Childhood predictors of future psychiatric morbidity in offspring of mothers with psychotic disorder

Results from the Helsinki High-Risk Study

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Background   The Helsinki High-Risk Study monitors women treated for schizophrenia-spectrum disorders in Helsinki mental hospitals before 1975, their offspring, and controls.

Aims   To compare the development of high-risk and control group children, and investigate which factors predicted future psychiatric disorders.

Method   We examined information from childhood and school health record cards of 159 high-risk and 99 control group offspring. Logistic regression was used to assess whether developmental abnormalities predicted later mental disorders.

Results   Compared with controls, children in the high-risk group had more emotional symptoms before school age, attentional problems and social inhibition at school age, and neurological soft signs throughout. In this group pre-school social adjustment problems (OR=9.7, 95% CI 1.8–51.8) or severe neurological symptoms (Fisher's test, P=0.006) predicted future schizophrenia-spectrum disorder. Social adjustment problems and emotional symptoms during school age predicted future non-psychotic psychiatric disorders.

Conclusions   Our study supports the validity of neurological, emotional, social and behavioural markers as vulnerability indicators of psychotic and other mental disorders, particularly among children genetically at high risk of psychosis.

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Adults who develop severe mental disorders have often had developmental problems in childhood and adolescence (Rutter, 1984; Caspi *et al*, 1996). High-risk research refers to a method of studying the early antecedents of a disorder by investigating individuals who are at increased risk of developing it, typically those with a family history of the disorder (Niemi *et al*, 2003). The Helsinki High-Risk Study began in 1974 and is one of the largest-ever high-risk investigations. Being based on information derived from several registers and their records, and on hospital and out-patient unit case notes rather than face-to-face assessments, the study sample has included all eligible mothers and their offspring. The aims of our study were to compare childhood development of high-risk offspring and controls, and to determine which developmental factors predicted future emergence of mental disorders among the high-risk offspring.

METHOD

Cohort identification

The sample consisted of all children born between 1960 and 1964 in Helsinki to all women born between 1916 and 1948 who had been treated in a psychiatric hospital in Helsinki before 1975 for a hospital diagnosis of schizophrenia-spectrum disorder, and of controls (previous same-sex birth at the same maternity hospital) (Niemi *et al*, 2004). Based on information in the Finnish Hospital Discharge Register, all in-patient and out-patient treatment records were gathered, and used by us to assign DSM–IV–TR diagnoses (American Psychiatric Association, 2000) and assess symptoms (Niemi *et al*, 2004). The final high-risk group consisted of 179 offspring of 161 mothers, and the control group of 176 offspring of 176 mothers. The mothers of the high-risk group were divided into the following DSM–IV–TR diagnostic groups:

schizophrenia (*n*=92), other schizophrenia-spectrum psychosis (*n*=28), affective psychosis (*n*=23) and schizoaffective psychosis (*n*=18) (Niemi *et al*, 2004). For this follow-up study we found the childhood and school health cards for 159 high-risk offspring of 143 mothers, and because we had less information on controls, for 99 control offspring of 99 mothers.

Finnish child health guidance in child welfare clinics and schools

Child health guidance in Finland is provided by public health nurses and primary care physicians, and it extends to all children under school age (7 years). Thereafter the children visit school health nurses and physicians in their school area. After the initial home visit from a public health nurse when they are 8–14 days old, infants attend the child health centre at 1 month and thereafter at 2, 3, 5, 6, 10, 12 and 15 months of age; toddlers attend when they are 2, 3, 4 and 5 years old. They see a doctor at age 1.5, 4, 8 and 18 months, and at 3 and 6 years. Nurses and physicians complete a standard form with measurements (e.g. weight, height) and other standard observations (e.g. reaching motor milestones) at every visit. School children visit the school nurse once a year and are seen by the school doctor at age 7, 12, 15 and 17 years.

Childhood health cards

Health cards for all individuals in the sample were obtained from their home districts. The card data cover childhood health checks for each visit from infancy to the end of school age. The following items were extracted from each card: whether the child was walking at 12 months and speaking words at 2 years; whether the child had a speech problem during childhood (age 5–6 years) or at school (age 7–17 years); whether there were emotional symptoms during childhood (before age 7 years) or at school (age 7–17 years); problems in social adjustment (only at 5–6 years); problems in neurological development (coded as 'severe neurological symptoms' in severe cases, e.g. with hemiplegia or spasticity, and as 'neurological soft signs' in less severe cases, e.g. with tics or subthreshold hypotony) during childhood or adolescence; rating of failure to reach the age-appropriate level of mental development (coded as delayed mental development, assessed yearly between 1 year and 6 years of age) and of

need for extra follow-up in the school health system for any reason (assessed at school age); rating during school years of being socially inhibited, of having conduct problems, attention problems or academic impairment (indicated by repeating the same class, having been examined by a psychologist or doctor because of severe problems in academic performance or having been transferred to a special school owing to severe problems in academic performance).

Dependent variables

For this analysis, offspring who later developed a psychiatric disorder were classified into six diagnostic groups: all schizophrenia-spectrum disorders ($n=12$; 8 males), including schizophrenia, schizoaffective disorder, delusional disorder and psychotic disorder not otherwise specified; any psychotic disorder ($n=17$; 11 males); any mood disorder ($n=15$; 9 males); substance-related disorder ($n=15$; 11 males); personality disorders ($n=10$; 6 males); and any mental disorder ($n=30$; 21 males). Because comorbidity was common, some offspring appeared in more than one diagnostic group.

Explanatory variables

All explanatory variables were dichotomised and coded as 0 (child had reached expected level or had no problem with the assessed variable) or 1 (had not reached the expected level or had the assessed problem). In a separate analysis we also used missing data as an explanatory variable, because missing health assessments could reflect family problems possibly associated with increased risk of psychiatric morbidity.

Gender and social class were incorporated in the models as covariates. Socio-economic group classification was based on the City of Helsinki Social Group classification (Central Statistical Office of Finland, 1989). In the analysis, the groups were collapsed into two groups: professional/clerical became 'upper social class' (for the high-risk sample $n=61$, for controls $n=53$), and skilled/unskilled workers 'lower social class' (for the high-risk sample $n=91$, for controls $n=44$). Social class data were lacking for seven children in the high-risk group and two in the control group. We used paternal occupation to classify socio-economic status; if this was missing, we used maternal occupation.

Statistical assessment

The occurrence of developmental problems was compared between the high-risk and control group offspring using the chi-squared test, or Fisher's exact test when the expected number in any cell was below five. Developmental problems were compared between offspring in each maternal diagnostic group using the likelihood ratio test. Examination of the relationship between childhood developmental problems and psychiatric morbidity in adulthood was confined to the high-risk group, because the cumulative incidence of mental disorders in the control group was low (Niemi *et al*, 2004). To investigate the relationship within the high-risk group we used logistic regression models in which the six dichotomised diagnostic outcomes were used as dependent variables. Univariate models were calculated for all combinations of dependent and explanatory variables; gender and social class were incorporated as covariates. Odds ratios with 95% confidence intervals and Wald test statistics with significance levels were calculated. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 11.5.1.

RESULTS

The number of cases available for each developmental variable and the number of offspring with and without the given developmental problem are listed in Tables 1 and 2. Information was often missing for variables assessing walking at 12 months and speaking at 2 years. Otherwise, missing information was minimal (Table 1). The following variables had no influence on psychiatric morbidity in adulthood: not walking at 12 months; not speaking at 2 years; speech problem during childhood or adolescence; and academic impairment.

Factors differentiating the development of high-risk and control group offspring

Offspring in the high-risk group more often had emotional symptoms during childhood ($\chi_1^2=7.4$, d.f.$=1$, $P=0.006$) and neurological soft signs ($\chi_1^2=4.8$, d.f.$=1$, $P=0.024$), and were more prone to social inhibition during their school years (Fisher's exact test, $P=0.044$) (Table 1). Table 2 displays the proportion of individuals with developmental problems in each maternal diagnostic group.

Table I Number of cases available for each developmental explanatory variable

Variable	Proportion of cases with the given problem	
	High-risk group % (n/N)[1]	Control group % (n/N)[1]
Not walking at age 12 months	39 (43/111)	34 (18/53)
Not speaking at age 2 years	4 (3/75)	6 (2/33)
Speech problem (C)	13 (19/144)	14 (14/97)
Emotional symptoms (C)**	15 (21/141)	3 (2/73)
Problems in social adjustment at age 5–6 years	8 (11/140)	6 (4/70)
Neurological soft sign*	11 (17/154)	3 (3/97)
Severe neurological symptom	1 (2/154)	2 (2/97)
Delayed mental development	8 (11/145)	3 (2/77)
Academic impairment	16 (23/145)	8 (8/97)
Speech problem (S)	13 (19/144)	14 (14/97)
Emotional symptoms (S)	34 (49/146)	25 (24/97)
Conduct problem (S)	8 (11/145)	2 (2/97)
Being socially inhibited (S)*	5 (7/138)	0 (0/97)
Attentional problems (S)	3 (5/145)	0 (0/97)
Need for extra follow-up in the school health system	58 (84/146)	45 (44/97)

C, childhood (under 7 years old); S, school age (7–17 years old).
1. n, number of cases with the problem; N, number of cases for which specific information was available.
*$P<0.05$, **$P<0.01$; χ^2 or Fisher's exact test.

Table 2 Number of cases with the given developmental problem in each maternal diagnostic group

	Maternal diagnostic group					P^2
	Schizophrenia ($n=92$) n/N (%)[1]	Schizoaffective disorder ($n=19$) n/N (%)[1]	Other schizophrenia-spectrum disorder ($n=27$) n/N (%)[1]	Affective disorder ($n=21$) n/N (%)[1]	Control ($n=99$) n/N (%)[1]	
Developmental problem						
Emotional symptoms (C)	11/78 (14)	4/18 (22)	5/25 (20)	1/20 (5)	2/73 (3)	0.02
Neurological soft sign	8/88 (9)	1/19 (5)	3/26 (12)	5/21 (24)	3/97 (3)	0.05
Academic impairment	12/83 (14)	0/18	7/24 (26)	4/20 (20)	8/97 (8)	0.01
Conduct problems (S)	5/83 (6)	0/18	4/24 (17)	2/20 (10)	2/97 (2)	0.05
Social inhibition (S)	5/83 (6)	1/18 (5)	1/24 (4)	0/20	0/97	0.05
Attentional problems (S)	0/83	0/18	3/24 (13)	2/20 (10)	0/97	0.001
Social class (lower)	57/86 (66)	9/18 (50)	16/27 (59)	9/21 (43)	44/97 (45)	0.04
Gender (male)	54/92 (59)	10/19 (53)	12/27 (44)	10/21 (48)	63/99 (64)	0.03

C, childhood (under 7 years old); S, school age (7–17 years old).
1. n, offspring with given problem; N, number for whom information was available (missing cases excluded from analysis).
2. Difference between the groups counted by likelihood ratio test (includes only variables where significant differences emerged).

Factors predicting later development of mental disorders in high-risk offspring

Neither of the dependent variables (social class or gender) significantly influenced the odds of developing mental disorders. Among the high-risk offspring, after adjusting for gender and social class, problems in social adjustment at age 5–6 years predicted later development of schizophrenia-spectrum disorder (OR=9.73, 95% CI 83–51.8; $P=0.008$). Two offspring in this group had severe neurological symptoms in childhood and both developed schizophrenia (Fisher's exact test, $P=0.006$); odds ratios could not be calculated because of the zero denominator (Table 3).

Problems in social adjustment at age 5–6 years (OR=4.51, 95% CI 0.99–20.6; $P=0.052$) and emotional symptoms at school age (OR=2.88, 95% CI 0.99–8.34; $P=0.051$) tended to predict later development of any psychotic disorder.

Emotional symptoms (OR=15.7, 95% CI 3.32–74.1; $P=0.001$), conduct problems (OR=18.0, 95% CI 4.41–73.5; $P<0.001$) and social inhibition (OR=34.9, 95% CI 5.71–>100; $P<0.001$) at school age predicted later development of any mood disorder; attentional problems were an almost significant predictor (OR=6.71, 95% CI 0.99–45.5; $P=0.051$).

Emotional symptoms (OR=7.23, 95% CI 1.82–28.6; $P=0.005$), conduct problems (OR=13.2, 95% CI 3.14–55.8; $P<0.001$) and attentional problems (OR=7.62, 95% CI 1.09–53.4; $P=0.041$) at school age all predicted later development of substance-related disorder.

Delayed mental development (OR=10.5, 95% CI 1.95–56.4; $P=0.005$), problems in

Table 3 Odds ratios of developing mental disorders among high-risk offspring, adjusted for gender and social class

	Schizophrenia-spectrum disorder ($n=12$) OR (95% CI)	Any psychotic disorder ($n=17$) OR (95% CI)	Any mood disorder ($n=15$) OR (95% CI)	Substance-related disorder ($n=15$) OR (95% CI)	Personality disorder ($n=10$) OR (95% CI)	Any mental disorder ($n=30$) OR (95% CI)
Problems in social adjustment at age 5–6 years	9.73 (1.83–51.8)**	4.51 (0.99–20.6)‡	2.79 (0.52–15.1)	1.48 (0.16–13.5)	6.22 (1.00–38.7)*	4.10 (0.99–17.0)‡
Delayed mental development	2.80 (0.50–15.7)	3.19 (0.73–14.0)	2.22 (0.42–11.8)	2.44 (0.44–13.48)	10.5 (1.95–56.4)**	3.98 (1.07–14.9)*
Emotional symptoms (S)	2.56 (0.73–8.99)	2.88 (0.99–8.34)††	15.7 (3.32–74.1)§	7.23 (1.82–28.6)**	9.55 (1.91–47.8)**	4.70 (1.92–11.5)§
Conduct problems (S)	2.52 (0.45–14.1)	1.63 (0.31–8.67)	18.0 (4.41–73.5)***	13.2 (3.14–55.8)***	5.88 (1.23–28.2)*	9.44 (2.44–36.3)§
Social inhibition (S)	4.73 (0.75–29.7)	3.10 (0.53–18.3)	34.9 (5.71–>100)***	4.19 (0.67–26.2)	12.3 (2.19–68.6)**	13.6 (2.30–80.6)*
Attentional problems (S)	2.82 (0.28–28.8)	1.79 (0.18–17.5)	6.71 (0.99–45.5)††	7.62 (1.09–53.4)*	3.30 (0.32–33.9)	6.09 (0.94–39.7)

S, school age (7–17 years old).
*$P \leqslant 0.05$, **$P<0.01$, ***$P<0.001$; ††$P=0.051$, ‡$P=0.052$, §$P=0.001$ (Wald test).

Table 4 Odds ratios of developing mental disorders among high-risk offspring whose mothers had a schizophrenia-spectrum disorder, adjusted for gender and social class

	Schizophrenia-spectrum disorder (n=12) OR (95% CI)	Any psychotic disorder (n=16) OR (95% CI)	Any mood disorder (n=13) OR (95% CI)	Substance-related disorder (n=15) OR (95% CI)	Personality disorder (n=10) OR (95% CI)	Any mental disorder (n=28) OR (95% CI)
Emotional symptoms (C)	2.38 (0.53–10.7)	1.35 (0.33–5.56)	0.46 (0.05–3.87)	0.43 (0.05–3.70)	10.2 (2.05–52.1)*	1.00 (0.28–3.49)
Problems in social adjustment at age 5–6 years	8.08 (1.51–43.1)*	4.40 (0.92–21.0)	3.01 (0.53–17.1)	1.23 (0.13–11.2)	5.17 (0.83–32.3)	4.00 (0.92–17.3)
Neurological soft sign	4.48 (0.98–20.5)‡	2.85 (0.66–12.3)	0.94 (0.10–7.16)	1.85 (0.35–9.86)	0.00 (0.00–>100)	2.01 (0.56–7.86)
Delayed mental development	2.46 (0.43–14.1)	3.05 (0.66–14.0)	2.50 (0.45–14.0)	2.12 (0.38–12.0)	9.70 (1.76–54.0)**	4.10 (1.03–16.3)*
Emotional symptoms (S)	2.75 (0.78–9.73)	3.73 (1.21–11.5)*	31.8 (3.89–>100)§	7.90 (1.98–31.7)**	10.3 (2.05–52.1)**	5.60 (2.15–14.6)***
Conduct problems (S)	2.75 (0.47–16.0)	1.84 (0.33–10.2)	18.4 (3.9–86.9)***	17.0 (3.60–80.0)***	6.73 (1.33–34.2)*	9.51 (2.09–43.4)**
Social inhibitions (S)	4.11 (0.66–25.7)	2.81 (0.47–16.8)	38.4 (6.09–>100)***	3.60 (0.59–22.6)	10.60 (1.91–59.2)**	12.8 (2.15–76.8)**
Attentional problems (S)	4.35 (0.35–54.7)	2.81 (0.23–34.1)	20.6 (1.61–>100)*	17.4 (1.38–>100)*	5.21 (0.41–66.8)	>100 (0.00–>100)

C, childhood (under 7 years old); S, school age (7–17 years old).
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; ‡$P = 0.053$, §$P = 0.001$ (Wald test).

social adjustment at age 5–6 years (OR=6.22, 95% CI 1.0–38.7; $P=0.050$), and emotional symptoms (OR=9.55, 95% CI 1.91–47.8; $P=0.006$), conduct problems (OR=5.88, 95% CI 1.23–28.2; $P=0.027$) and social inhibition (OR=12.3, 95% CI 2.19–68.6; $P=0.004$) at school age, predicted later development of personality disorder.

Delayed mental development (OR=3.98, 95% CI 1.07–14.9; $P=0.040$), emotional symptoms (OR=4.70, 95% CI 1.92–11.5; $P=0.001$), conduct problems (OR=9.44, 95% CI 2.44–36.3; $P=0.001$) and social inhibition (OR=13.6, 95% CI 2.30–80.6; $P=0.004$) at school age, predicted later development of any mental disorder. Problems in social adjustment at age 5–6 years (OR=4.10, 95% CI 0.99–17.0; $P=0.052$) tended to predict later development of any mental disorder.

Factors predicting later development of mental disorders among offspring of women with schizophrenia

Separate analysis of the data for the offspring of mothers with schizophrenia-spectrum disorder changed the results only slightly (Table 4). Neurological soft signs tended to predict later development of schizophrenia-spectrum disorder (OR=4.48, 95% CI 0.98–20.5; $P=0.053$), whereas problems in pre-school social adjustment no longer predicted later development of any psychotic disorder, personality disorder or any mental disorder. Social inhibition no longer predicted later development of any mood disorder.

DISCUSSION

In this follow-up of the Helsinki High-Risk Study we found that the childhood development of the high-risk offspring differed from that of controls, and that several developmental problems recognised in primary care predicted future development of psychiatric disorder. Of our neuromotor and cognitive development measures, only those related to neurological development predicted future psychiatric morbidity. Severe neurological symptoms and pre-school problems in social adjustment predicted development of schizophrenia-spectrum disorders. In contrast, school-age emotional symptoms and problems in social adjustment were strong predictors particularly of mood, substance-related and personality disorders. Only offspring who developed personality disorders had several problems both at pre-school and school-age assessments.

Factors differentiating the development of high-risk and control offspring

The high-risk offspring more often had emotional symptoms before school age than controls. This accords with previous

findings that children at high-risk are more depressive, hyperactive and immature (Niemi et al, 2003). Consistent with previous studies (Niemi et al, 2003), high-risk children more often had neurological signs than controls. A recent family study found that neurological soft signs were more common among parents of patients with schizophrenia, who were the presumed carriers of the genetic loading based on their family history, than among parents who were presumed non-carriers, supporting the hypothesis that neurological signs are associated with genetic risk of schizophrenia (Gourion et al, 2004). The high-risk offspring, particularly those whose mothers had schizophrenia, also differed from controls in being socially inhibited at school age. Also in previous studies the behaviour of high-risk offspring was more often disturbed at school age compared with controls (for review see Niemi et al, 2003).

Developmental factors predicting future development of schizophrenia-spectrum disorders

Problems in social adjustment during childhood were equally likely in the high-risk and control offspring; however, they predicted later development of schizophrenia-spectrum disorder, and tended to predict any psychotic disorder, only in the high-risk group. Problems in pre-school social adjustment in our cohort were assessed at age 5–6

years, when a health assessment priority is to identify children who may be unable to start education at the normal age of 7 years. Two of the five high-risk boys and one of the six high-risk girls with problems in pre-school social adjustment developed schizophrenia-spectrum disorder. High-risk individuals who developed schizophrenia-spectrum disorders in our cohort did not differ significantly as adolescents in their social adjustment from high-risk offspring who did not develop a mental disorder. Conduct and attentional problems and social inhibition at school age were more common among high-risk offspring who developed schizophrenia-spectrum disorders, but not to a statistically significant extent. It may be that these children's problems did not draw as much attention at school age as they did at the pre-school assessments.

Severe neurobiological symptoms predicted future development of schizophrenia-spectrum disorders, and neurological soft signs tended to predict the same among high-risk offspring whose mothers were diagnosed with these disorders. Severe neurological symptoms were rare, but both of the high-risk children who had these symptoms had mothers with schizophrenia, and both went on to develop schizophrenia-spectrum disorders. The girl had febrile seizures at age 2 years, and from age 5 years was found to have spasticity, to be slow and to have coordination problems; she later developed schizophrenia with depressive symptoms and alcohol misuse. The boy had hemiplegia; he went on to develop schizoaffective disorder with alcohol misuse. Previous high-risk studies have also found that neurological symptoms predicted schizophrenia (Niemi *et al*, 2003). It seems that problems in neurological development are more specific to schizophrenia-spectrum disorders, whereas emotional problems are more unspecific predictors of mental disorder (Gottesman, 1991; Jones & Murray, 1991; Cannon *et al*, 2002).

Developmental factors predicting development of other mental disorders

Emotional symptoms in school-age children tended to predict later development of any psychotic disorder. Previous studies have found that at school age internalising and externalising symptoms both predict future psychotic disorder (Cannon *et al*, 2001). Emotional symptoms, conduct problems,

social inhibition and attentional problems at school age were strong predictors of future mood disorders among high-risk offspring. The Dunedin Multidisciplinary Health and Development Study found that individuals with juvenile-onset depression have an excess of behavioural and emotional problems, as well as motor development problems (Jaffee *et al*, 2002). Our results suggest that emotional and conduct problems and social inhibition increase the risk of future mood disorders among individuals with a high genetic risk of psychotic disorder. The odds ratios increased when only the data for high-risk offspring whose mothers had a schizophrenia-spectrum disorder were analysed, suggesting that the observed associations were not caused by an elevated genetic risk of affective disorder. Conduct and attentional problems were also highly predictive of future mood disorders. The Dunedin study found that juvenile-onset depression in particular is highly comorbid with conduct disorder and attention-deficit disorder (Jaffee *et al*, 2002), which complements our findings. Although neurological soft signs did not predict later development of mood disorders in our study, it is interesting that the British 1946 National Birth Cohort found excess twitching and grimacing among children with childhood affective disturbance (van Os *et al*, 1997), and in our cohort, neurological soft signs were most common among offspring of mothers with affective disorder, suggesting a possible connection also between familial risk of affective disorder and soft neurological signs.

Interestingly, besides psychotic disorders, only personality disorder was predicted by behavioural problems before school age, and was the only diagnosis for which developmental predictors were observed from early childhood through adolescence. Two children in the high-risk group developed antisocial personality disorder, five developed borderline personality disorder and two personality disorder not otherwise specified. That no cluster A personality disorder was found reflects our method of case selection. As the Copenhagen High-Risk Study showed, individuals with cluster A personality disorders rarely receive hospital treatment (Parnas *et al*, 1993), whereas individuals with cluster B disorders are often admitted to hospital because of their impulsive, aggressive or self-destructive behaviour. Cluster B personality disorders being so common in our sample,

our findings concerning delayed mental development in early childhood could be explained by previous research suggesting that persistent antisocial behaviour is associated with both pre-school and school-age neurocognitive deficits (Moffitt, 1993; Raine *et al*, 2002). Consistent with our findings, earlier studies have found that childhood aggression, withdrawal, lack of social skills, and mental health problems are risk factors for antisocial personality disorder (Holmes *et al*, 2001; Moffitt *et al*, 2002). Individuals who develop borderline personality disorder also have more emotional symptoms and conduct disorder throughout childhood and adolescence (Joyce *et al*, 2003). Conduct problems self-evidently predict future antisocial personality disorder, since they are part of its diagnostic criteria.

Emotional symptoms, conduct problems and attentional problems at school age predicted future substance-related disorders. Similarly, the Danish Longitudinal Study of Alcoholism found that childhood unhappiness and antisocial personality disorder predicted alcohol misuse and dependence (Knop *et al*, 2003).

Overall, developmental problems predicting personality, mood and substance use disorders among individuals at high genetic risk of schizophrenia do not differ from those identified in population-based cohort studies, but the observed odds ratios are much higher. Thus, the effect of these problems is more severe in the presence of genetic vulnerability to psychotic disorders.

Some developmental problems, such as speech problems, academic impairment, lateness in learning to walk and childhood emotional symptoms, did not predict any psychiatric disorder in adulthood. In cohort studies, children who later developed schizophrenia have been found to reach motor milestones later, and to learn to speak later, than those who remained unaffected (Niemi *et al*, 2003). Our different finding might be explained by our smaller sample size or by the less-detailed information we had (only whether the child had reached the milestones by a certain age). Because of the nature of our data, we are cautious about drawing any further conclusions at this point, although it might also be that the degree of developmental adversity necessary for the development of schizophrenia is somewhat different in offspring who have an especially high genetic risk compared with those who have no family history of schizophrenia.

Limitations

Although this was one of the largest high-risk studies, sample sizes were still small and the statistical power was insufficient to detect moderate-sized associations. All differences reaching significance in the numerous statistical tests performed were in the expected direction, which supports the reliability of our results. Multiple regression analysis was not possible because for most developmental problems the number of affected individuals was small, and collinearity became a problem. Thus our results were mostly descriptive. Larger samples would be needed to assess the significance of developmental abnormalities in relation to each other, and possible interactive mechanisms.

Missing data could have influenced our results. This problem was more common among controls in the pre-school variables, and among the high-risk group at school age. Non-participation in child health guidance could reflect an unstable family lifestyle, possibly with frequent change of residence or social problems. However, when 'missing data' was entered as a separate variable in the models, it did not predict future development of any of the examined mental disorders.

The psychotic disorders developed by offspring in the high-risk group might represent a special form of psychosis, since all the individuals in this group were at high genetic risk. Thus, the findings may not be generalisable to less familial forms of the disorder. Also, all the high-risk children lived in a family environment where the mother had a psychotic disorder, or else were adopted away: this might have increased psychological and social stress in the offspring and influenced the overall outcome.

When assigning diagnoses, the researchers could not always remain masked to the offspring's risk status, since it was often mentioned in the case notes. However, they were always masked to the actual identity of the mother–child pairs.

Compared with other high-risk studies, our information was less detailed, consisting of ratings in regular childhood assessments coded in standard forms used throughout the country. The benefit of this is that ratings were made without awareness of the ongoing study, and that all these problems were severe enough to be observable in primary care. However, only severe problems were recorded in the health cards; more subtle developmental problems might have remained unrecognised or unrecorded. Despite the lack of detailed data we were able to identify predictive factors that distinguished the high-risk children who later developed mental disorders. When supportive measures for high-risk children are planned, special attention should go to children who already have neuromotor, emotional, social or behavioural problems.

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CLINICAL IMPLICATIONS

■ Children at increased familial risk of psychotic disorder had more emotional and neurological symptoms and more problems in social adjustment than controls, and most of these problems predicted future psychiatric morbidity.

■ Problems elevating the risk of schizophrenia-spectrum disorders manifested before school age, were caught in primary care, and were related to neurological development and social adjustment.

■ Our study supports the validity of neurological, emotional, social and behavioural markers as vulnerability indicators of psychotic disorders and other Axis I and II mental disorders, particularly among children genetically at high risk of psychosis.

LIMITATIONS

■ Our case ascertainment was mainly based on the Finnish Hospital Discharge Register; thus, the adulthood diagnoses included only severe cases treated in hospital.

■ Although this was one of the largest high-risk studies, sample sizes were still small, and our results were mostly descriptive.

■ Compared with other high-risk studies, our information was less detailed, consisting of ratings from regular childhood health assessments. The benefit of this is that the results are more useful to the health care system, because these problems were caught in primary care.

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REFERENCES

American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn, text revision) (DSM–IV–TR). Washington, DC: APA.

Cannon, M., Walsh, E., Hollis, C., et al (2001) Predictors of later schizophrenia and affective psychosis among attendees at a child psychiatry department. *British Journal of Psychiatry*, **178**, 420–426.

Cannon, M., Caspi, A., Moffitt, T. E., *et al* **(2002)** Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Archives of General Psychiatry*, **59**, 449–456.

Caspi, A., Moffitt, T. E., Newman, D. L., *et al* **(1996)** Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. *Archives of General Psychiatry*, **53**, 1033–1039.

Central Statistical Office of Finland (1989) *Classification of Socio-Economic Groups*. Helsinki: Central Statistical Office of Finland.

Gottesman, I. I. (1991) *Schizophrenia Genesis: The Origin of Madness*. New York: Freeman.

Gourion, D., Goldberger, C., Olie, J. P., *et al* **(2004)** Neurological and morphological anomalies and the genetic liability to schizophrenia: a composite phenotype. *Schizophrenia Research*, **67**, 23–31.

Holmes, S. E., Slaughter, J. R. & Kashani, J. (2001) Risk factors in childhood that lead to the development of conduct disorder and antisocial personality disorder. *Child Psychiatry and Human Development*, **31**, 183–193.

Jaffee, S. R., Moffitt, T. E., Caspi, A., *et al* **(2002)** Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Archives of General Psychiatry*, **59**, 215–222.

Jones, P. & Murray, R. M. (1991) The genetics of schizophrenia is the genetics of neurodevelopment. *British Journal of Psychiatry*, **158**, 615–623.

Joyce, P. R., McKenzie, J. M., Luty, S. E., *et al* **(2003)** Temperament, childhood environment and psychopathology as risk factors for avoidant and borderline personality disorders. *Australian and New Zealand Journal of Psychiatry*, **37**, 756–764.

Knop, J., Penick, E. C., Jensen, P., *et al* **(2003)** Risk factors that predicted problem drinking in Danish men at age thirty. *Journal of Studies on Alcohol*, **64**, 745–755.

Moffitt, T. E. (1993) Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. *Psychological Review*, **100**, 674–701.

Moffitt, T. E., Caspi, A., Harrington, H., *et al* **(2002)** Males on the life-course-persistent and adolescence-limited antisocial pathways: follow-up at age 26 years. *Development and Psychopathology*, **14**, 179–207.

Niemi, L., Suvisaari, J., Tuulio-Henriksson, A., *et al* **(2003)** Review. Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. *Schizophrenia Research*, **60**, 239–258.

Niemi, L. T., Suvisaari, J. M., Haukka, J. K., *et al* **(2004)** Cumulative incidence of mental disorders among offspring of mothers with psychotic disorder: results from the Helsinki High-Risk Study. *British Journal of Psychiatry*, **185**, 11–17.

Parnas, J., Cannon, T., Jacobsen, B., *et al* **(1993)** Lifetime DSM−III−R diagnostic outcomes in the offspring of schizophrenic mothers. *Archives of General Psychiatry*, **50**, 707–714.

Raine, A., Yaralian, P. S., Reynolds, C., *et al* **(2002)** Spatial but not verbal cognitive deficits at age 3 years in persistently antisocial individuals. *Development and Psychopathology*, **14**, 25–44.

Rutter, M. (1984) Psychopathology and development: I. Childhood antecedents of adult psychiatric disorder. *Australian and New Zealand Journal of Psychiatry*, **18**, 225–234.

van Os, J., Jones, P., Lewis, G., *et al* **(1997)** Developmental precursors of affective illness in a general population birth cohort. *Archives of General Psychiatry*, **54**, 625–631.