewpoints. In a conflictual family system, children may not learn to handle stress and conflicts, or they learn maladaptive ways to deal with them, which may make them more vulnerable to future environmental stressors (Danese and McEwen, 2012; Jones and Jablonski, 1998). Conflicts and disturbed parental relationships may also complicate the separation-individuation processes (Daniels, 1990). In families with dysfunctional processes, intra-family relationships can include maladaptive habits such as rejection and withdrawal (Faubert et al., 1990), psychological control, rejection and neglect (see Hoeve et al., 2009), that are all known to associate with children's internalized problems.

Table 2

The characteristics of the adoptees by their genetic status and psychiatric disorders.

	HR (n = 175)		χ^2	Df	P-value	LR (n = 171)		χ^2	Df	P-value
	Adoptee's psychiatric disorder YES (n = 98)	NO (n = 77)				Adoptee's psychiatric disorder YES (n = 59)	NO (n = 112)			
Gender, female	51 (52.0%)	42 (54.5%)	0.109	1	0.742	32 (54.2%)	60 (53.6%)	0.007	1	0.934
Global Family Ratings			12.923	2	0.002			4.929	2	0.085
Families with functional processes	31 (31.9%)	39 (50.6%)				13 (22.0%)	43 (38.4%)			
Families with mildly dysfunctional processes	23 (23.5%)	14 (18.2%)				20 (33.9%)	34 (30.4%)			
Families with dysfunctional processes	35 (35.7%)	10 (13.0%)				18 (30.5%)	23 (20.5%)			
Early parental death, yes	16 (16.3%)	14 (18.2%)	0.104	1	0.747	4 (6.8%)	7 (6.2%)	0.018	1	1.000
Early parental divorce, yes	5 (5.1%)	3 (3.9%)	0.144	1	0.736	0 (0%)	2 (1.80%)	1.066	1	0.545

The total *n* on which the percentages are based varies because of data missing for some subjects.

HR = high-risk for schizophrenia spectrum disorder.

LR = 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).

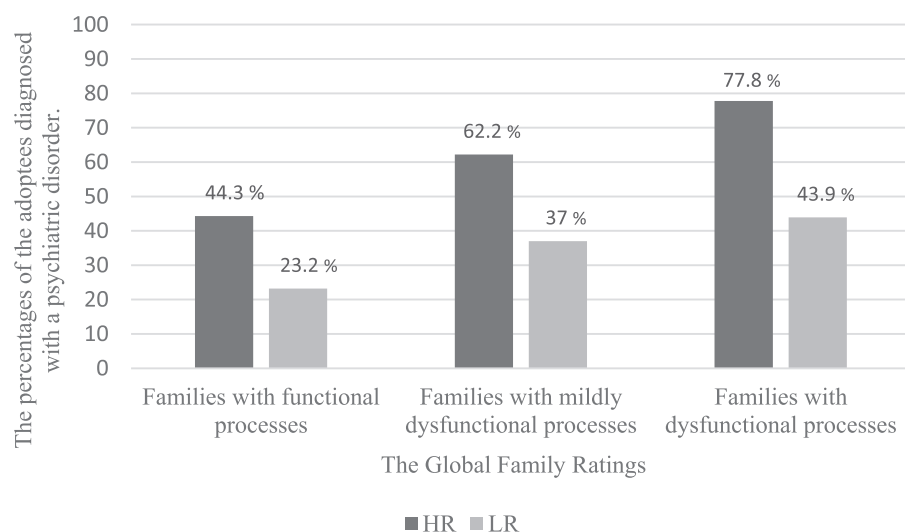


Fig. 1. The prevalence of psychiatric disorders, according to the genetic status for schizophrenia spectrum disorders and family functioning categories, based on the Global Family Ratings.

HR = high-risk for schizophrenia spectrum disorder

LR = 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).

Furthermore, parental conflicts and discord are found to associate with damaged relationships between family members (Amato and Afifi, 2006). Thus, the conflictual nature of family relationships may be related to blurred boundaries and weakened interpersonal patterns in the family system.

The stress-vulnerability model (Nuechterlein, 1987; Rosenthal, 1970; Zubin and Spring, 1977) suggests that, besides genetic vulnerability, individual vulnerability involves propensities acquired from the environment. Various marital and social environments are understood to supply children with different propensities, development outcomes and psychological qualities (see Belsky, 1984). Nuechterlein (1987) sees the adversities in family environment as socio-environmental stressors that may increase individual vulnerability. Thus, we assume that families with functional, and families with dysfunctional processes, affect children's internalized propensities differently, which may further enhance the development of psychiatric disorders.

Socio-environmental issues are significant factors in the development of psychiatric disorders. Family related negative events, such as parental death, divorce and decline in economic status are examples of several socio-environmental factors which form the concept of adverse childhood experiences (ACEs) (Felitti et al., 1998). These are shown to associate to an increased risk for various mental health issues, including psychiatric disorders (Longden and Read, 2016; Misiak et al., 2016; Najman et al., 2010), suicidality (Perez et al., 2016) and behavioral problems (Jimenez et al., 2016; Shetgiri et al., 2015). Very few previous studies have focused on the joint impact of both psychosocial and biological factors in the family, on the offspring's psychological well-being.

Surprisingly, in our study, early parental death and early parental divorce did not associate with psychiatric diagnoses in either the HR adoptees or LR adoptees. One possible explanation for this is that their adverse effects may ease over time, as has been found with early parental death (Feigelman et al., 2017). In addition, children can be supported to cope with parental bereavement, which can protect them from future psychiatric disorders (see Haine et al., 2008). Furthermore, parental divorce can be a protective factor for children in contentious families (Amato and Afifi, 2006; Riggio, 2004). Conflict-free relationships and positive rearing between family members may help children to adapt to parental divorce (see Hetherington et al., 1998) or parental death (see Haine et al., 2008).

In this study, we were able to demonstrate, that all studied adversities had a more significant association to psychiatric disorders among offspring with biological mother with schizophrenia. This indicates a genetic vulnerability of the adopted-away offspring of mothers with schizophrenia. Earlier studies indicate that two or more simultaneously occurring ACEs increase the risk for negative outcomes, such as psychiatric disorders, for the exposed individuals (Bellis et al., 2014; Curran et al., 2016; Felitti et al., 1998; Hughes et al., 2016; Klassen et al., 2016; Mersky et al., 2013; Rasic et al., 2014; Sugaya et al., 2012). Therefore, it is important to focus preventive actions on any potential ACE, with the aim of reducing the adverse cumulative effect on individuals exposed. The primary target for preventive interventions should be those individuals identified as having a genetic vulnerability for psychiatric disorders.

Table 3

The association of genetic vulnerability of the adoptees and family adversities to the likelihood for adoptee psychiatric disorder.

	HR (n = 175) Likelihood for psychiatric disorder ^a			LR (n = 171) Likelihood for psychiatric disorder ^a		
	OR	95% CI	P-value	OR	95% CI	P-value
Gender, female	0.6	0.3–1.25	0.184	1.3	0.62–2.55	0.511
Global Family Ratings						
Families with functional processes	ref.			ref.		
Families with mildly dysfunctional processes	2.1	0.9–4.89	0.083	2.1	0.89–4.77	0.091
Families with dysfunctional processes	4.8	2–11.44	<0.001	2.6	1.08–6.33	0.032
Early parental death, yes	1.1	0.45–2.72	0.819	1.3	0.33–5.37	0.686
Early parental divorce, yes	1.4	0.24–8.2	0.284	ne		

HR = high-risk for schizophrenia spectrum disorder.

LR = 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).

^a Odds ratio (OR), 95% confidence interval (95% CI) and p-value from logistic regression model after adjusting for covariates. ne = not estimable.

4.1. Limitations and strengths of the study

The findings of this study need to be considered in light of various limitations. Firstly, family functioning was measured using the Global Family Rating (GRF) scale (Wynne et al., 2006a), when interviewing family members. The GRF does not assess potential changes in GRFs that may have occurred during each adoptee's childhood. Several studies from the Finnish Adoptive Family Study of Schizophrenia, however, have indicated that factors relating to family relationships, such as poor communication between family members, have remained relatively stable during the time course (Keskitalo, 2000; Roisko et al., 2011; Wahlberg et al., 2001). Secondly, the details of the rearing practices of the adoptive families were not available from the study data. Further, the number of cases in some subgroup analyses, including those for parental death and divorce, was small, causing a lack of power in statistical analyses (Type II error). Consequently, we were not able to focus our analysis on specific psychiatric disorders, such as schizophrenia.

The major strength of the present study was the use of comprehensive national data from the Finnish Adoptive Family Study of Schizophrenia, with methodologically sound assessments of various family environment related factors (Tienari et al., 2000, 2004). To ascertain high diagnostic reliability, the diagnoses of study subjects were thoroughly reviewed by the researchers including several steps and checks on rater drift over time (Tienari et al., 2000, 2004).

4.2. Conclusion

Our study findings provide further evidence of gene-environment interactions in the development of psychiatric disorders. Dysfunctional family processes seem to increase the risk for psychiatric disorders, particularly among those with a genetic vulnerability to schizophrenia. Based on our results, early parental divorce and death do not associate with psychiatric morbidity in the adoptees, regardless of their genetic status. This study strongly highlights the need for preventive strategies and interventions, designed to reduce adversities in family functioning and to provide targeted support to vulnerable families.

Acknowledgment

We thank Pekka Tienari, Lyman C. Wynne, Heljä Anias, Pirjo Keskitalo, Pekka Koistinen, Ilpo Lahti, Juha Moring, Mikko Naarala, Anneli Sorri, Taneli Tarvainen and Markku Seitamaa for their contribution to the psychological testing and psychiatric diagnoses of participants in this study.

This study was supported by Oulu University Hospital.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.06.017.

References

- Agid, O., Shapira, B., Zislin, J., Ritsner, M., Hanin, B., Murad, H., Troudart, T., Bloch, M., Heresco-Levy, U., Lerer, B., 1999. Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. *Mol. Psychiatry* 4, 163–172. <https://doi.org/10.1038/sj.mp.4000473>.
- Amato, P.R., Afifi, T.D., 2006. Feeling caught between parents: adult children's relations with parents and subjective well-being. *J. Marriage Family* 68, 222–235. <https://doi.org/10.1111/j.1741-3737.2006.00243.x>.
- Amato, P.R., Cheadle, J.E., 2008. Parental divorce, marital conflict and children's behavior problems: a comparison of adopted and biological children. *Soc. Forces* 86, 1139–1161. <https://doi.org/10.1353/sof.0.0025>.
- American Psychiatric Association, 1987. *Diagnostic and Statistical Manual for Mental Disorders*, 3rd ed. Revised American Psychiatric Association, Washington DC.
- Asarnow, R.F., Nuechterlein, K.H., Fogelson, D., Subotnik, K.L., Payne, D.A., Russell, A.T., Asamen, J., Kuppinger, H., Kendler, K.S., 2001. Schizophrenia and schizophrenia-

- spectrum personality disorders in the first-degree relatives of children with schizophrenia: the UCLA family study. *Arch. Gen. Psychiatry* 58, 581–588. <https://doi.org/10.1001/archpsyc.58.6.581>.
- Barrett, A.E., Turner, R.J., 2005. Family structure and mental health: the mediating effects of socioeconomic status, family process, and social stress. *J. Health Soc. Behav.* 46, 156–169. <https://doi.org/10.1177/002214650504600203>.
- Bellis, M.A., Hughes, K., Leckenby, N., Jones, L., Baban, A., Kachaeva, M., Povilaitis, R., Pudule, I., Qirjako, G., Ulukol, B., Raleva, M., Terzic, N., 2014. Adverse childhood experiences and associations with health-harming behaviours in young adults: surveys in eight eastern European countries. *Bull. World Health Organ.* 92, 641–655. <https://doi.org/10.2471/BLT.13.129247>.
- Belsky, J., 1984. The determinants of parenting: a process model. *Child Dev.* 55, 83–96. <https://doi.org/10.2307/1129836>.
- Benjet, C., Borges, G., Medina-Mora, M.E., 2010. Chronic childhood adversity and onset of psychopathology during three life stages: childhood, adolescence and adulthood. *J. Psychiatr. Res.* 44, 732–740. <https://doi.org/10.1016/j.jpsychires.2010.01.004>.
- Cuijpers, P., Smit, F., Unger, F., Stikkelbroek, Y., Ten Have, M., de Graaf, R., 2011. The disease burden of childhood adversities in adults: a population-based study. *Child Abuse Negl.* 35, 937–945. <https://doi.org/10.1016/j.chiabu.2011.06.005>.
- Curran, E., Adamson, G., Stringer, M., Rosato, M., Leavey, G., 2016. Severity of mental illness as a result of multiple childhood adversities: US National Epidemiologic Survey. *Soc. Psychiatry Psychiatr. Epidemiol.* 51, 647–657. <https://doi.org/10.1007/s00127-016-1198-3>.
- Danese, A., McEwen, B.S., 2012. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol. Behav.* 106, 29–39. <https://doi.org/10.1016/j.physbeh.2011.08.019>.
- Daniels, J.A., 1990. Adolescent separation-individuation and family transitions. *Adolescence* 25, 105–116.
- Erlenmeyer-Kimling, L., Adamo, U.H., Rock, D., Roberts, S.A., Bassett, A.S., Squires-Wheeler, E., Cornblatt, B.A., Endicott, J., Pape, S., Gottesman, I.I., 1997. The New York high-risk project: prevalence and comorbidity of axis I disorders in offspring of schizophrenic parents at 25-year follow-up. *Arch. Gen. Psychiatry* 54, 1096–1102. <https://doi.org/10.1001/archpsyc.1997.01830240052008>.
- European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI), 2014. Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. *Schizophr. Bull.* 40, 729–736. <https://doi.org/10.1093/schbul/sbu069>.
- Fauber, R., Forehand, R., Thomas, A.M., Wiersma, M., 1990. A mediational model of the impact of marital conflict on adolescent adjustment in intact and divorced families: the role of disrupted parenting. *Child Dev.* 61, 1112–1123. <https://doi.org/10.2307/1130879>.
- Feigelman, W., Rosen, Z., Joiner, T., Silva, C., Mueller, A.S., 2017. Examining longer-term effects of parental death in adolescents and young adults: evidence from the national longitudinal survey of adolescent to adult health. *Death Stud.* 41, 133–143. <https://doi.org/10.1080/07481187.2016.1226990>.
- Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., Koss, M.P., Marks, J.S., 1998. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the adverse childhood experiences (ACE) study. *Am. J. Prev. Med.* 14, 245–258. [https://doi.org/10.1016/S0749-3797\(98\)00017-8](https://doi.org/10.1016/S0749-3797(98)00017-8).
- Fergusson, D.M., Horwood, J.L., 2001. The christchurch health and development study: review of findings on child and adolescent mental health. *Aust. N.Z. J. Psychiatry* 35, 287–296. <https://doi.org/10.1046/j.1440-1614.2001.00902.x>.
- Furukawa, T., Mizukawa, R., Hirai, T., Fujihara, S., Kitamura, T., Takahashi, K., 1998. Childhood parental loss and schizophrenia: evidence against pathogenic but for some pathoplastic effects. *Psychiatry Res.* 81, 353–362. [https://doi.org/10.1016/S0165-1781\(98\)00113-9](https://doi.org/10.1016/S0165-1781(98)00113-9).
- Gianfrancesco, O., Bubb, V.J., Quinn, J.P., 2019. Treating the “E” in “G × E”: trauma-Informed approaches and psychological therapy interventions in psychosis. *Front Psychiatry* 10. <https://doi.org/10.3389/fpsy.2019.00009>.
- Gilman, S.E., Kawachi, I., Fitzmaurice, G.M., Buka, S.L., 2003. Family disruption in childhood and risk of adult depression. *Am. J. Psychiatry* 160, 939–946. <https://doi.org/10.1176/appi.ajp.160.5.939>.
- Gottesman, I.I., Laursen, T.M., Bertelsen, A., Mortensen, P.B., 2010. Severe mental disorders in offspring with 2 psychiatrically ill parents. *Arch. Gen. Psychiatry* 67, 252–257. <https://doi.org/10.1001/archgenpsychiatry.2010.1>.
- Haine, R.A., Ayers, T.S., Sandler, I.N., Wolchik, S.A., 2008. Evidence-based practices for parentally bereaved children and their families. *Prof. Psychol. Res. Pr.* 39, 113–121. <https://doi.org/10.1037/0735-7028.39.2.113>.
- Hankin, B.L., Abela, J.R.Z., 2005. *Development of Psychopathology: A Vulnerability-Stress Perspective*. SAGE Publications, Thousand Oaks.
- Hans, S.L., Auerbach, J.G., Styr, B., Marcus, J., 2004. Offspring of parents with schizophrenia: mental disorders during childhood and adolescence. *Schizophr. Bull.* 30, 303–315. <https://doi.org/10.1093/oxfordjournals.schbul.a007080>.
- Hansagi, H., Brandt, L., Andréasson, S., 2000. Parental divorce: psychosocial well-being, mental health and mortality during youth and young adulthood A longitudinal study of Swedish conscripts. *Eur. J. Public Health* 10, 86–92. <https://doi.org/10.1093/eurpub/10.2.86>.
- Helgeland, M.I., Torgersen, S., 2005. Stability and prediction of schizophrenia from adolescence to adulthood. *Eur. Child Adolesc. Psychiatry* 14, 83–94. <https://doi.org/10.1007/s00787-005-0436-0>.
- Hetherington, E.M., Bridges, M., Insabella, G.M., n.d. What matters? What does not? Five perspectives on the association between marital transitions and children's adjustment. *American Ann. Psychologist Psychol.* 53, 167–84. <https://doi.org/10.1037/0003-066X.53.2.167>.
- Hoeve, M., Dubas, J.S., Eichelsheim, V.I., van der Laan, P.H., Smeenk, W., Gerris, J.R.M.,

2009. The relationship between parenting and delinquency: a Meta-analysis. *J. Abnorm. Child Psychol.* 37, 749–775. <https://doi.org/10.1007/s10802-009-9310-8>.
- Hughes, K., Lowey, H., Quigg, Z., Bellis, M.A., 2016. Relationships between Adverse Childhood Experiences and Adult Mental Well-being: Results from an English National Household Survey. *BMC Public Health*, pp. 16. <https://doi.org/10.1186/s12889-016-2906-3>.
- Jimenez, M.E., Wade, R., Lin, Y., Morrow, L.M., Reichman, N.E., 2016. Adverse experiences in early childhood and kindergarten outcomes. *Pediatrics* 137, e20151839. <https://doi.org/10.1542/peds.2015-1839>.
- Jones, R.A., Jablonski, A.L., 1998. Family-focused relational psychotherapy: an integrative approach and its application to adult children of divorce. *J. Psychother. Integr.* 8, 69–95. <https://doi.org/10.1023/A:1023285422736>.
- Kendler, K.S., McGuire, M., Gruenberg, A.M., O'Hare, A., Spellman, M., Walsh, D., 1993. The Roscommon family study: III. Schizophrenia-related personality disorders in relatives. *Arch. Gen. Psychiatry* 50, 781–788. <https://doi.org/10.1001/archpsyc.1993.01820220033004>.
- Kendler, K.S., O'Neill, F.A., Burke, J., Murphy, B., Duke, F., Straub, R.E., Shinkwin, R., Nuallain, M.N., MacLean, C.J., Walsh, D., 1996. Irish study of high-density schizophrenia families: field methods and power to detect linkage. *Am. J. Med. Genet.* 67, 179–190. [https://doi.org/10.1002/\(SICI\)1096-8628\(19960409\)67:2<179::AID-AJMG8>3.0.CO;2-N](https://doi.org/10.1002/(SICI)1096-8628(19960409)67:2<179::AID-AJMG8>3.0.CO;2-N).
- Keskitalo, P., 2000. Vanhempien Kommunikaatiohäiriöiden Pysyvyys Ja Yhteys Skitsofrenialle Altistuneiden Adoptiolasten Ja Heidän Verokkiensa Ajattelu Kehitykselle. *Psykiatrian klinikka, Oulun yliopisto, Oulu*.
- Klassen, S.A., Chirico, D., O'Leary, D.D., Cairney, J., Wade, T.J., 2016. Linking systemic arterial stiffness among adolescents to adverse childhood experiences. *Child Abuse Negl.* 56, 1–10. <https://doi.org/10.1016/j.chiabu.2016.04.002>.
- Lang, K., Zagorsky, J.L., 2001. Does growing up with a parent absent really hurt? *J. Hum. Resour.* 36, 253–273. <https://doi.org/10.2307/3069659>.
- Larson, K., Halfon, N., 2013. Parental divorce and adult longevity. *Int. J. Public Health* 58, 89–97. <https://doi.org/10.1007/s00038-012-0373-x>.
- Löhrrs, L., Hasan, A., 2019. Risk factors for the development of schizophrenia. *Fortschr. Neurol. Psychiatr.* 87, 133–143. <https://doi.org/10.1055/a-0836-7839>.
- Longden, E., Read, J., 2016. Social adversity in the etiology of psychosis: a review of the evidence. *Am. J. Psychother.* 70, 5–33. <https://doi.org/10.1176/appi.psychotherapy.2016.70.1.5>.
- Mack, K.Y., 2001. Childhood family disruptions and adult well-being: the differential effects of divorce and parental death. *Death Stud.* 25, 419–443. <https://doi.org/10.1080/074811801750257527>.
- Mäki, P., Veijola, J., Jones, P.B., Murray, G.K., Koponen, H., Tienari, P., Miettunen, J., Tanskanen, P., Wahlberg, K.-E., Koskinen, J., Lauronen, E., Isohanni, M., 2005. Predictors of schizophrenia—a review. *Br. Med. Bull.* 73–74, 1–15. <https://doi.org/10.1093/bmb/ldh046>.
- Mäkiyö, T., Sauvala, A., Moring, J., Veijola, J., Nieminen, P., Järvelin, M.R., Isohanni, M., 1998. Hospital-treated psychiatric disorders in adults with a single-parent and two-parent family background: a 28-year follow-up of the 1966 northern Finland birth cohort. *Fam. Process* 37, 335–344. <https://doi.org/10.1111/j.1545-5300.1998.00335.x>.
- Marcus, J., Hans, S.L., Nagler, S., Auerbach, J.G., Mirsky, A.F., Aubrey, A., 1987. Review of the NIMH Israeli kibbutz-city study and the Jerusalem infant development study. *Schizophr. Bull.* 13, 425–438. <https://doi.org/10.1093/schbul/13.3.425>.
- Mersky, J.P., Topitzes, J., Reynolds, A.J., 2013. Impacts of adverse childhood experiences on health, mental health, and substance use in early adulthood: a cohort study of an urban, minority sample in the U.S. *Child Abuse Negl.* 37, 917–925. <https://doi.org/10.1016/j.chiabu.2013.07.011>.
- Misiak, B., Moustafa, A.A., Kiejna, A., Frydecka, D., 2016. Childhood traumatic events and types of auditory verbal hallucinations in first-episode schizophrenia patients. *Compr. Psychiatry* 66, 17–22. <https://doi.org/10.1016/j.comppsy.2015.12.003>.
- Najman, J.M., Hayatbakhsh, M.R., Clavarino, A., Bor, W., O'Callaghan, M.J., Williams, G.M., 2010. Family poverty over the early life course and recurrent adolescent and young adult anxiety and depression: a longitudinal study. *Am. J. Public Health* 100, 1719–1723. <https://doi.org/10.2105/AJPH.2009.180943>.
- Nickerson, A., Bryant, R.A., Aderka, I.M., Hinton, D.E., Hofmann, S.G., 2013. The impacts of parental loss and adverse parenting on mental health: findings from the national comorbidity survey-replication. *Psychol. Trauma Theo. Res. Pract. Policy* 5, 119–127. <https://doi.org/10.1037/a0025695>.
- Nimgaonkar, V.L., Prasad, K.M., Chowdari, K.V., Severance, E.G., Yolken, R.H., 2017. The complement system: a gateway to gene-environment interactions in schizophrenia pathogenesis. *Mol. Psychiatry* 22, 1554–1561. <https://doi.org/10.1038/mp.2017.151>.
- Parnas, J., Cannon, T.D., Jacobsen, B., Schulsinger, H., Schulsinger, F., Mednick, S.A., 1993. Lifetime DSM-III-R diagnostic outcomes in the offspring of schizophrenic mothers: results from the Copenhagen high-risk study. *Arch. Gen. Psychiatry* 50, 707–714. <https://doi.org/10.1001/archpsyc.1993.01820210041005>.
- Perez, N.M., Jennings, W.G., Piquero, A.R., Baglivio, M.T., 2016. Adverse childhood experiences and suicide attempts: the mediating influence of personality development and problem behaviors. *J. Youth Adolesc.* 45, 1527–1545. <https://doi.org/10.1007/s10964-016-0519-x>.
- Pietrek, C., Elbert, T., Weierstall, R., Müller, O., Rockstroh, B., 2013. Childhood adversities in relation to psychiatric disorders. *Psychiatry Res.* 206, 103–110. <https://doi.org/10.1016/j.psychres.2012.11.003>.
- Pirkola, S., Iso Metsä, E., Aro, H., Kestilä, L., Hämäläinen, J., Veijola, J., Kiviruusu, O., Lönnqvist, J., 2005. Childhood adversities as risk factors for adult mental disorders: results from the health 2000 study. *Soc. Psychiatry Psychiatr. Epidemiol.* 40, 769–777. <https://doi.org/10.1007/s00127-005-0950-x>.
- Ragan, P.V., McGlashan, T.H., 1986. Childhood parental death and adult psychopathology. *Am. J. Psychiatry* 143, 153–157. <https://doi.org/10.1176/ajp.143.2.153>.
- Rasic, D., Hajek, T., Alda, M., Uher, R., 2014. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. *Schizophr. Bull.* 40, 28–38. <https://doi.org/10.1093/schbul/sbt114>.
- Read, J., Perry, B.D., Moskowitz, A., Connolly, J., 2001. The contribution of early traumatic events to schizophrenia in some patients: a traumatic neurodevelopmental model. *Psychiatry Interpers. Biol. Process.* 64, 319–345. <https://doi.org/10.1521/psyc.64.4.319.18602>.
- Read, J., van Os, J., Morrison, A.P., Ross, C.A., 2005. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatr. Scand.* 112, 330–350. <https://doi.org/10.1111/j.1600-0447.2005.00634.x>.
- Riggio, H.R., 2004. Parental marital conflict and divorce, parent-child relationships, social support, and relationship anxiety in young adulthood. *Pers. Relatsh.* 11, 99–114. <https://doi.org/10.1111/j.1475-6811.2004.00073.x>.
- Roisko, R., Wahlberg, K.-E., Hakko, H., Wynne, L., Tienari, P., 2011. Communication deviance in parents of families with adoptees at a high or low risk of schizophrenia-spectrum disorders and its associations with attributes of the adoptee and the adoptive parents. *Psychiatry Res.* 185, 66–71. <https://doi.org/10.1016/j.psychres.2010.04.018>.
- Rubino, I.A., Nanni, R.C., Pozzi, D.M., Siracusano, A., 2009. Early adverse experiences in schizophrenia and unipolar depression. *J. Nerv. Ment. Dis.* 197, 65–68. <https://doi.org/10.1097/NMD.0b013e3181925342>.
- Schiffman, J., LaBrie, J., Carter, J., Cannon, T., Schulsinger, F., Parnas, J., Mednick, S., 2002. Perception of parent-child relationships in high-risk families, and adult schizophrenia outcome of offspring. *J. Psychiatr. Res.* 36, 41–47. [https://doi.org/10.1016/S0022-3956\(01\)00046-2](https://doi.org/10.1016/S0022-3956(01)00046-2).
- Schroeder, K., Langeland, W., Fisher, H.L., Huber, C.G., Schäfer, I., 2016. Dissociation in patients with schizophrenia spectrum disorders: what is the role of different types of childhood adversity? *Compr. Psychiatry* 68, 201–208. <https://doi.org/10.1016/j.comppsy.2016.04.019>.
- Schubert, E.W., McNeil, T.F., 2003. Prospective study of adult mental disturbance in offspring of women with psychosis. *Arch. Gen. Psychiatry* 60, 473–480. <https://doi.org/10.1001/archpsyc.60.5.473>.
- Shafer, K., Jensen, T.M., Holmes, E.K., 2017. Divorce stress, stepfamily stress, and depression among emerging adult stepchildren. *J. Child Fam. Stud.* 26, 851–862. <https://doi.org/10.1007/s10826-016-0617-0>.
- Shetgiri, R., Lin, H., Flores, G., 2015. Suboptimal maternal and paternal mental health are associated with child bullying perpetration. *Child Psychiatry Hum. Dev.* 46, 455–465. <https://doi.org/10.1007/s10578-014-0485-z>.
- Siira, V., Wahlberg, K.-E., Hakko, H., Läsky, K., Tienari, P., 2007. Interaction of genetic vulnerability to schizophrenia and communication deviance of adoptive parents associated with MMPI schizophrenia vulnerability indicators of adoptees. *Nord. J. Psychiatry* 61, 418–426. <https://doi.org/10.1080/08039480701691786>.
- Sørensen, H.J., Mortensen, E.L., Reinisch, J.M., Mednick, S.A., 2009. Parental psychiatric hospitalisation and offspring schizophrenia. *World J. Biol. Psychiatry* 10, 571–575. <https://doi.org/10.1080/15622970701472078>.
- Sugaya, L., Hasin, D.S., Olsson, M., Lin, K.-H., Grant, B.F., Blanco, C., 2012. Child physical abuse and adult mental health: a national study. *J. Trauma Stress* 25, 384–392. <https://doi.org/10.1002/jts.21719>.
- Tennant, C., 1988. Parental loss in childhood: its effect in adult life. *Arch. Gen. Psychiatry* 45, 1045–1050. <https://doi.org/10.1001/archpsyc.1988.01800350079012>.
- Tienari, P., Lahti, I., Sorri, A., Naarala, M., Moring, J., Wahlberg, K.-E., Wynne, L.C., 1987a. The Finnish adoptive family study of schizophrenia. *J. Psychiatr. Res.* 21, 437–445. [https://doi.org/10.1016/0022-3956\(87\)90091-4](https://doi.org/10.1016/0022-3956(87)90091-4).
- Tienari, P., Sorri, A., Lahti, I., Naarala, M., Wahlberg, K.-E., Moring, J., Pohjola, J., Wynne, L.C., 1987b. Genetic and psychosocial factors in schizophrenia: the Finnish adoptive family study. *Schizophr. Bull.* 13, 477–484. <https://doi.org/10.1093/schbul/13.3.477>.
- Tienari, P., Sorri, A., Lahti, I., Naarala, M., Wahlberg, K.E., Rönkkö, T., Pohjola, J., Moring, J., 1985. The Finnish adoptive family study of schizophrenia. *Yale J. Biol. Med.* 58, 227–237.
- Tienari, P., Wynne, L.C., Läsky, K., Moring, J., Nieminen, P., Sorri, A., Lahti, I., Wahlberg, K.-E., 2003. Genetic boundaries of the schizophrenia spectrum: evidence from the Finnish adoptive family study of schizophrenia. *Am. J. Psychiatry* 160, 1587–1594. <https://doi.org/10.1176/appi.ajp.160.9.1587>.
- Tienari, P., Wynne, L.C., Moring, J., Läsky, K., Nieminen, P., Sorri, A., Lahti, I., Wahlberg, K.-E., Naarala, M., Kurki-Suonio, K., Saarento, O., Koistinen, P., Tarvainen, T., Hakko, H., Miettunen, J., 2000. Finnish adoptive family study: sample selection and adoptee DSM-III-R diagnoses. *Acta Psychiatr. Scand.* 101, 433–443. <https://doi.org/10.1034/j.1600-0447.2000.101006433.x>.
- Tienari, P., Wynne, L.C., Sorri, A., Lahti, I., Läsky, K., Moring, J., Naarala, M., Nieminen, P., Wahlberg, K.-E., 2004. Genotype-environment interaction in schizophrenia-spectrum disorder: long-term follow-up study of Finnish adoptees. *Br. J. Psychiatry* 184, 216–222. <https://doi.org/10.1192/bjp.184.3.216>.
- Tienari, P., Wynne, L.C., Sorri, A., Lahti, I., Moring, J., Nieminen, P., Joukamaa, M., Naarala, M., Seitamaa, M., Wahlberg, K.-E., Miettunen, J., 2005. Observing relationships in Finnish adoptive families: Oulu family rating scale. *Nord. J. Psychiatry* 59, 253–263. <https://doi.org/10.1080/08039480500227683>.
- Varese, F., Smeets, F., Drukker, M., Lieveer, R., Lataster, T., Vichtbauer, W., Read, J., van Os, J., Bentall, R.P., 2012. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr. Bull.* 38, 661–671. <https://doi.org/10.1093/schbul/sbs050>.
- Wahlberg, K.-E., Wynne, L.C., Hakko, H., Läsky, K., Moring, J., Miettunen, J., Tienari, P.,

2004. Interaction of genetic risk and adoptive parent communication deviance: longitudinal prediction of adoptee psychiatric disorders. *Psychol. Med.* 34, 1531–1541. <https://doi.org/10.1017/S0033291704002661>.
- Wahlberg, K.-E., Wynne, L.C., Keskitalo, P., Nieminen, P., Moring, J., Läksy, K., Sorri, A., Koistinen, P., Tarvainen, T., Miettunen, J., Tienari, P., 2001. Long-term stability of communication deviance. *J. Abnorm. Psychol.* 110, 443–448. <https://doi.org/10.1037/0021-843X.110.3.443>.
- Wahlberg, K.E., Wynne, L.C., Oja, H., Keskitalo, P., Pykäläinen, L., Lahti, I., Moring, J., Naarala, M., Sorri, A., Seitamaa, M., Läksy, K., Kolassa, J., Tienari, P., 1997. Gene-environment interaction in vulnerability to schizophrenia: findings from the Finnish adoptive family study of schizophrenia. *Am. J. Psychiatry* 154, 355–362. <https://doi.org/10.1176/ajp.154.3.355>.
- Whitfield, C.L., Dube, S.R., Felitti, V.J., Anda, R.F., 2005. Adverse childhood experiences and hallucinations. *Child Abuse Negl.* 29, 797–810. <https://doi.org/10.1016/j.chiabu.2005.01.004>.
- Wynne, L.C., Tienari, P., Nieminen, P., Sorri, A., Lahti, I., Moring, J., Naarala, M., Läksy, K., Wahlberg, K.-E., Miettunen, J., 2006a. I. Genotype-environment interaction in the schizophrenia spectrum: genetic liability and global family ratings in the Finnish adoption study. *Fam. Process* 45, 419–434. <https://doi.org/10.1111/j.1545-5300.2006.00180.x>.
- Wynne, L.C., Tienari, P., Sorri, A., Lahti, I., Moring, J., Wahlberg, K.-E., 2006b. II. Genotype-environment interaction in the schizophrenia spectrum: qualitative observations. *Fam. Process* 45, 435–447. <https://doi.org/10.1111/j.1545-5300.2006.00181.x>.
- Zubin, J., Spring, B., 1977. Vulnerability: a new view of schizophrenia. *J. Abnorm. Psychol.* 86, 103–126. <https://doi.org/10.1037/0021-843X.86.2.103>.