

Evidence for Early-Childhood, Pan-Developmental Impairment Specific to Schizophreniform Disorder

Results From a Longitudinal Birth Cohort

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Background: Childhood developmental abnormalities have been previously described in schizophrenia. It is not known, however, whether childhood developmental impairment is specific to schizophrenia or is merely a marker for a range of psychiatric outcomes.

Methods: A 1-year birth cohort (1972-1973) of 1037 children enrolled in the Dunedin Multidisciplinary Health and Development Study was assessed at biennial intervals between ages 3 and 11 years on emotional, behavioral, and interpersonal problems, motor and language development, and intelligence. At age 11 years, children were asked about psychotic symptoms. At age 26 years, DSM-IV diagnoses were made using the Diagnostic Interview Schedule. Study members having schizophreniform disorder ($n=36$ [3.7%]) were compared with healthy controls and also with groups diagnosed as having mania ($n=20$ [2%]) and nonpsychotic anxiety or depression disorders ($n=278$ [28.5%]) on childhood variables.

Results: Emotional problems and interpersonal difficulties were noted in children who later fulfilled diagnostic criteria for any of the adult psychiatric outcomes assessed. However, significant impairments in neuromotor, receptive language, and cognitive development were additionally present only among children later diagnosed as having schizophreniform disorder. Developmental impairments also predicted self-reported psychotic symptoms at age 11 years. These impairments were independent of the effects of socioeconomic, obstetric, and maternal factors.

Conclusions: The results provide evidence for an early-childhood, persistent, pan-developmental impairment that is specifically associated with schizophreniform disorder and that predicts psychotic symptoms in childhood and adulthood.

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SCHIZOPHRENIA IS a clinical syndrome with peak onset in late adolescence or early adulthood, whose symptoms are manifest in multiple domains of behavior, language, thought, and affect, and whose etiology remains obscure.¹ A neurodevelopmental etiologic model or hypothesis of schizophrenia has been influential during the past decade.^{2,3} It proposes a subtle deviance in early brain development whose full adverse consequences do not emerge until adolescence or early adulthood. Central to this hypothesis is the identification of developmental deficits preceding overt clinical symptoms of adult schizophrenia.^{4,6} In this study, we apply a life-course approach to the study of schizophrenia and focus on developmental risk factors in early life

Several different research strategies have been used to examine the developmental precursors of adult schizophrenia, including the use of archived infor-

mation, follow-up studies of existing birth cohorts, and genetic high-risk studies that follow offspring of an affected parent throughout childhood and adolescence. Such strategies have uncovered robust evidence for childhood motor, language, cognitive, and behavioral precursors to schizophrenia⁷⁻²³ but there are 3 caveats. First, different developmental impairments have been examined in separate studies using a variety of case ascertainment methods and developmental scales. As a result, conclusions about the etiologic significance of developmental impairments may have been confounded by these variations. One should examine whether different types of developmental impairment predict the same adult schizophrenic outcome in one longitudinal study. Second, evidence of specificity for schizophrenia is limited. Childhood developmental problems associated with schizophrenia may also occur in patients with other psychiatric disorders^{24,25} and may thus be

PARTICIPANTS AND METHODS

SAMPLE

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behavior in a complete birth cohort.³⁵ The study members were born in Dunedin, New Zealand, between April 1972 and March 1973. Of these, 1037 children (91% of eligible births; 52% males) participated in the first follow-up assessment at age 3 years, and they constitute the base sample for the remainder of the study. Cohort families represent the full range of socioeconomic status (SES) in the general population of New Zealand's South Island and are primarily white. Assessments have been conducted at ages 3 (n=1037), 5 (n=991), 7 (n=954), 9 (n=955), 11 (n=925), 13 (n=850), 15 (n=976), 18 (n=993), 21 (n=961), and most recently at age 26 years (n=980; 96% of living cohort members). Participants are brought to the research unit within 60 days of their birthday for a full day of individual data collection. Various research topics are presented as standardized modules, each administered by a different trained examiner. Informed consent was obtained for all procedures.

CHILDHOOD MEASURES

SES, Obstetric Complications, and Maternal Factors

Family SES measured the average SES level of the study members' families across the first 15 years of life,³⁶ using a 6-point scale designed for New Zealand where 1=unskilled laborer and 6=professional.³⁷

Each child was examined shortly after birth and prenatal information was taken from the hospital records.^{38,39} The obstetric complications assessed in this study were maternal diabetes; glycosuria; epilepsy; hypertension; eclampsia; antepartum hemorrhage; accidental hemorrhage; placenta previa; having had a previous small baby; gestational age younger than 37 weeks or older than 41 weeks; birth weight less than 2500 g or greater than 4 kg; small or large for gestational age; major or minor neurologic signs; Rh incompatibility; ABO incompatibility; nonhemolytic hyperbilirubinemia; hypoxia at birth (idiopathic respiratory distress syndrome or apnea), and low Apgar score at birth. (The infant was defined as having a low Apgar score if one of the following conditions applied: [1] at 5 minutes of life, the infant's heart rate was <100 beats/min, respiration was irregular or absent, and the infant was centrally cyanosed; [2] the infant took more than 10 minutes to establish normal respiration; or [3] the infant's asphyxia at birth warranted resuscitation.) Each complication was weighted equally and summed to yield an obstetric complication index.³⁸

Mothers were rated on their general attitude and behavior in relation to their child by a psychologist or medical doctor during the course of the child's assessment at age 3 years. Mothers were rated on 8 features: harshness toward the child; critical or negative evaluation of the child; rough, awkward handling of the child; no effort to help the

child; unaware or unresponsive to the child's needs, indifference to the child's performance; demanding of the child's attention; and soiled, unkempt appearance of the child. This assessment has been found in previous research to be reliable and valid.⁴⁰ Scores on these 8 ratings were summed to create a mother-child interaction variable for each mother, and a score of 1 or more indicated atypical mother-child interaction for the purposes of this study.

Neuromotor Development

Infant milestones were assessed retrospectively at age 3 years. Mothers were asked to remember to the nearest month when their child attained various milestones: smiling, sitting up, walking, dry-by-day, dry-by-night, fed self, talked (words), and talked (sentences). Responses were recorded only when the mother was certain that she could recall this information accurately. Most mothers referred to their "Plunkett books," in which study mothers had recorded this information as their baby developed.

Neurologic abnormalities were assessed at age 3 years based on procedures described by Touwen and Prechtl.⁴¹ Each child was examined by a pediatric neurologist for neurologic signs, including assessment of motility, passive movements, reflexes, facial musculature, strabismus, nystagmus, foot posture, and gait. Motor development was assessed at age 3 years with the Bayley Motor Scales,⁴² at age 5 years using the McCarthy Motor Scales,⁴³ and at ages 7 and 9 years using the Basic Motor Ability Test.⁴⁴

Language and Cognitive Development

Receptive and expressive language development was assessed at ages 3 and 5 years using the Reynell Developmental Language Scales,⁴⁵ which have separate subtests for receptive (verbal comprehension) and expressive language. At ages 7 and 9 years, language development was assessed using the Auditory Reception and Verbal Expression subtests of the Illinois Test of Psycholinguistic Abilities.⁴⁶

Intelligence was assessed at age 3 years with the Peabody Picture Vocabulary Test,⁴⁷ at age 5 years with the Stanford-Binet Intelligence Scales,⁴⁸ and at ages 7, 9, and 11 years with the Weschler Intelligence Scales for Children-Revised.⁴⁹ All tests were administered by trained psychometrists according to standard protocol.⁵⁰

Internalizing and Externalizing Behavior Problems

At ages 5, 7, 9, and 11 years, parents and teachers completed the Rutter Child Scales,^{51,52} which inquire about children's emotional and behavioral functioning during the past year. The Internalizing Problems scale describes children who worry about many things or who often appear miserable, unhappy, and tearful. The Externalizing Problems scale describes children who frequently fight, bully other children, lie, steal, disobey, truant, destroy property, and have irritable tempers. The relevant items were summed across the 4 age periods and 2 raters (parents and teachers) to derive measures indexing children's internalizing and externalizing problems, respectively.

nonspecific markers for a wide range of psychological disturbances in adulthood. A third area of debate is the etiology of such developmental precursors. A genetic

cause is suggested by the occurrence of developmental problems in 25% to 40% of children at genetically high risk for schizophrenia^{7,8,16} but it has been suggested that

Interpersonal Adjustment

At ages 5, 7, 9, and 11 years, parents evaluated 2 statements about their child: "my child is a loner" and "my child is not much liked by other children." Each statement was rated on a 3-point scale. At ages 7, 9, and 11 years, teachers independently evaluated the same statements. Mean scores for each statement were calculated separately for parents and teachers and these ratings were averaged for each child to derive 2 measures indexing social isolation and peer rejection, respectively.

Psychotic Symptoms at Age 11 Years

At age 11 years, 789 study members were administered the Diagnostic Interview Schedule for Children⁵³ by a child psychiatrist.⁵⁴ The schizophrenia section of the Diagnostic Interview Schedule for Children was composed of 5 questions regarding possible psychotic symptoms, which were scored by the psychiatrist as no (0); yes, likely (1); and yes, definitely (2). The scores for each item were summed. Most study members (n=673) obtained a score of 0, 103 (13%) obtained a score of 1 and were called the weak-symptom group, and the remaining 13 obtained a score of 2 or higher and were called the strong-symptom group. Individuals in the strong-symptom group at age 11 years were found to have a very high risk of schizophreniform disorder at age 26 years (odds ratio [OR], 16.4; 95% confidence interval [CI], 3.9-67.8).³⁴ Individuals in the weak-symptom group also had an increased risk of schizophreniform disorder at age 26 years but to a lesser degree (OR, 5.1; 95% CI, 1.7-18.3).

Psychiatric Status at Age 26 Years

Psychiatric interviews at age 26 years were available for 976 of the 1019 cohort members still living. The Diagnostic Interview Schedule⁵⁵ was administered by health professionals with either a medical or master's degree to yield *DSM-IV* diagnoses.⁵⁶ The reporting period was 12 months prior to the interview. The Axis I disorders diagnosed at age 26 years were grouped into the following diagnostic outcome groups: (1) schizophreniform disorder (n=36 [3.7%]), (2) manic episodes (n=20 [2.0%]), and (3) anxiety or depressive disorders (n=278 [28.5%]). The primary outcome for this study was schizophreniform disorder. Diagnostic procedures for schizophreniform disorder are explained in detail by Poulton et al.³⁴ To enhance the validity of our research diagnosis, we took 2 additional steps: (1) We required the presence of hallucinations (not substance-related) plus at least 2 other symptoms from Criterion A of the *DSM-IV* (this is more strict than the *DSM-IV* diagnostic criteria). and (2) We required objective evidence of impairment from informants to complement self-reports. Following this protocol, 1% of the sample met criteria for formal schizophrenia at age 26 years and a further 2.7% met all criteria except 6-month chronicity. For the purposes of this analysis, study members who were comorbid for 2 or more disorders were assigned to 1 of 3 diagnostic groups, in the following order of priority: schizophreniform disorder, mania, and anxiety/depression.

STATISTICAL ANALYSIS

Analyses compare 4 mutually exclusive groups defined according to psychiatric outcomes at age 26 years: schizophreniform disorder, mania, anxiety/depression, and a control group composed of the remainder of the cohort, who had none of the aforementioned disorders. χ^2 Tests were used to examine the associations among adult psychiatric disorders, sex, and family SES.

The raw scores for childhood developmental variables were standardized, within age, on the entire cohort, using the z-score transformation so that the cohort had a mean of 0 and an SD of 1 on these variables. The figures show the standardized scores for each outcome group. Differences between outcome groups can be evaluated by comparing differences in z scores (SD units), where 0.2 is a small, 0.5 is a moderate, and 0.8 is a large effect size.⁵⁷

Relationships between childhood developmental impairments and psychiatric outcomes at age 26 years were examined using a collection of regression techniques as required by the different types of developmental variables examined in this study (categorical, continuous, and repeated). Each regression equation was composed of 3 dummy variables for diagnostic status (schizophreniform, mania, and anxiety/depression groups), with the control group as the reference category. All reported regression coefficients and ORs were adjusted for sex and SES. Logistic regression analysis examined the following categorical variables: individual obstetric complications, maternal rejection, and presence of 1 or more neurologic signs at age 3 years. Ordinary least squares regression examined the following continuous variables: peer rejection and social isolation. Motor and language development, IQ, and internalizing and externalizing problems were measured on multiple occasions and analyzed using the generalized estimating equation (GEE) approach—a form of repeated-measures regression analysis in which any required covariance structure may be assumed and parameters estimated without specifying the joint distribution of the repeated observations.⁵⁸ We specified an unstructured correlation matrix and used robust SEs to protect against model misspecification.⁵⁹ The GEE approach can accommodate noninformative missing values.^{60,61} We report regression coefficients adjusted for sex and SES and their 95% CIs. These coefficients represent the average difference among diagnostic groups. To test whether relationships between developmental impairments and psychiatric outcomes at age 26 years were obtained independently of perinatal and postnatal environmental factors, all GEE analyses were repeated, controlling for obstetric complications and maternal rejection.

To test whether the developmental impairments that were associated with a schizophreniform outcome at age 26 years were also associated with psychotic symptoms at age 11 years, we repeated the GEE analyses using 2 dummy variables representing the weak- and strong-symptom groups at age 11 years, with the nonsymptom group as the reference category. All analyses were carried out using Stata version 6.0 (Stata Corp, College Station, Tex).⁶² Interactions between sex and diagnosis were not examined owing to power limitations. All significance tests were 2-tailed.

maternal and social factors²⁶⁻²⁹ or obstetric factors^{7,8,30} may be partly responsible for these associations. Therefore, a comprehensive investigation of developmental

processes involved in the genesis of psychopathology should also incorporate perinatal and postnatal environmental factors.³¹⁻³³

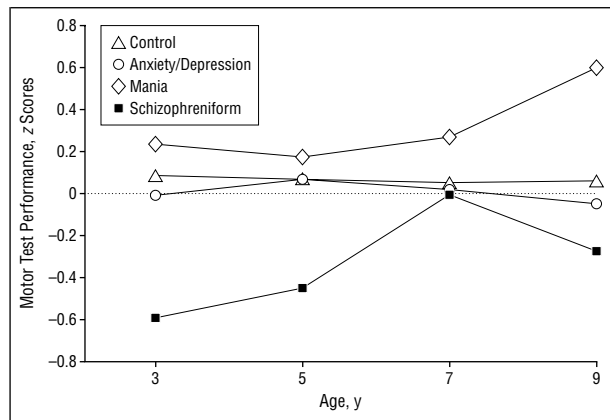


Figure 1. The mean standardized scores for motor development at ages 3, 5, 7, and 9 years for adults diagnosed as having schizophreniform disorder (n=36), mania (n=20), anxiety/depression (n=278), and controls (n=642).

The longitudinal Dunedin Study has followed up 1000 children from the general population from birth to age 26 years and offers several advantages for investigating childhood risk factors for adult outcomes. First, we can examine multiple developmental risk factors within one sample using detailed childhood data that were prospectively collected from age 3 years using well-established and validated instruments. Second, we can examine the specificity of early developmental risk factors for schizophreniform outcomes since psychiatric diagnoses were made for all study members at age 26 years based on structured diagnostic interviews conducted by trained health professionals. A third unique strength is that we can study whether the same developmental risk factors predict psychotic symptoms in childhood and in adulthood. In an earlier report from the Dunedin cohort, we showed that children's self-reported psychotic symptoms at age 11 years predicted a schizophreniform diagnosis at age 26 years.³⁴ If the same (or similar) relationships are found between childhood developmental risk factors and psychotic symptoms at age 11 years as with schizophreniform disorder at age 26 years, it would suggest that the psychotic symptoms at age 11 years are part of the disease process itself rather than an independent risk factor/marker for later schizophreniform disorder.

RESULTS

There were significant overall sex and family SES differences among the adult diagnostic groups. The adult anxiety/depression group contained significantly more females than the control group (60.1% vs 45%; $\chi^2_1=17.6$; $P<.01$) and a significantly higher proportion of adults in the schizophreniform group came from low-SES families (categories 1 and 2) compared with controls (47.2% vs 9.2%; $\chi^2_1=16.5$; $P<.01$).

OBSTETRIC COMPLICATIONS, MATERNAL FACTORS, AND PSYCHIATRIC OUTCOMES

There was a significant association between the obstetric complications index and later schizophreniform disorder ($\beta=.38$; 95% CI, 0.25-0.52; $P=.02$) but no significant as-

sociation with later mania ($\beta=.03$; 95% CI, -0.15 to 0.21) or anxiety/depression ($\beta=-.03$; 95% CI, -0.08 to 0.03). Post hoc analyses revealed that 3 complications were associated with an increased risk of schizophreniform disorder: low Apgar score at birth (OR, 5.9; 95% CI, 1.1-32.0); hypoxia at birth (apnea or idiopathic respiratory distress syndrome) (OR, 5.0; 95% CI, 1.5-16.4); and small-for-gestational-age status (OR, 2.8; 95% CI, 1.1-6.9). The mothers of the schizophreniform group (OR, 2.65; 95% CI, 1.2-5.6) but not the manic group (OR, 1.7; 95% CI, 0.6-4.9) or the anxiety/depression group (OR, 1.4; 95% CI, 0.9-2.03) were significantly more likely to have atypical mother-child interactions when compared with mothers of controls.

NEUROMOTOR DEVELOPMENT AND PSYCHIATRIC OUTCOMES

The schizophreniform group began to walk significantly later than controls (mean [SE], 14.9 [1.0] months vs 13.6 [0.13] months; $F_{3,661}=5.01$ [adjusted for sex and SES]; $P=.02$) but there were no differences for any other infant milestones. At age 3 years, the schizophreniform group was significantly more likely than controls to have one or more neurologic signs (OR, 4.6; 95% CI, 1.9-10.9). The mania group (OR, 0.8; 95% CI, 0.1-6.4) and the anxiety/depression group (OR, 1.7; 95% CI, 0.9-2.8) were not significantly more likely to have neurologic signs than controls. The schizophreniform group also performed worse than controls (more than 0.3 SDs) on standard tests of motor skill at ages 3, 5, and 9 years but not at age 7 years (**Figure 1**). The repeated-measures analysis showed that the schizophreniform group performed significantly worse than the control group overall, while the mania group performed significantly better than the control group on motor performance, even after controlling for sex and SES (**Table 1**). The anxiety/depression group did not differ significantly from controls on any of these motor assessments.

LANGUAGE DEVELOPMENT, COGNITIVE DEVELOPMENT, AND PSYCHIATRIC OUTCOMES

The schizophreniform group did not exhibit any problems with expressive language but their receptive language skills were significantly poorer than those of the controls (between 0.2-0.6 SDs) at each of the 4 biennial testings during the first decade of life (**Figure 2**). The schizophreniform group also performed more poorly than controls (about 0.4 SDs) on standard IQ tests at each of 5 assessments between ages 3 and 11 years (**Figure 3**). These significant impairments in receptive language and cognitive development among the schizophreniform group were independent of sex and SES (Table 1). The mania and the anxiety/depression groups did not differ significantly from controls on either language measure or on IQ test performance (Table 1).

INTERNALIZING AND EXTERNALIZING PROBLEMS, INTERPERSONAL ADJUSTMENT, AND PSYCHIATRIC OUTCOMES

The schizophreniform group and the anxiety/depression group exhibited significantly more childhood internaliz-

Table 1. Results From Regression Analyses Showing the Association Between Developmental Functioning During the First Decade of Life and Adult Psychiatric Outcomes at Age 26 Years*

Developmental Variables	Psychiatric Outcomes at Age 26 Years					
	Schizophreniform Disorder (n = 36)		Mania (n = 20)		Anxiety/Depression (n = 278)	
	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value
Motor development, age 3-9 y	-0.39 (-0.67 to -0.12)	.005	0.33 (0.06-0.6)	.01	-0.05 (-0.15 to 0.04)	.3
Receptive language, age 3-9 y	-0.31 (-0.54 to -0.06)	.01	0.02 (-0.2 to 0.24)	.8	-0.04 (-0.14 to 0.06)	.4
Expressive language, age 3-9 y	0.09 (-0.15 to 0.34)	.4	0.11 (-0.16 to 0.37)	.4	-0.03 (-0.12 to 0.06)	.5
IQ, age 3-11 y	-0.33 (-0.6 to -0.07)	.01	0.11 (-0.1 to 0.32)	.3	-0.07 (-0.19 to 0.03)	.16
Internalizing problems, age 5-11 y	0.27 (0.02-0.53)	.03	0.28 (-0.01 to 0.58)	.06	0.17 (0.05-0.28)	.004
Externalizing problems, age 5-11 y	0.32 (-0.05 to 0.7)	.09	0.36 (-0.04 to 0.75)	.07	0.09 (-0.01 to 0.2)	.09
Peer rejection, mean score, age 5-11 y	0.46 (0.01-0.9)	.04	0.54 (0.02-1.06)	.04	0.16 (0.01-0.31)	.03
Social isolation, mean score, age 5-11 y	0.17 (-0.18 to 0.53)	.3	0.46 (0.09-0.82)	.01	0.16 (0.01-0.31)	.04

*The reference group in the regression equations comprises control subjects who did not meet diagnostic criteria for schizophreniform disorder, mania, or anxiety/depression at age 26 years (n = 642). The regression coefficients are interpretable as SD unit differences between each psychiatric group and the control group, adjusted for sex and family socioeconomic status. Negative coefficients for motor development, receptive language, expressive language, and IQ (intelligence quotient) indicate worse performance; positive coefficients for internalizing problems, externalizing problems, peer rejection, and social isolation indicate worse adjustment. CI indicates confidence interval.

ing problems as rated by parents and teachers than the control group (**Figure 4**). These effects were independent of sex and SES (Table 1). All 3 diagnostic groups exhibited more childhood externalizing problems than the control group (Figure 4) but, when adjusted for sex and SES, these differences just missed significance at the 5% level (Table 1). All 3 diagnostic groups were significantly more likely than the control group to be rejected by peers, as rated by parents and teachers (Table 1). The mania group and the anxiety/depression group, but not the schizophreniform group, were significantly more likely than controls to be rated by parents and teachers as socially isolated (Table 1).

OBSTETRIC AND MATERNAL FACTORS IN RELATION TO DEVELOPMENTAL IMPAIRMENT

We investigated whether the relationships between developmental deficits and schizophreniform disorder were independent of obstetric complications and atypical mother-child interaction. Adjusting for the obstetric complications that were significantly related to schizophreniform outcome and for atypical mother-child interaction (as well as sex and SES), the associations between schizophreniform disorder and motor development ($\beta = -.35$; 95% CI, -0.59 to -0.12 ; $P = .003$), receptive language ($\beta = -.22$; 95% CI, -0.45 to 0.02 ; $P = .07$), and IQ ($\beta = -.26$; 95% CI, -0.52 to -0.004 ; $P = .04$) did not change significantly.

CHILDHOOD DEVELOPMENTAL IMPAIRMENT AND PSYCHOTIC SYMPTOMS AT AGE 11 YEARS

Self-reported strong psychotic symptoms at age 11 years were associated with significant developmental impairments in neuromotor development, receptive language, intelligence, and emotional development (**Table 2**). The effect sizes were generally even larger than those noted for schizophreniform disorder at age 26 years. Apart from an association with receptive language impairment, self-reported weak psychotic symptoms at age 11 years were

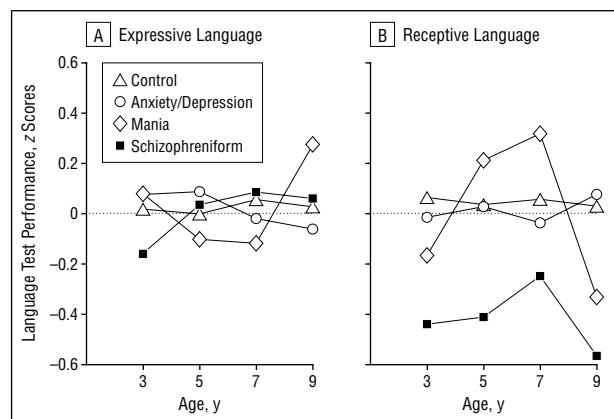


Figure 2. The mean standardized scores for expressive and receptive language development at ages 3, 5, 7, and 9 years for adults diagnosed as having schizophreniform disorder (n=36), mania (n=20), anxiety/depression (n=278), and controls (n=642).

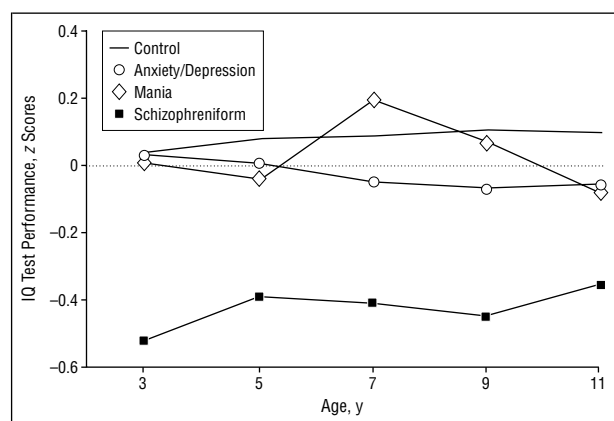


Figure 3. The mean standardized scores for intelligence tests at ages 3, 5, 7, 9, and 11 years for adults diagnosed as having schizophreniform disorder (n=36), mania (n=20), anxiety/depression (n=278), and controls (n=642).

not significantly associated with childhood developmental impairments. However, the direction of the coefficients for the weak-symptom group was in the same direction as the coefficients for the strong-symptom group.

This longitudinal investigation of an unselected birth cohort examined several childhood risk factors in relation to 3 adult psychiatric outcomes. Children who later fulfilled diagnostic criteria for schizophreniform disorder at age 26 years exhibited significant impairments across a range of developmental domains (neuromotor, language, cognitive, emotional, and interpersonal development) from as young as 3 years. In contrast, children who later fulfilled diagnostic criteria for mania and anxiety/depression exhibited problems only in the areas of emotional and interpersonal development. Early neuromotor, language, and cognitive developmental impairments therefore seem to show specificity to schizophreniform disorder, whereas childhood emotional and interpersonal difficulties are associated with a range of psychiatric disorders in adulthood. Of special interest is the finding that similar childhood developmental deficits were observed in relation to self-reported psychotic symptoms at age 11 years and in relation to schizophreniform disorder at age 26 years. This suggests that these developmental deficits are associated with psychotic ill-

ness processes that begin in childhood, and that childhood psychotic symptoms may be part of a disease process rather than an independent risk factor/marker for later schizophreniform disorder.

The relationship between neuromotor developmental problems and later schizophreniform disorder in this study was particularly strong, with evidence of delay in learning to walk during infancy, an excess of neurologic signs at age 3 years, and significant impairments on repeated motor testing between ages 3 and 9 years. We found that the schizophreniform group exhibited deficits in receptive language development (verbal comprehension) rather than expressive language development. Previous work on this cohort has shown that receptive but not expressive language delay at age 3 years was significantly associated with behavior problems in late childhood,⁶³ and a follow-up study of a group of children with developmental receptive language disorder has found that 10% of the children later developed schizophrenia.⁶⁴ Our study also revealed that childhood cognitive impairments among the schizophreniform group were emerged early and were persistent, with significant deficits in IQ detectable from age 3 years. In sum, our findings on motor, language, and cognitive impairments add to a body of work showing that childhood developmental deficits are found among individuals with schizophrenia and among those at genetic risk for schizophrenia.⁷⁻²³ Our study provides new evidence that these impairments may be specific to schizophrenia. Although 2 previous studies have noted some (albeit weaker) associations between childhood motor and speech problems and affective disorder, these abnormalities were mainly confined to childhood-onset cases.^{24,25}

Recent work has found that obstetric complications involving hypoxia and fetal growth retardation are risk factors for schizophrenia,⁶⁵⁻⁶⁹ and such effects were also noted in this study. In agreement with other cohort studies,^{9,70} we found that aspects of the mother-child interaction were associated with later schizophreniform disorder. However, these perinatal and maternal risk factors could not entirely account for the early developmental impairments found in our schizophreniform group. We therefore surmise, along with others,²⁰⁻²² that neurode-

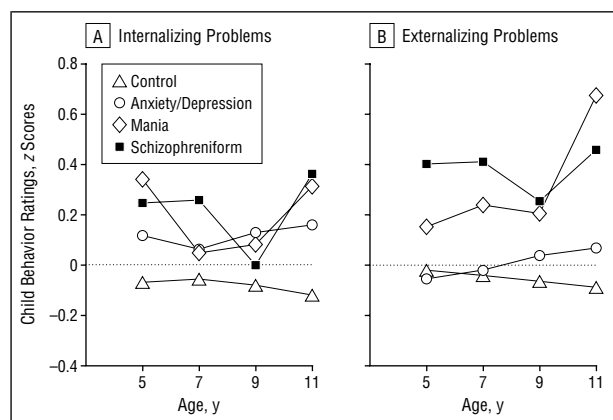


Figure 4. The mean standardized scores for internalizing and externalizing problems at ages 5, 7, 9, and 11 years for adults diagnosed as having schizophreniform disorder (n=36), mania (n=20), anxiety/depression (n=278), and controls (n=642).

Table 2. Results From Regression Analyses Showing the Association Between Developmental Functioning During the First Decade of Life and Psychotic Symptoms at Age 11 Years*

Developmental Variables	Psychotic Symptoms at Age 11 y			
	Weak Symptoms (Score=1) (n=103)		Strong Symptoms (Score>1) (n=13)	
	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value
Motor development, age 3-9 y	-0.11 (-0.25 to -0.02)	.11	-0.62 (-1.2 to -0.04)	.03
Expressive language, age 3-9 y	0.015 (-0.11 to 0.14)	.8	-0.11 (-0.42 to 0.19)	.5
Receptive language, age 3-9 y	-0.14 (-0.27 to -0.005)	.04	-0.57 (-0.92 to -0.22)	<.01
IQ, age 3-11 y	-0.12 (-0.26 to 0.03)	.13	-0.52 (-0.83 to -0.21)	<.01
Internalizing problems, age 5-11 y	0.15 (-0.05 to 0.34)	.13	0.74 (0.18 to 1.3)	.01
Externalizing problems, age 5-11 y	0.15 (-0.03 to 0.33)	.11	0.34 (-0.28 to 0.94)	.28
Peer rejection, mean score, age 5-11 y	0.17 (-0.03 to 0.37)	.10	0.51 (-0.2 to 1.2)	.16
Social isolation, mean score, age 5-11 y	0.03 (-0.17 to 0.24)	.73	0.46 (-0.14 to 1.06)	.14

*The reference group in the regression equations includes subjects who did not report any psychotic symptoms at age 11 years (n = 673). The regression coefficients are interpretable as SD unit differences between the weak- and strong-symptom groups and the control group, adjusted for sex and family socioeconomic status. Negative coefficients for motor development, receptive language, expressive language, and IQ (intelligence quotient) indicate worse performance; positive coefficients for internalizing problems, externalizing problems, peer rejection, and social isolation indicate worse adjustment. CI indicates confidence interval.

developmental impairments are not merely mediators of the effects of obstetric complications on risk for schizophrenia. These early developmental impairments are more likely to reflect the expression of schizophrenia-susceptibility genes,^{71,72} and reports of developmental impairments among offspring at high genetic risk for schizophrenia lend support to this view.^{7,8,16,19}

Emotional problems and poor interpersonal functioning in childhood were associated with a host of different adult psychiatric outcomes at age 26 years, including schizophreniform disorder, manic episodes, and anxiety/depression disorders. These predictive associations are of actuarial interest—they span more than 15 years and do not exhibit specificity to any one outcome. Lack of specificity is important because it indicates a common pathway to the development of a range of different disorders. Although this constellation of childhood behaviors observed in children as young as 5 years is unlikely to represent a prodrome, it may index, more generally, a vulnerable personality that is at risk for all adult psychiatric disorders. Although we found no significant association between childhood social isolation and schizophreniform disorder, as noted by others,^{9,73-75} it is possible that such peer problems become more evident during adolescence.^{76,77}

Limitations of our study should be noted. First, the sample sizes in the schizophreniform and manic groups are not large. Nevertheless, the developmental impairments in the schizophreniform group were consistently detected on repeated testings throughout childhood and were robust to adjustment for sex and social class effects. Second, the study members have not passed through the entire period of risk for psychosis. However, the childhood developmental risk factors found in this study are remarkably similar to those found in a cohort study that has followed up participants to age 43 years,⁹ suggesting that our findings can be extrapolated throughout the age-incidence distribution. Last, throughout this analysis we have reported on findings for schizophreniform disorder rather than schizophrenia alone, partly because of sample-size considerations and also because dimensional or continuum models of psychosis are becoming established as the most likely theoretically⁷⁸ and the most useful clinically.⁷⁹ Indeed, it is impressive that the same childhood developmental risk factors seem to apply to the broader phenotype of schizophreniform disorder as to the narrower concept of schizophrenia itself.

In conclusion, this study demonstrates that schizophreniform disorder is associated with childhood developmental deficits across a range of domains. Motor, language, and cognitive developmental deficits emerge early and are persistent and specific to schizophreniform disorder. In addition, we have shown that pan-developmental impairments are associated with psychotic symptoms both in childhood and in adulthood. Taken as a whole, the evidence from this study provides support for a neurodevelopmental model of schizophrenia,²⁻⁶ echoing the earlier theoretical concept of schizotaxia.⁸⁰⁻⁸² It is increasingly evident that understanding the complex mechanisms governing brain development will ultimately hold the key to the etiology of schizophrenia.

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