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Interaction of genetic risk and adoptive parent communication deviance: longitudinal prediction of adoptee psychiatric disorders

KARL-ERIK WAHLBERG*, LYMAN C. WYNNE, HELINÄ HAKKO, KRISTIAN LÄKSY, JUHA MORING, JOUKO MIETTUNEN AND PEKKA TIENARI

Department of Psychiatry, University of Oulu, Oulu, Finland; Department of Psychiatry, University of Rochester, School of Medicine and Dentistry, Rochester, NY, USA

ABSTRACT

Background. In the Finnish Adoptive Family Study of Schizophrenia, adoptee thinking disorders have been shown to be a joint effect of genetic liability for schizophrenia spectrum disorders and adoptive rearing-parent communication patterns. However, longitudinal predictions of clinical psychiatric disorders of the adoptees have not been reported.

Method. Adoptees ($n=109$) who had no DSM-III-R disorder at initial assessment (median age 18 years) were selected from the total sample of the Finnish Adoption Study of Schizophrenia. They were defined as at high *versus* low genetic risk based upon the lifetime diagnoses of their biological, adopting-away mothers – schizophrenia spectrum disorder *versus* no spectrum disorder. At initial assessment, adoptive rearing parents were independently evaluated from tape-recorded Rorschach protocols scored as manifesting either high or low Communication Deviance (CD), a composite index of communication patterns that distract and befuddle listeners. Adoptees were independently re-diagnosed after a median interval of 14 years and followed-up from national registers for an additional 7 years.

Results. The main effects of genetic liability (G) and CD of the adoptive parents (E), each taken separately, predicted significantly for psychiatric disorders of the adoptees as adults. However, when G, E, and their joint interaction effect were entered into the same logistic model, only the interaction effect was significant. The sample included seven adoptees with schizophrenia spectrum disorders, but a separate analysis to predict them was non-significant.

Conclusion. Genetic liability for schizophrenia spectrum disorder and an adoptive family rearing variable interact, predicting longitudinally and significantly to broadly defined adoptee psychiatric disorder.

INTRODUCTION

Schizophrenia, resembling other complex disorders such as diabetes, has been increasingly viewed as non-mendelian, polygenic, and multifactorial with multiple genes of small effect (Nasrallah, 1993; Tsuang *et al.* 2001). Using diverse approaches to schizophrenia spectrum disorders and other psychiatric disorders, a consensus view has emerged that both genetic and environmental factors contribute to schizophrenia spectrum disorders (Weinberger, 1987; Andreasen, 1999; Cooper, 2001; Rutter & Silberg, 2002). Primary efforts are being made to integrate this genetic complexity with variables in the biological environment, especially the fetal environment and early postnatal biological

* Address for correspondence: Dr Karl-Erik Wahlberg, University of Oulu, Department of Psychiatry, Box 5000, FIN-90014, University of Oulu, Finland.
(Email: karl-erik.wahlberg@oulu.fi)

environment (Mednick *et al*. 1988; Cannon *et al*. 1993; Huttunen *et al*. 1994; McNeil *et al*. 1994; Jones *et al*. 1998; Cannon *et al*. 2000).

Viewed more broadly across the life-cycle, the later psychosocial environment, especially the rearing family, has sometimes been mentioned as possibly being contributory to gene expression, but has been empirically neglected in schizophrenia research. However, this important problem has been investigated earlier, for example in the area of parenthood and other mental disorders (Cadoret *et al*. 1995; Kendler, 1996). Adoption research is optimally suited for disentangling family rearing variables and genetic risk and can thereby make possible the study of this form of genetic liability (G) × Communication Deviance of adoptive parents (E) interaction (Tienari *et al*. 1994, 2002; Wahlberg *et al*. 1997).

Earlier findings have indicated that offspring of a schizophrenic parent have an elevated risk not only for schizophrenia (Gottesman, 1991) but also for schizophrenia spectrum disorders (Parnas *et al*. 1993; Erlenmeyer-Kimling *et al*. 1997; Tienari *et al*. 2000). Also, taking all psychiatric disorders together, offspring at genetic high risk for schizophrenia have a higher frequency than offspring at genetic low risk (Parnas *et al*. 1993; Tienari *et al*. 2000; Schubert & McNeil, 2003). However, in these studies (except for the Finnish Study, Tienari *et al*. 2000), the biological parents were also the rearing parents, so genetic and environmental risk could not be differentiated. In earlier adoption studies of schizophrenia (Heston, 1966; Rosenthal *et al*. 1971, 1975; Kety *et al*. 1978) the rearing family environment and, thus, the interaction of genotype and rearing family environment, were not assessed.

Communication Deviance (CD) of adoptive rearing parents has been conceptualized as a relatively enduring and stable 'environmental' stressor (Wahlberg *et al*. 2001) within the adoptive family system, as a reciprocal interpersonal process between persons that is primarily important between rearing parents and their developing offspring, but is not in itself a measure of psychiatric disorder. The CD instrument provides an empirical measure of multiple qualities of communication that would leave a listener uncertain, puzzled and unable to share a focus of attention with the speaker (Singer & Wynne, 1966; Singer *et al*. 1978; Doane, 1985; Miklowitz & Stackman, 1992).

Cognitive development is especially difficult for children who have inborn difficulties in focusing attention, processing information, and deriving contextual meaning (Nuechterlein & Dawson, 1984; Nuechterlein *et al*. 1989). It is possible that genetic transmission of this kind of vulnerability can interact with life experience, hypothetically including enduring parental patterns of high frequencies of CD. Previous reports from the Finnish Adoption Study have documented that such G × E interaction impairs adoptee thinking on a subsyndromal level, assessed with the Index of Primitive Thought and the Thought Disorder Index (Wahlberg *et al*. 1997, 2000).

On the basis of other earlier research, we conclude that parental CD is relevant but nonspecific for schizophrenia (Wynne *et al*. 1977; Ditton *et al*. 1987). The relationship of CD to schizophrenia and other disorders is a matter of frequency along a continuum without a sharp cutting point related to psychiatric diagnoses. Prospectively, in families studied longitudinally after initial contact in a clinic for non-psychotic, distressed adolescents, those who had parents with high CD tended to develop schizophrenia spectrum disorder more frequently during the subsequent 15 years than did adolescents with low CD parents (Goldstein, 1987).

Because CD is not specific for schizophrenia or spectrum disorders in offspring, the development of additional psychiatric disorders (such as non-schizophrenia-related personality disorders, non-psychotic depression, anxiety disorders, and alcohol abuse) can hypothetically be included in a hierarchy of disorders that is most distinctively at risk for schizophrenia and schizophrenia spectrum disorders. It is also plausible to hypothesize that an interaction between genetic liability to schizophrenia and familial environment may have its impact in the development of either positive mental health or a mental disorder, including, but not restricted to, schizophrenia spectrum disorders. 'Healthy' communication, or low CD of adoptive parents may, hypothetically, neutralize or forestall the full expression of illness. Alternatively, the likelihood of illness may be elevated when genetic vulnerability interacts with a high-CD rearing environment.

Table 1. *Criteria for excluding cases from the total sample of the Finnish Adoption Study*

	High risk adoptees	Low risk adoptees	Total
Total sample of the Finnish Adoptive Study of Schizophrenia	190	192	382
Exclusion criteria			
DSM-III-R diagnosis not obtained at initial assessment of adoptee	20	23	43
DSM-III-R diagnosis given adoptee at initial assessment	58	35	93
One or both adoptive parents were dead	41	37	78
CD of both adoptive parents was not measured	29	30	59
Total number of families included in subsample	42	67	109

The primary hypothesis to be tested here is: CD of adoptive parents, assessed antecedent to adoptee disorder, interacts with genetic risk from biological mothers to predict longitudinally for later psychiatric disorders, including both spectrum and non-spectrum disorders, of adoptees. Further, we hypothesize that this joint effect of CD and genetic risk will be a more significant predictor of adoptee illness than either genetic risk or adoptive-parent CD alone.

METHOD

Subject selection for the sample

The total Finnish national adoption high-risk sample includes the adoptive families of all the children adopted away by women hospitalized because of schizophrenia (or paranoid psychosis) in Finland from 1960 to 1979. A final sample included 190 offspring at genetic high risk, defined as having biological mothers with DSM-III-R diagnoses (APA, 1987) in the broad schizophrenia spectrum (Kendler, 1996; Tienari *et al*. 2000, 2003). Correspondingly, 192 adoptees in the final sample were at genetic low risk, with biological mothers who had a non-spectrum diagnosis or no psychiatric disorder. Details of the selection procedures for the adoption study as a whole have been described earlier (Tienari *et al*. 1987, 2000).

In this report, we shall describe longitudinal findings from a subsample of 109 adoptees and their adoptive parents. This subsample was screened to include only those adoptees who had no psychiatric disorder at initial assessment. An exception was Adjustment Disorder, diagnosed using DSM-III-R criteria as a response to an identifiable stressor with a reaction persisting for less than 6 months. Because of our concern with longer-term outcomes, we did not exclude five adoptees, who had been given this diagnosis at initial assessment.

A second inclusion criterion was that test measures of CD of both adoptive parents had been obtained independently at initial family evaluation at the time of the initial assessment of the adoptees. Exceptions were three single-parent families (an adoptive father had never existed) in which the CD of the tested mother was multiplied by two. In these families, the mother represented the whole parental communication atmosphere in the family. Therefore, the mothers' scores were doubled to obtain a CD score that would be comparable to the CD score of families with two rearing parents. However, when the CD measure was missing for a parent who had been involved in rearing, the family was excluded from the sample. Our efforts to find an adequate statistical method to replace a missing CD for a non-rearing parent have not been successful. We do not have enough relevant information to calculate a satisfactory substitute for these missing CD scores. The exclusion criteria and frequencies of the excluded adoptive families are presented in Table 1.

Demographic variables

All of the adoptees in this subsample were disorder-free at initial assessment. They were independently re-diagnosed after a median interval of 14 years. Thereafter they were followed until the end of the year 2000 from national hospital and clinic registers (Tienari *et al*. 2000, 2003). The median interval for the whole follow-up was 21 years.

At initial assessment, the median age of the adoptees included in this subsample of 109 families was 18 years *versus* 30 years in the excluded adoptees. The greater age of the excluded

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adoptees can be expected because of the increased probability of a lifetime disorder as people become older. Additionally, the adoptive parents of relatively old adoptees had more often already died or were too old to be tested (exclusion criterion).

At the end of follow-up, the median age of adoptees was 39·0 [interquartile range (IR) 32·5–44·0] years. For the adoptive mothers, the median age at initial assessment was 52·6 (IR 47·2–57·7) years; and for the adoptive fathers, 53·8 (IR 50·5–60·7) years. Median age at separation from biological mother was 3 months. In this subsample 53 [16 high genetic risk (HR) and 37 low genetic risk (LR) adoptees] of the adoptees were female and 56 (26 HR and 30 LR adoptees) were male. Using the Finnish 4-level classification of socioeconomic status based on the social status of the main provider's occupation and education (Handbook for Office of Statistics 17, 1983), 12% of the families were rated as being in social class I, 50% in social class II, 37% in social class III, and 1% in social class IV. In the present subsample none of these demographic variables of the adoptive parents and adoptees differed significantly in the high *versus* low genetic risk group.

Diagnoses of the biological mothers

In this subsample 42 adoptees had biological mothers with diagnoses of a schizophrenia spectrum disorder. These adoptees, defined as at high genetic risk are compared with 67 adoptees, defined as at low genetic risk, with biological mothers who did not have a schizophrenia spectrum disorder. The DSM-III-R diagnosis of 30 of the 42 biological mothers of the HR adoptees was 'typical' schizophrenia at the definite or probable level of certainty. The other 12 mothers had DSM-III-R diagnoses in a 'broad schizophrenia spectrum' (Kendler *et al.* 1996; Tienari *et al.* 2003) – 4 schizophreniform, 1 schizoaffective, 3 schizotypal personality disorders (PD), 1 schizoid PD, 1 avoidant PD, 1 bipolar psychosis, and 1 depressive psychosis. All of these biological mothers were independently and reliably diagnosed using DSM-III-R criteria (Tienari *et al.* 2000). We report here the findings using this broad definition of schizophrenia spectrum disorders on the grounds that they have been found to be marginally included in at least two studies (Kendler *et al.* 1996; Tienari *et al.* 2000, 2003) of the spectrum. When we reanalyzed the sample excluding the four diagnostically marginal adoptees with biological mothers having schizoid PD, avoidant PD and affective psychoses, the findings were identical with those presented here.

CD of adoptive parents

CD of the adoptive parents was used as the primary environmental variable (E) for this report. We have used 42 categories adapted from the Singer–Wynne Rorschach scoring manual (Singer & Wynne, 1966; Singer *et al.* 1978; M. T. Singer and L. C. Wynne, unpublished 1986 version). Dr Singer provided earlier training for Dr Wahlberg in the scoring of CD and minor modifications of the scoring in Finnish compared to English were discussed (Wahlberg, 1994). The most frequent and influential items of the CD scale are 'Abandoned, abruptly ceased, uncorrected remarks', 'Inability or failure to verify own responses', 'Odd sentence construction' and 'Reiteration'.

CD of both adoptive parents was assessed from tape-recorded individual Rorschach test protocols, which had been transcribed according to standardized writing instructions. These test transcriptions had been obtained from the initial family evaluation (independently of the diagnostic procedure with the adoptees). CD of the adoptive parents was calculated separately for each parent as the frequency of scored CD categories divided by the number of transactions (responses) in the individual Rorschach test. The sum of these quotients was used as the CD for each parental pair. The intra-class correlation coefficient for total CD scored by two psychologists was 0·95 (51 records scored).

The adoptive parental pairs selected for this report, were partitioned into 55 low CD parents (CD below the CD median) and 54 high CD parents (CD above the CD median). The total CD for each adoptive parental pair has been used because growing children have been exposed to the communication patterns of both parents. However, we also report the main result having CD of the adoptive parents separately in logistic regression analyses.

In order to examine the content of CD categories, they have been divided into six subgroups that seem to be relatively clearly

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Table 2. *Classification of cases* (*proportions*) *of psychiatric disorders of the adoptees assessed by genetic and environmental risk*

Genetic liability of the adoptees	Communication Deviance of the adoptive parents					
	Low CD		High CD		Total	
	n	%	*n*	%	*n*	%
Low risk	4/37	10·8	4/30	13·3	8/67	11·9
High risk	2/18	11·9	15/24	62·5	17/42	40·5
Total	6/55	10·7	19/54	35·8	25/109	22·9

differentiated conceptually. The intra-class correlation coefficients for the subgroups were as follows: 0·93 for subgroup I (Disruptions of task and relationship with tester), 0·86 for subgroup II (Problems of commitment and sustaining task set), 0·91 for subgroup III (Unclear and unstable referents), 0·92 for subgroup IV (Language anomalies), 0·88 for subgroup V (Reasoning problems and contradictions), and 0·76 for subgroup VI (Indefinite and cryptic comments). The reliabilities of the subgroups from I to V are quite similar ranging from 0·86 to 0·93. However, reliability is lower in subgroup VI than on the other subscales because there are so few items on this subscale. Therefore, even minor inter-rater scoring differences are more significant than they would have been if the items had been more numerous.

DSM-III-R diagnoses of the adoptees

DSM-III-R diagnoses (APA, 1987) of the adoptees at follow-up have been obtained for all subjects of the study (Tienari *et al*. 2000). The kappa coefficient for inter-rater reliability varied between different raters from 0·71 to 0·80.

The adoptees were divided into two groups based on diagnoses at follow-up. The 'psychiatric disorder' group of 25 included 7 adoptees (5 HR and 2 LR adoptees) with a schizophrenia spectrum disorder (Kendler *et al*. 1996). None had typical schizophrenia. In the adoptees with non-spectrum disorders at follow-up, 3 had non-psychotic depression, 12 with cluster B and C personality disorders, 2 with anxiety disorder, and 1 with alcohol abuse. The 'no disorder' group consisted of 84 adoptees, who did not have any disorder at follow-up, this including the 5 adoptees with initial Adjustment Disorder.

Statistical analyses

All of the CD categories and groups had a distribution skewed to the right. Therefore, we have used non-parametric statistics (Bland, 1995). We modeled the association of psychiatric disorders with the risk factors, genetic liability and communication deviance, using logistic regression (e.g. McCullagh & Nelder, 1989). To control for confounding, we included age of the adoptees at the initial assessment, gender of the adoptees, age of adoptees at placement, and social class of the adoptive family at the time of adoption as covariates in all the models.

RESULTS

Genetic and environmental effects on the psychiatric disorders of the adoptees

Table 2 shows the proportion of adoptees with psychiatric disorders when they are classified according to the two dimensions of genetic liability and CD of the adoptive parental pairs.

The marginal percentages show the proportion of adoptees at low genetic risk (11·9%) compared to those at high genetic risk (40·5%) – almost a fourfold difference [adjusted odds ratio (OR) 5·06, $p < 0·01$, 95% confidence interval (CI) 1·76–14·60]. The proportion of disordered adoptees with rearing parents who have low CD (below the median for parental pairs) is 10·7% compared to adoptees with high-CD rearing parents (35·8%) – more than a threefold difference (adjusted OR 4·22, $p < 0·01$, 95% CI 1·43–12·46).

Logistic regression analysis predicting to adoptee psychiatric disorder

Table 3 reports the results for three logistic regression analyses. The likelihood of adoptee psychiatric disorder was predicted for high *versus* low genetic risk (G); for high *versus* low adoptive parent CD (E) (for both adoptive parents, adoptive mothers only and adoptive fathers only); and for the interaction of G × E.

In this logistic model the main effects of genetic risk and CD of the adoptive parents as pairs were both non-significant. However, when these two variables were entered into the same logistic model, only the G × E interaction effect was significant, with an adjusted OR of 10·00, $p = 0·05$, 95% CI 1·00–99·73. The interaction can be seen also in Table 2. The risk for adoptee

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Table 3. *Logistic regression analyses: likelihood for psychiatric disorder of the adoptees predicted from Communication Deviance (CD) of adoptive parental pairs, adoptive mothers and adoptive fathers, from genetic risk for schizophrenia spectrum disorders, and from the interaction of CD and genetic risk*

Risk factor	Adoptive parents ($n=109$) OR* (95% CI)	p	Adoptive mothers ($n=146$) OR* (95% CI)	p	Adoptive fathers ($n=112$) OR* (95% CI)	p
CD	1·40 (0·31–6·28)	0·66	0·38 (0·10–26·13)	0·14	1·04 (0·20–5·36)	0·96
Genetic risk	1·12 (0·18–7·14)	0·91	1·64 (0·58–4·69)	0·35	3·69 (0·90–15·02)	0·07
Interaction of CD and genetic risk	10·00 (1·00–99·73)	0·05	4·63 (0·82–26·13)	0·08	2·38 (0·30–18·69)	0·41

* Adjusted for age of the adoptees at the initial assessment, gender of the adoptees, age of adoptees at placement, and social class of the adoptive family at the time of adoption.

psychiatric illness increases substantially (to 62·5%) when an adoptee had both high genetic risk and rearing parents with high CD compared to other entries (from 10·8 to 13·3) of the table.

In 40 cases, the CD was only available for one of the parents. We, therefore, fitted two additional logistic models; one based on all available responses of adoptive mothers for the CD measure and the other on all available responses of adoptive fathers. Both models included main effects and interaction between the two risk dimensions adjusted for age, gender and social class (Table 3). At the 5% level, neither of these two models was significant. However, the model based on mothers' data showed a trend for the interaction effect ($p=0·08$) and for the fathers' data the main effect for genetic risk also showed a trend ($p=0·07$).

Prediction of schizophrenia spectrum disorders of the adoptees

Finally, in an effort to predict adoptee outcome of schizophrenia spectrum disorders, considered separately from other mental disorders, we attempted a multinomial logistic regression analysis, where the mental disorders of the adoptees were divided into three groups: no disorder, non-spectrum psychiatric disorders, and schizophrenia spectrum disorders. However, with the small numbers available, this effort was not successful; a meaningful model could not be produced.

Also, we fitted a logistic regression model predicting schizophrenia spectrum disorder of the adoptees (7 cases), as in previous analyses, with main effects and interaction. Four out of seven (57·1%) were spectrum cases, hinting at the possibility of a genotype–environment interaction (HR adoptees of high-CD adoptive parents). The prevalence of schizophrenia spectrum disorders was slightly higher (4/109, 3·7%) among the adoptees who had both a high genetic risk and high-CD adoptive parents compared to the other risk combinations (the remaining three cases were divided equally into these categories) of genetic risk and CD of adoptive parents (all other combinations 1/109, 0·9%). However, the logistic model did not produce a statistically significant effect either for main effects or the genotype–environment interaction. OR for genotype–environment interaction was 2·57 ($p=0·61$, 95% CI 0·07–96·59), 2·18 ($p=0·60$, 95% CI 0·13–36·91) for genetic liability and 1·32 ($p=0·85$, 95% CI 0·08–22·06) for CD of the adoptive parents.

Separate unsuccessful logistic regression analyses were attempted for adoptees taking CD of the adoptive mothers or CD of the adoptive fathers together with genetic risk and genotype–environment interaction as risk indicators in the models. However, schizophrenia spectrum adoptees could not be predicted in these logistic models.

CD subgroups as environmental variable in interaction with the genetics

Given that CD is a complex, multiform set of variables, we examined the predictive strength for each of the subgroups of CD categories. Four out of the six CD subgroups of the adoptive parents [(I) Disruptions of task and relationship with tester; (III) Unclear and unstable referents; (IV) Language anomalies; (VI) Indefinite and cryptic comments] had no

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predictive connection with adoptee disorder. However, with CD in subgroup II (Problems of commitment and sustaining task set), the adjusted ORs were 5·87 ($p=0·03$, 95% CI 1·19–29·05) for genotype–environment interaction, 0·39 ($p=0·47$, 95% CI 0·03–5·00) for genetic liability and 0·94 ($p=0·90$, 95% CI 0·37–2·39) for the CD of the adoptive parents. Also, CD in subgroup V (Reasoning problems and contradictions) the ORs were 28·09 ($p<0·01$, 95% CI 2·87–275·07) for genotype–environment interaction, 1·13 ($p=0·87$, 95% CI 0·26–4·82) for genetic liability and 0·34 ($p=0·22$, 95% CI 0·06–1·92) for CD of the adoptive parents.

Adoptee genetic liability and initial disorder in relation to rearing parent CD

Because of the possibility that genetic liability to schizophrenia spectrum disorder of the adoptees had induced increased CD in the adoptive rearing parents, we compared the CD of the rearing parents of adoptees at high genetic risk with the CD of rearing parents of adoptees at low genetic risk. There was no significant difference in the CD of these two cohorts of rearing parents ($\chi^2=1·58$, df = 1, $p=0·21$). Further, we examined the 93 adoptive families who had been excluded because of an initial DSM-III-R diagnosis of the adoptee. CD had been measured in both rearing parents of 30 of these adoptees. We found that these 30 excluded parental pairs had a distribution of high and low CD similar to that for the subsample of the 109 parental pairs who have been included in this report ($\chi^2=1·22$, df = 1, $p=0·31$). These two findings indicate that neither diagnosed disorders of excluded adoptees nor genetic liability of the adoptees, perhaps having a subsyndromal impact by the time of initial assessment, had significantly produced increased CD in their adoptive parents.

DISCUSSION

At first sight, the results support both the genetic and environmental hypotheses concerning psychiatric disorders. The adoptees at genetic high risk have more psychiatric disorders than the adoptees at low genetic risk, as demonstrated in other findings in which only genetic risk for schizophrenia spectrum disorders are reported (Parnas *et al.* 1993; Tienari *et al.* 2000; Schubert & McNeil, 2003). Similarly, the adoptees with high-CD adoptive parents have more mental disorders than the adoptees with low-CD adoptive parents.

However, when both genetic background and the CD of the adoptive parents and their interaction term were in the same logistic model, the genotype–environment interaction was highlighted as the only significant predictor of the mental disorder of the adoptees. The results of these three logistic regression models indicate that there is a genotype–environment interaction. When adoptees at genetic high risk have high-CD adoptive parents but neither CD of the adoptive parents nor genotype–environment interaction is entered in the model, these adoptees are included in the genetic main effect. Similarly, when the model starts with adoptees having high-CD adoptive parents without entering data for genetic high risk nor for $G \times E$ interaction, the OR for E is inflated by including the interaction effect.

The results confirm our first hypothesis that there is a genotype–environment interaction that predicts to mental disorder of the adoptees. This interaction is a more significant predictor of adoptee illness than either genetic high risk or CD of the adoptive parents taken alone, as stated in our second hypothesis.

CD has been calculated earlier as the sum of the CD of both parents. We wanted to see if CD of only one parent would predict adoptee mental disorder. This procedure adds to the number of cases because we need not then exclude those families in which the CD of only one parent has been assessed. We found that the best predictor was the CD of both adoptive parents. Predictions of mental illness from the CD of one adoptive parent were not significant. We recommend that studies using CD, and perhaps other family variables, as a rearing parent variable should include data from both parents. This finding indicates that growing children are influenced by the communication patterns of both parents.

The CD of the adoptive parents was measured 21 years before the final follow-up research evaluation was carried out. Few psychiatric disorders (including schizophrenia spectrum disorders), were found in the group of adoptees at genetic low risk with high-CD adoptive parents, and in adoptees at genetic

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high risk with low-CD adoptive parents. In this context, the adjusted OR of 10·00 when genetic high risk was combined with high-CD rearing parents is striking. This pattern of the findings is in accord with the hypothesis of Kendler & Eaves (1986) that genotype–environment interaction can be expressed as genetic control of sensitivity to the environment or as environmental control of gene expression. The results here also are consistent with the idea that growing up in a clear and understandable family environment (low CD environment) is supportive of healthy cognitive development, even in adoptees at genetic high risk.

The findings of this study are consistent with an epigenetic view of development (Singer & Wynne, 1965; Gottesman, 1991). From this developmental perspective, the individual's biological capacities are shaped and modified at each developmental phase by interchange with the environment. In recent years, considerable research has emerged examining aspects of neurodevelopmental theory (Weinberger, 1987, 1996; Bassett *et al*. 2001). These studies have used genetic evidence as a starting point but have emphasized sequential changes between brain functioning and the biological environment. We suggest that this interchange continues with psychosocial life experience that can help shape not only interpersonal and psychological processes but also diagnostic phenotypes and, conceivably, may even modify patterns of brain functioning (Brody *et al*. 2001).

The adoptees at high genetic risk in this study may manifest genetic vulnerability similar to that found as abnormalities in attentional functioning and information processing in nonpsychotic offspring and siblings of schizophrenic patients (Nuechterlein & Dawson, 1989; Nuechterlein *et al*. 1994). Hypothetically, these difficulties would be interwoven and augmented with the effects of an unstable environment during the early development of cognitive functions.

CD was found with equal frequency in the adoptive parents of children at both genetic high and low risk. This supports the hypothesis and the previous finding that genetic high risk of the adoptees is not in itself the source of elevated CD of the adoptive parents (Wahlberg *et al*. 1997). Alternative genotypes and diverse biological and psychosocial environments should be considered from a joint interactional perspective.

This subsample of families with adoptees who were initially disorder-free had a distribution of high and low CD similar to that in the families excluded from the subsample because of initial disorders of the adoptees. That may be interpreted to mean that adoptee disorder has not caused the high CD of the adoptive parents nor has high CD of the adoptive parents alone contributed to psychiatric disorders of the adoptees. Unfortunately, in only one third of the excluded families had the CD of both adoptive parents been measured and, therefore, this interpretation must be regarded as tentative.

The total CD and two CD subscales of the adoptive parents predicted the psychiatric disorder of the adoptees at high genetic risk. The Problems of Commitment and Sustaining Task Set subscale measures verbal behavior where a speaker is incapable of continuing the expression of a thought or is not able to confirm and take responsibility for his words. This subscale is very different from the subscale on Reasoning Problems and Contradictions, which also predicted significantly the mental disorder of the adoptees. Items on this subscale may be associated with more severe forms of thought disorder, also measured in the Thought Disorder Index (TDI) (Johnston & Holzman, 1979; Solovay *et al*. 1986). Thus, the CD scale is not only a composite of certain forms of communication disturbances between people but also may be related to features of formal thought disorder. More research is needed concerning the components and details of CD, especially in relation to the development of neurocognitive measures of the child and adolescent.

Strengths and limitations of the study

A major strength of the study is that the effects of environment and genetic liability to schizophrenia have been separated by independent assessment of the biological (birth) parents and the adoptive rearing families. Further, the study is longitudinal, with a median interval of 14 years between initial assessment of the adoptees and the follow-up evaluation by a new investigator.

In this report we have partially 'purified' the subsample by excluding adoptees who had

almost any psychiatric disorder at initial assessment. We intended to reduce the frequency of early problems that could have had an impact upon the communication patterns of the adoptive parents. However, this sharply reduced the sample size even though the statistical significance is high for the combination of genetic liability and high CD of adoptive rearing parents.

Because the adoptees selected for this subsample were uniformly free of a formal diagnosis at the time of initial assessment, the follow-up adoptee diagnoses, when found, did involve definite longitudinal change. However, this may mean that these adoptees were less severely vulnerable genetically than the excluded adoptees who were already disordered at initial assessment or were fortunate enough to have had adoptive parents who showed less disordered CD. But, if so, then the difference between the adoptees at high and low genetic risk would be diminished and our positive findings become all the more persuasive.

CD is stable in adulthood over a substantial time span, but is unstable during adolescence (Wahlberg *et al*. 2001). This suggests that CD of the adoptive parents, as adults, was presumably undergoing minimal change during adoptee development. Even though the adoptees were uniformly disorder-free initially, it is nevertheless possible that subsyndromal problems of the adoptees may have had some degree of impact upon their adoptive parents prior to the initial assessment. This interesting hypothesis requires further investigation.

Both in this study and in other studies of the relatives of schizophrenic subjects, when only the genetic contribution is examined, the genetic liability fades away gradually to non-significance for biological relatives of non-spectrum subjects. Surprisingly, in this report, when the non-specific effect of the environmental variable is viewed in interaction with genetic liability, the result extends beyond the schizophrenia spectrum to include other long-lasting disorders found in the adoptees who have become adults. This result is consistent with the finding that rearing parent CD is not specific for schizophrenia but does emerge as relevant when combined with genetic liability.

A limitation in this study is that the genetic effects of the biological fathers have not been assessed. As previously reported (Tienari *et al*. 2000), 57·3% of the biological fathers have been identified. We may assume that men who impregnated these women are a selected group of men who may have had personality traits or other problems connected to genetic liability. However, this question must be left open because we do not have enough information from the biological fathers to use statistical analyses. Further, even though the onset of illness in most of the biological mothers in this subsample took place after the birth of the child, it is nevertheless possible that the premorbid traits of the biological mothers may have been an undiagnosed factor.

From a broad perspective, it should be recognized that the composite 'environmental' variable that we have selected for this report – Communication Deviance assessed in the adoptive parents – taps only a small fraction of the multifactorial environmental influences that may modify genetic expression leading to the multifactorial 'entity' that has been called the schizophrenia spectrum. This cautionary note is applicable to the biological environment as well as the psychosocial environment.

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DECLARATION OF INTEREST

None.

REFERENCES

Andreasen, N. C. (1999). Understanding the causes of schizophrenia. *New England Journal of Medicine* **340**, 645–647.

APA (1987). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association: Washington, DC.

Bassett, A. S., Chow, E. W. C., O'Neill, S. & Brzustowicz, L. M. (2001). Genetic insights into the neurodevelopmental hypothesis of schizophrenia. *Schizophrenia Bulletin* **27**, 417–430.

Bland, M. (1995). *An Introduction to Medical Statistics*. Oxford University Press: Oxford.

Brody, A. L., Saxena, S., Stoessel, P., Gillies, L. A., Fairbanks, L. A., Alborzian, S., Phelps, M. E., Huang, S. C., Wu, H. M., Ho, M. L., Ho, M. K., Au, S. C., Maidment, K. & Baxter Jr., L. R. (2001). Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. *Archives of General Psychiatry* **58**, 631–640.

Cadoret, R. J., Yates, W. R., Troughton, E., Woodworth, G. & Stewart, M. A. (1995). Genetic-environmental interaction in the genesis of aggressivity and conduct disorders. *Archives of General Psychiatry* **52**, 916–924.

Cannon, T. D., Mednick, S. A., Parnas, J., Schulsinger, F., Praestholm, J. & Vestergaard, A. (1993). Developmental brain abnormalities in the offspring of schizophrenic mothers. I. Contributions of genetic and perinatal factors. *Archives of General Psychiatry* **50**, 551–564.

Cannon, T. D., Rosso, I. M., Hollister, J. M., Bearden, C. E., Sanchez, L. E. & Hadley, T. (2000). A prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia. *Schizophrenia Bulletin* **26**, 351–366.

Cooper, B. (2001). Nature, nurture and mental disorder: old concepts in the new millennium. *British Journal of Psychiatry* **178**, 91–101.

Ditton, P., Green, R. J. & Singer, M. T. (1987). Communication Deviances: a comparison between parents of disabled and normally achieving students. *Family Process* **26**, 75–88.

Doane, J. A. (1985). Parental communication deviance and offspring psychopathology. In *The Handbook of Family Psychology and Therapy* (ed. L. L'Abate), pp. 937–958. Dorsey Press: Homewood, IL.

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. *Archives of General Psychiatry* **54**, 1096–1102.

Goldstein, M. J. (1987). Family interaction patterns that antedate the onset of schizophrenia and related disorders: a further analysis of data from a longitudinal, prospective study. In *Understanding Major Mental Disorder: The Contribution of Family Interaction Research* (ed. H. Hahlweg and M. J. Goldstein). Family Process Press: New York.

Gottesman, I. I. (1991). *Schizophrenia Genesis. The Origins of Madness*. W. H. Freeman and Company: New York.

Handbook for Office of Statistics 17 (1983). The Center for Statistics: Helsinki.

Heston, L. L. (1966). Psychiatric disorders in foster home reared children of schizophrenic mothers. *British Journal of Psychiatry* **112**, 819–825.

Huttunen, M., Machon, R. A. & Mednick, S. A. (1994). Prenatal factors in the pathogenesis of schizophrenia. *British Journal of Psychiatry* **23** (Suppl.), 15–19.

Johnston, M. H. & Holzman, P. S. (1979). *Assessing Schizophrenic Thinking*. Jossey-Bass Publishers: San Francisco.

Jones, P., Rantakallio, P., Hartikainen, A.-L., Isohanni, M. & Sipilä, P. (1998). Schizophrenia as a long-term outcome of pregnancy, delivery and perinatal complications: a 28 year follow-up of the 1966 Northern Finland general population birth cohort. *Journal of American Psychiatry* **155**, 355–364.

Kendler, K. (1996). Parenting: a genetic-epidemiologic perspective. *American Journal of Psychiatry* **153**, 11–20.

Kendler, K. S. & Eaves, L. J. (1986). Models for the joint effect of genotype and environment on liability to psychiatric illness. *Journal of American Psychiatry* **143**, 279–289.

Kendler, K. S., O'Neill, F. A., Burke, J., Murphy, B., Duke, F., Straub, R. E., Shinkwin, R., Ni Nuallain, M., MacLean, C. J. & Walsh, D. (1996). Irish study on high-density schizophrenia families: field methods and power to detect linkage. *American Journal of Medical Genetics* **67**, 179–190.

Kety, S. S., Rosenthal, D., Wender, P. H., Schulsinger, F. & Jacobsen, B. (1978). The biologic and adoptive families of adopted individuals who became schizophrenic: prevalence of mental illness and other characteristics. In *The Nature of Schizophrenia* (ed. L. C. Wynne, R. L. Cromwell and S. Matthysse), pp. 25–37. Wiley: New York.

McCullagh, P. & Nelder, J. A. (1989). *Generialized Linear Models*. Chapman and Hall: New York.

McNeil, T. F., Cantor-Graae, E. & Sjöström, K. (1994). Obstetric complications as antecedents of schizophrenia: empirical effects of using different obstetric complication scales. *Journal of Psychiatric Research* **28**, 519–530.

Mednick, S. A., Machon, R. A., Huttunen, M. O. & Bonett, D. (1988). Adult schizophrenia following prenatal exposure to an influenza epidemic. *Archives of General Psychiatry* **45**, 189–192.

Miklowitz, D. J. & Stackman, D. (1992). Communication Deviance in families of schizophrenic and other psychiatric patients: current state of the construct. In *Psychopathology Research*, vol. 15 (ed. E. F. Walker), pp. 1–46. Springer Publishing Company: New York.

Nasrallah, H. A. (1993). Neurodevelopmental pathogenesis of schizophrenia. *Psychiatric Clinics of North America* **16**, 269–280.

Nuechterlein, K. H., Buchsbaum, M. S. & Dawson, M. E. (1994). Neuropsychological vulnerability to schizophrenia. In *The Neuropsychology of Schizophrenia* (ed. A. S. David and J. C. Cutting), pp. 53–77. Lawrence Erlbaum Associates: Hillsdale.

Nuechterlein, K. H. & Dawson, M. E. (1984). A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophrenia Bulletin* **10**, 300–312.

Nuechterlein, K. H., Goldstein, M. J., Ventura, J., Dawson, M. E. & Doane, J. A. (1989). Patient-environment relationships in schizophrenia: information processing, communication deviance, autonomic arousal, and stressful life events. *British Journal of Psychiatry* **5** (Suppl.), 84–89.

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. *Archives of General Psychiatry* **50**, 707–714.

Rosenthal, D., Wender, P. H., Kety, S. S., Schulsinger, F., Welner, J. & Rieder, R. O. (1975). Parent-child relationships and psychopathological disorder in the child. *Archives of General Psychiatry* **32**, 466–476.

Rosenthal, D., Wender, P. H., Kety, S. S., Welner, J. & Schulsinger, F. (1971). The adopted-away offspring of schizophrenics. *Journal of American Psychiatry* **128**, 307–311.

Rutter, M. & Silberg, J. (2002). Gene-environment interplay in relation to emotional and behavioral disturbance. *Annual Review of Psychology* **53**, 463–490.

Schubert, E. W. & McNeil, T. (2003). Prospective study of adult mental disturbance in offspring of woman with psychosis. *Archives of General Psychiatry* **60**, 473–480.

Singer, M. T. & Wynne, L. C. (1965). Thought disorder and family relations of schizophrenics. III. Methodology Using Projective Techniques. *Archives of General Psychiatry* **12**, 187–200.

Singer, M. T. & Wynne, L. C. (1966). Principles for scoring communication defects and deviances in parents of schizophrenics: Rorschach and TAT scoring manual. *Psychiatry* **29**, 260–288.

Singer, M. T., Wynne, L. C. & Toohey, M. T. (1978). Communication disorders and the families of schizophrenics. In *The Nature of Schizophrenia* (ed. L. C. Wynne, R. L. Cromwell and S. Matthysse), pp. 499–511. John Wiley & Sons: New York.

Solovay, M. R., Shenton, M. E., Gasperetti, C., Colleman, M., Kestenbaum, E., Carpenter, J. T. & Holzman, P. S. (1986). Scoring manual for the Thought Disorder Index. *Schizophrenia Bulletin* **12**, 483–496.

Tienari, P., Sorri, A., Lahti, I., Naarala, M., Wahlberg, K.-E., Moring, J., Pohjola, J. & Wynne, L. C. (1987). Genetic and psychosocial factors in schizophrenia: the Finnish adoptive family study. *Schizophrenia Bulletin* **13**, 477–484.

Tienari, P., Wynne, L. C., Moring, J., Lahti, I., Naarala, M., Sorri, A., Wahlberg, K.-E., Saarento, O., Seitamaa, M., Kaleva, M. & Läksy, K. (1994). The Finnish adoptive family study of schizophrenia: implications for family research. *British Journal of Psychiatry* **23** (Suppl.), 20–26.

Tienari, P., Wynne, L. C., Moring, J., Läksy, 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 Psychiatrica Scandinavica* **101**, 433–443.

Tienari, P., Wynne, L. C., Läksy, 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. *American Journal of Psychiatry* **160**, 1587–1594.

Tienari, P, Wynne, L. C., Sorri, A., Lahti, I., Läksy, K., Moring, J., Naarala, M., Nieminen, P., Wahlberg, K.-E. & Miettunen, J. (2002). Genotype-environment interaction in the Finnish adoptive family study – Interplay between genes and environment? In *Risk and Protective Factors in Schizophrenia* (ed. H. Häfner), pp. 29–38. Steinkopff Verlag: Darmstadt.

Tsuang, M. T., Stone, W. S. & Faraone, S. V. (2001). Genes, environment and schizophrenia. *British Journal of Psychiatry* **178** (Suppl.), S19–S24.

Wahlberg, K.-E. (1994). Parental communication and thought disorders of the offspring: an adoptive study. *Acta Universitatis Ouluensis D* **305**, 116–132.

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). Stability of Communication Deviance. *Journal of Abnormal Psychology* **110**, 443–448.

Wahlberg, K.-E., Wynne, L. C., Oja, H., Keskitalo, P., Anias-Tanner, H., Koistinen, P., Tarvainen, T., Hakko, H., Lahti, I., Moring, J., Naarala, M., Sorri, A. & Tienari, P. (2000). Thought Disorder Index of Finnish adoptees and communication deviance of their adoptive parents. *Psychological Medicine* **30**, 127–136.

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. *American Journal of Psychiatry* **154**, 355–362.

Weinberger, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry* **44**, 660–669.

Weinberger, D. R. (1996). On the plausibility of the neurodevelopmental hypothesis of schizophrenia. *Neuropsychopharmacology* **14** (Suppl. 3), S1–S11.

Wynne, L. C., Singer, M. T., Bartko, J. & Toohey, M. L. (1977). Schizophrenics and their families: research on parental communication. In *Developments in Psychiatric Research* (ed. J. M. Tanner), pp. 254–286. Hodder & Stoughton: London.