

The Long-Term Course of Childhood-Onset Schizophrenia: A 42-Year Followup

by Christian Eggers and Detlef Bunk

Abstract

This article presents results of a 42-year long-term followup of 44 patients (19 males, 25 females) with childhood-onset schizophrenia. Age at onset ranged from 6 to 14 years (mean = 11.8 years). The patients and their first-degree relatives were interviewed in 1994, 27 years after the first followup, by the same investigator with the Present-State Examination (PSE) and the Disability Assessment Schedule. The clinical records were analyzed with the Instrument for the Retrospective Assessment of Onset of Schizophrenia and with sections of the PSE. The cases were re-diagnosed according to *DSM-III-R*, based on longitudinal data obtained between onset and the first hospital admission. Although cumulative prevalence is earlier in females than in males, no gender differences exist in average age at onset. An acute onset was significantly more frequent after 12 years of age. An early age at onset was correlated with high social disability scores. Of the patients, 25 percent were completely, 25 percent partially, and 50 percent were poorly remitted at the second followup. None of the patients with chronic onset remitted completely. The results are discussed with respect to epidemiology, gender differences, and etiological hypotheses of childhood schizophrenia.

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Despite enormous research efforts, there is still a great deal that we do not know about schizophrenia. Karl Jaspers (1963) cited this dilemma as the “enigma of being human itself.” Careful evaluation and description of the course in individual patients, if possible for the entirety of their lives, would provide a useful opportunity to fill some of the gaps in our knowledge about schizophrenia. Long-term studies of schizophrenic psychoses are rare, and those that exist relate almost exclusively to schizophrenia in adults. Few contain patient histories longer than 15

years (Tsuang and Winokur 1975; Ciompi and Müller 1976; Bleuler 1978; Huber et al. 1979; Harding et al. 1987; Marneros et al. 1991). Comparable studies of the long-term course in schizophrenic psychoses with onset before age 15 are even more rare, primarily because of the low incidence of early-onset schizophrenia. The estimated prevalence of schizophrenia in children below age 15 is 0.14 in 1,000—almost 50 times lower than after the age of 15 (McKenna et al. 1994).

Until recently, it was doubted whether childhood-onset and adult-onset schizophrenic psychoses formed a continuum (Asarnow 1994; McKenna et al. 1994). Earlier publications often reported psychotiform disorders of organic origin (e.g., catatonic hyperkinesia with autistic features) under the heading of “childhood psychosis.” It was not usual to distinguish between late-onset psychosis (Kolvin et al. 1971) or “adult-type schizophrenia in childhood” (Eggers 1973) and “atypical psychosis in childhood.” Instead, “childhood schizophrenia” was used to designate an “astonishingly heterogeneous mixture of disorders” (Rutter 1972) whose only common features were the severity of the symptoms, their chronicity, the age at manifestation, and lack of knowledge about their etiology. In particular, distinction was rarely made between autistic syndromes and other pervasive developmental disorders in childhood. It has now become a common practice—mostly due to the influence of *DSM-III*, *DSM-III-R*, and *DSM-IV* (American Psychiatric Association 1980, 1987, 1994) and the International Classification of Diseases (ICD; World Health Organization 1978, 1992)—to distinguish between autism, adult-type schizophrenia with childhood onset, and other psychotiform disorders. In the pre-ICD-9, pre-*DSM-III* era, we provided evidence that strict nosological evaluation shows a continuity between

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schizophrenic psychosis of childhood onset and adult schizophrenia (Eggers 1973). This view is now widely accepted (Green et al. 1992; Werry 1992; Asarnow 1994).

Werry et al. (1994) showed that the majority of patients with a psychotic onset in adolescence continue to suffer disorders as adults and that affective disorders have a better prognosis than those typical of schizophrenia. Schizophrenia beginning before age 10 is now believed to carry a worse prognosis than late-onset schizophrenia (Eggers 1973; Gillberg et al. 1993). However, this assumption rests on barely confirmed empirical observations. Both our own and Werry et al.'s long-term studies (Eggers 1978; Werry et al. 1991) suggest that early- and late-onset psychoses actually have similar prognoses. This result might be related to the fact that it is often impossible to draw a definite distinction in prepubertal patients between affective, schizoaffective, and purely schizophrenic psychoses (Eggers 1986, 1989).

The variable course and the difficulty of establishing a valid classification constitute great problems even in schizophrenia of adult onset. Even Bleuler (1978) in his study of more than 200 cases of adult-onset schizophrenia, which he observed for more than 20 years, was surprised about the heterogeneity and individuality of the course of the disease in different cases and was unable to define the group of schizophrenias by way of a particular symptomatology. The heterogeneity of research findings is further confounded by methodological inadequacies and different applications of diagnostic criteria (Angst 1988; Häfner et al. 1991, 1992).

Objective

The main objective of our ongoing study is the detailed description of the long-term course of 44 patients with

childhood-onset schizophrenia (i.e., before age 14). In this preliminary report we present data on social class status; age at first signs of psychological abnormality, first definite psychotic symptoms, and first inpatient admission; gender differences with regard to age at the start of inpatient treatment; and the type of disease onset. We will also provide preliminary data on course and outcome.

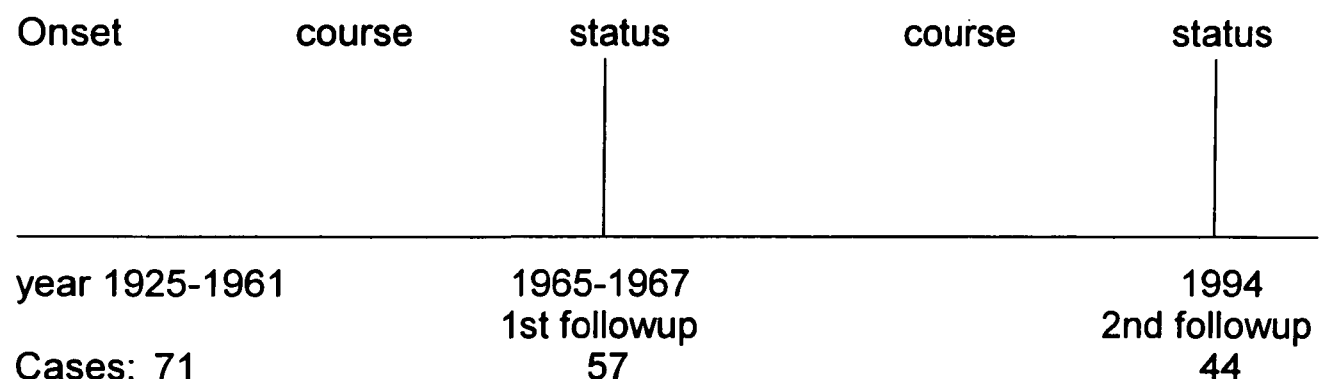
In this first report the following questions will be discussed: What is the age distribution? Is there a difference between boys and girls with regard to disease onset, interval from first psychological abnormality to start of treatment, or development of psychopathological symptoms? Is there any relationship between the type of onset and age at onset, and is outcome related to these variables?

Methods

Design. The project started in 1965 with the first followup study. The results were published in 1973 and 1978 (Eggers 1973, 1978). The second followup took place between April and October 1994 and was carried out by the same interviewer as the first, ensuring observer consistency. The timetable of the study is shown in figure 1. Variables relating to psychopathological and biographical status were measured three times: at first hospitalization, at the first followup between 1965 and 1967, and at the second followup in 1994.

Original Sample. The original sample consisted of 71 patients who had been diagnosed with childhood schizophrenia. They were inpatients at a university psychiatric hospital in West Germany between 1925 and 1961. The sample is representative of a typical hospital's patients. Age at onset ranged from 3 to 14 years. At the end of the 1960s, all inpatient admissions from 1925 to 1961 were

Figure 1. Timetable and design of 42-year long-term followup study of childhood-onset schizophrenia



scrutinized for patients with a diagnosis of childhood schizophrenia resulting in an age-selected patient population of a psychiatric hospital. Selection criteria were a suspected diagnosis of childhood schizophrenia and onset before age 14. Recruitment was based on a careful analysis of the admission records, which included date of birth, dates of admission and discharge, and diagnosis at discharge; all schizophrenia patients in this age group were recruited.

First Followup. The average followup period was 14.7 years (standard deviation [SD] = 7.1). The oldest patient was 54 at the first followup. Fourteen patients were withdrawn from the study because the diagnosis of schizophrenia could not be verified on the basis of their history. Onset in the oldest patients was during the mid-1920s, so the diagnostic classification, especially of those with onset before age 6 or 7, was uncertain, which explains the high rate of error (20%, $n = 14$). The diagnostic process was oriented to Eugen Bleuler's (1911/1950) concept of primary and secondary disorders and Kurt Schneider's (1959) first- and second-rank symptoms. Since schizoaffective psychosis was not differentiated as a special entity until 1978, the original sample included this subtype, which was indicated if first-rank symptoms had been observed. Five patients died before the first followup, but their records were examined completely and first-degree relatives were interviewed.

Second Followup. Of the 57 patients (26 male, 31 female) in the first followup study (Eggers 1973, 1978), only 44 (19 male, 25 female) could be traced after about 27 years (SD = 4.2). Of this remaining group, 35 (79.6%) were interviewed in person. First-degree relatives of 9 subjects were available to give further detailed information. Two patients refused a home visit but gave several extended telephone interviews. For these patients, we had complete sets of medical records on their in- and out-patient psychiatric treatment. We also had complete medical records for the 7 patients who died between the first and second followups and were able to interview their relatives in person. One patient died 10 weeks after the second followup interview, 28 years after the first followup in 1966. One advantage of the present study is that the second followup examination was carried out by the same researcher who conducted the first, allowing a reevaluation of the results published in 1973 and 1978. Another advantage is that the questionnaire developed for the first followup covers almost the same ground as the now widely used Present-State Examination (PSE; Wing et al. 1974).

Measures for Diagnosis and Outcome, Data Analysis. Patients' hospital admissions and other details of their

complete psychiatric history, including the data from the first followup, were evaluated using the Instrument for the Retrospective Assessment of Onset of Schizophrenia (IRAOS; Häfner et al. 1992). Diagnostic classification of psychotic states was based on Schneider's symptom lists at the first followup. To avoid contaminating the diagnoses with outcome judgments made at different times, *DSM-III-R* criteria were applied to the key psychopathological symptoms observed during the first psychotic period after the onset of the illness, with the exception of the *DSM-III-R* criteria of changes in adaptive functioning. Difficult cases were discussed to obtain a consensus diagnosis. The key symptomatology of all patients met the criteria of one of the *DSM-III-R* 295-type diagnoses (schizophrenia, schizopreniform, or schizoaffective).

For the 1994 investigation, we used two structured interviews: the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) and the German version of the PSE (Wing et al. 1974). We used parts of these instruments to evaluate even the patients who had died before the second followup, on the basis of their medical records. To analyze the symptomatology described during the first episode of illness, the frequencies of positive, negative, and global symptoms were determined according to the PANSS. Patients' general level of psychosocial functioning and psychosocial adaptation at the second followup were assessed using the method of Eggers (1973) and the Disability Assessment Schedule-Mannheim (DAS-M; Jung et al. 1989). The ratings were based on the data from the PSE structured interview and the IRAOS. For further data analysis, we performed nonparametric comparisons between logically independent patient groupings classified according to period of onset, patient gender, type of onset, and outcome.

Results

The average length of the observation time of our study group was 41.9 years (SD = 8.2). This period of time is much longer than other long-term followup studies of childhood-onset schizophrenia, allowing us to draw some fairly certain conclusions about the prognosis of psychotic processes that begin at this early age and about the future of those who suffer from them.

Only 13 patients from the first followup could not be evaluated at the second followup. One of these cases did not meet the *DSM-III-R* criteria for schizophrenia when re-diagnosing the onset episode. Of the other 12 patients lost, 7 had died and 5 had moved to unknown locations. This group of lost patients and the group of 44 patients investigated at the second followup did not differ significantly in gender ($\chi^2 = 0.87$; $p = 0.35$) or in average age at

first psychotic symptoms ($F = 0.74$; $p = 0.39$). Furthermore, we found no significant group differences in the mean frequencies of negative ($F = 0.31$; $p = 0.57$), positive ($F = 0.81$; $p = 0.36$), or global ($F = 2.5$; $p = 0.11$) symptoms on the PANSS during the first psychotic episode.

Social Class. The social class of the 44 patients was based on the father's occupation using the method of Moore and Kleining (1960). Sixty-four percent of the patients scored as lower class, 26 percent as middle class and 10 percent as upper class. The distribution differed significantly ($\chi^2 = 7.7$; $p = 0.02$) from the proportion of the classes in the normal population reported by Moore and Kleining (6% upper, 45% middle, 49% lower class).

Age at Onset. Three different time points were distinguished: (1) age at first signs of psychological abnormality or first psychiatric symptoms (AFS), (2) age at first occurrence of distinctly psychotic symptoms (AFPS; onset of psychosis in the strict sense), and (3) age at first hospitalization (AFH). Table 1 shows the distribution of AFS, AFPS, and AFH. The age distribution at the three different time points is shown in figure 2.

Gender Distribution. There was a slight predominance of female patients (male:female ratio = 19:25). One-way analysis of variance showed no significant differences between boys and girls in AFS, AFPS, or the time lag from AFS to AFH. Setting the cutoff for a definitely pre-

Table 1. Mean age at first psychiatric symptoms (AFS), mean age at first psychotic symptoms (AFPS), and mean age at first hospitalization (AFH)

	AFS	AFPS	AFH
Mean	11.8	13.0	13.4
Standard deviation	2.0	1.7	1.5
Range	6-14	7-18	9-16

pubertal onset at 12 years (i.e., before age 12), no gender differences were found with regard to AFS ($\chi^2 = 1.6$; $p = 0.20$).

For a comparison of gender differences in the risk of morbidity, a Kaplan-Meier survival analysis with sex as grouping factor was carried out for the variable AFPS. Figure 3 shows the cumulative survival of first productive psychotic symptoms in boys and girls as a function of age. Although in boys the onset lies between 10 and 18 years of age and shows a flatter curve than in girls, for whom the period of onset is markedly earlier (between 7 and 15 years of age), no gender differences were found between the two survival distributions (log rank = 0.24; $p = 0.62$).

Type of Onset. There are various ways of classifying the type of onset. In previous publications (Eggers 1973, 1978), onset was classified into acute versus chronic-insidious (acute was within 4 weeks, chronic was more than 4 weeks). *DSM-III-R* and Shepherd et al. (1989) dis-

Figure 2. Age distribution at first psychiatric symptoms, first psychotic symptoms, and first hospitalization

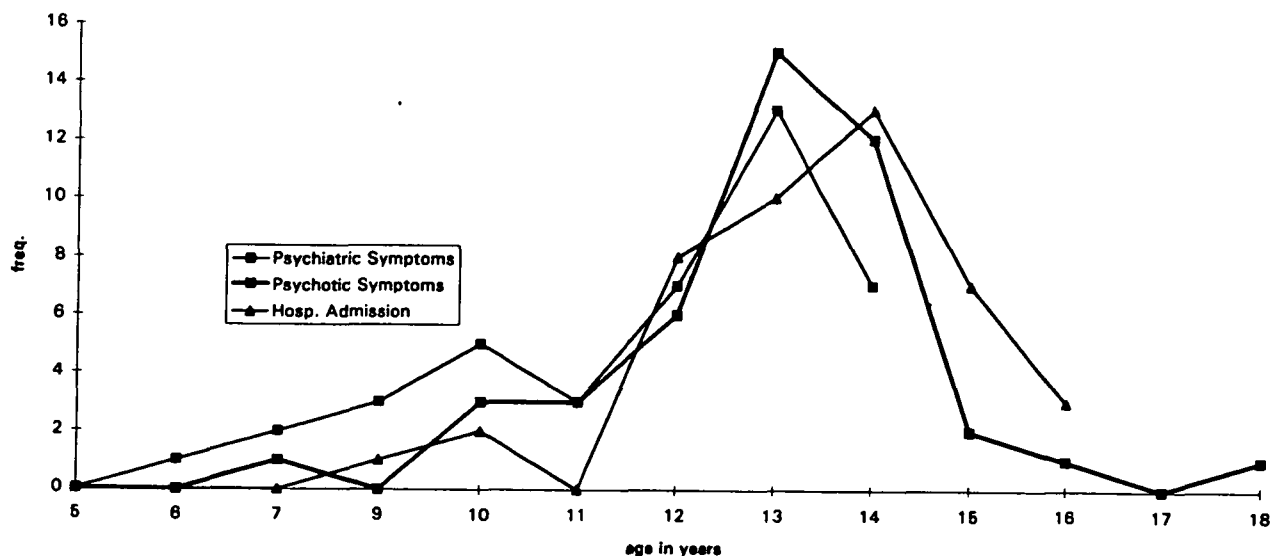
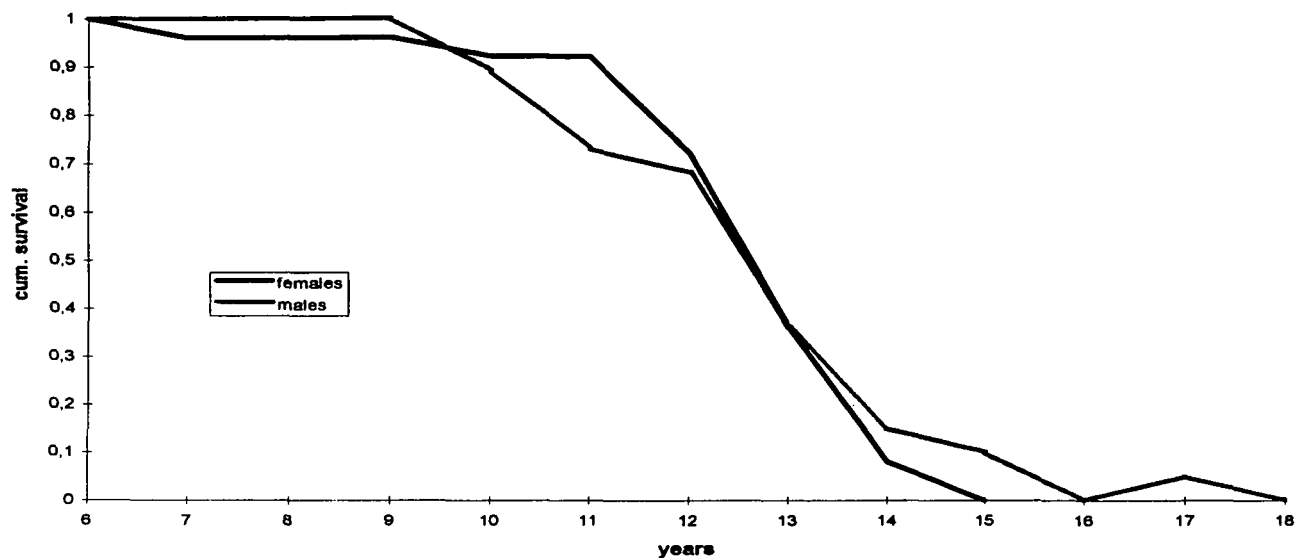


Figure 3. Cumulative survival for age at first psychotic symptoms in females ($n = 25$) and males ($n = 19$)



tinguish between acute (onset within 1 week) and subacute (onset within 4 weeks). Applying the latter classification to our patients, the onset lasted 1 week or less for 6 patients (acute), and in another 27 it was within 4 weeks (subacute), making a total of 33 patients with onset within 4 weeks (i.e., with acute onset). The other 11 patients showed an insidious onset over more than 4 weeks. An acute onset was significantly more frequent after age 12, whereas insidious onset predominated before age 12 ($\chi^2 = 16.9$; $p = 0.000$).

Outcome. There was very good agreement between two independent raters in all the selected DAS-M variables: communication deficit/social withdrawal, working behavior, interest in work and occupation, interests/need for information, and global social adaptation. The interrater reliabilities (Pearson correlation) ranged from 0.77 to 0.93.

We compared two outcome measures used to define a three-category remission grade at the second followup. The first instrument for assessing social adjustment was the 6-point scale of the DAS-M global social adaptation rating. Second, we applied the definitions of the first followup study (Eggers 1973), which take into account both clinical and social variables:

1. Complete remission. The patient has distanced him- or herself completely from the psychotic experiences: unrestricted ability to work, no disease-related psychological abnormalities.

2. Very good social remission. As (1), except for slight psychological abnormalities: mood fluctuations,

slight irritability, slightly reduced capacity for affect modulation, slight reduction of social contact.

3. Good to satisfactory social remission. Slight deficiency signs, slight loss of creative energy, reduced capacity for stress, affective instability, impulsiveness, markedly reduced emotional responsivity, bizarre behavior.

4. Moderate to poor social remission. Continuation of psychotic symptoms, marked signs of deficit in motivation and affective reactivity, limited ability to work.

5. Very poor remission. As (4), completely unable to work or can work only with intensive support from others, marked apathy.

6. Severe residual disease. With or without acute psychotic symptoms, no communication possible; mutism or confusion.

The two 6-point rating scales (DAS-M and the Eggers scale) correlated significantly (Pearson $r = 0.93$; $p < 0.05$). A three-category outcome rating was derived from each scale: complete remission (values 1–2), partial remission (values 3–4), and poor remission (values 5–6). The global assessment according to Eggers' original categories and the assessment of social remission using the DAS-M agree in 38 of the 44 cases (86.4%). Three patients evaluated as chronic-residual by Eggers' categories were categorized as partially remitted using DAS-M criteria and vice versa. According to both assessment methods, 11 of the 44 patients (25%) were in complete remission, 11 (25%) were in partial remission, and 22 (50%) were in poor remission and had developed a severe residual syndrome or were chronically psychotic. The rela-

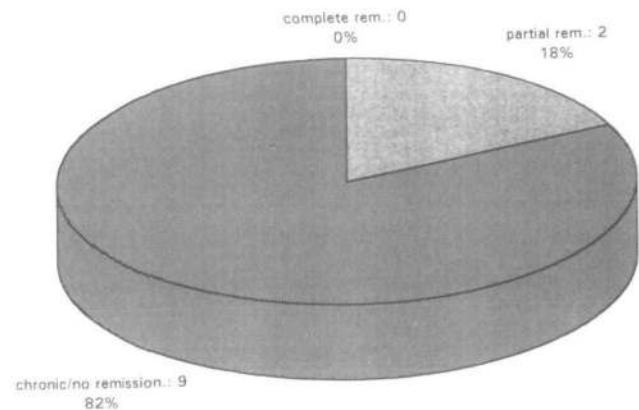
tionship of remission grade to type of onset (acute vs. chronic-insidious) as shown in figures 4 and 5. In our sample, no subject with a chronic-insidious onset showed a complete remission.

The whole sample was subdivided into three groups using the DAS-M remission grade as a grouping variable. These groups were compared with respect to the three PANSS measures (frequencies of positive, negative, and global pathology during the first episode) and two features of their course (frequencies of episodes and total length in years of all episodes). The length of the catamnestic observation time was included in the analysis as a covariate for the two course features. Table 2 shows the results of the analyses. The three groups did not differ significantly in their average frequencies of PANSS symptoms, but the completely remitted group shows a lower frequency of episodes, and the total length of all episodes was significantly higher in patients with poor or no remission.

Relationship Between Age at Onset and Outcome. In the first followup study, we found that early-onset disease carried a worse prognosis than later-onset disease (Eggers 1973). This finding was confirmed in the 44 patients reexamined at the second followup. Table 3 shows the Pearson correlations between AFS and AFPS and the DAS-M social disability variables. The earlier the appearance of AFS and AFPS, the more pronounced were the impairments in social adaptation at the second followup.

To exclude any pubertal effects, we divided our study group into those under age 12 at AFS and those age 12 or

Figure 5. Distribution of outcome categories of 11 chronic-onset psychotic patients



older. Table 4 shows the results of the analysis of variance of age groups by DAS-M scores. The extent of social disability in the group with onset before age 12 ($n = 14$) is significantly greater than that in the group that was older at onset ($n = 30$).

Discussion

Gender, age, and the distribution of positive, negative, and global symptoms did not differ among the 44 cases of the study group and the omitted patients. We therefore suppose that no selective attrition took place due to misdiagnosis at the time of the first followup.

Figure 4. Distribution of outcome categories of 33 acute-onset psychotic patients

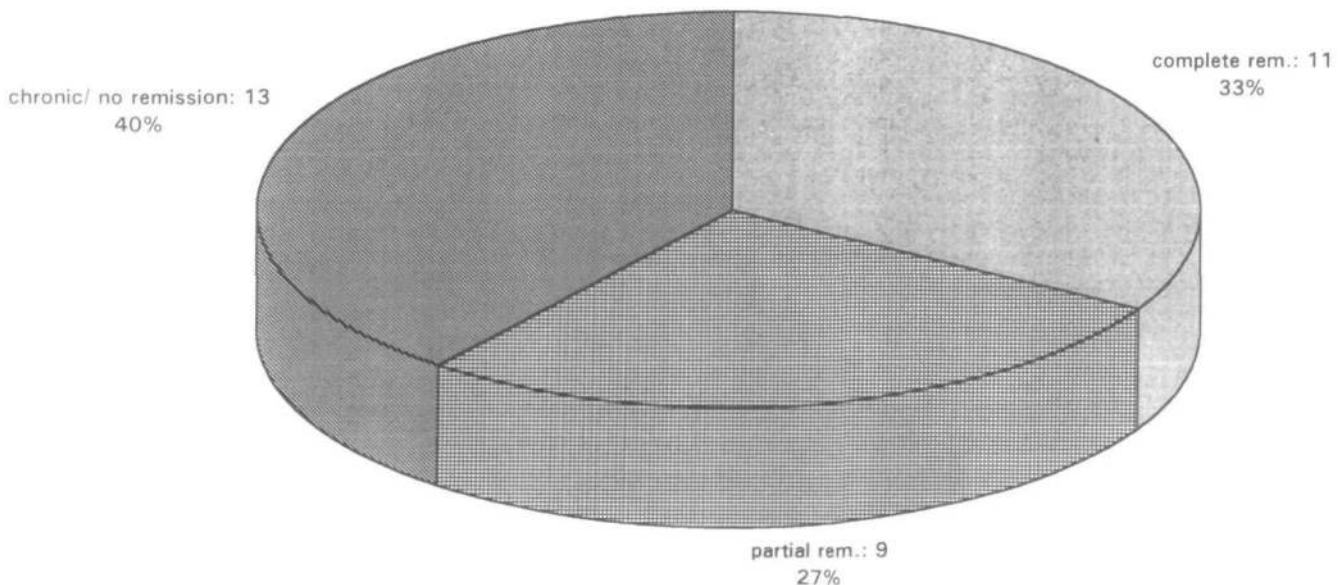


Table 2. Analysis of covariance: Differences in average frequencies of Positive and Negative Syndrome Scale symptoms and course features of completely remitted (CR), partially remitted (PR), and not remitted (NR) cases with total catamnestic observation time (COT) as a covariate

Variable	CR	PR	NR	Effect	
				Group <i>p</i>	COT <i>p</i>
Positive symptoms	2.6	2.2	2.4	0.78	—
Negative symptoms	1.2	1.2	2.1	0.37	—
Global symptoms	3.3	4.11	3.8	0.73	—
Frequency of episodes	4.8	10.0	9.6	0.09	0.18
Total length of all episodes, in years	1.2	2.9	13.3	0.005	0.42

Note.—Positive and Negative Syndrome Scale (Kay et al. 1987).

Table 3. Pearson correlations of age at first psychiatric symptoms (AFS), age at first psychotic symptoms (AFPS), and Disability Assessment Schedule–Mannheim (DAS–M) variables

	DAS–M14	DAS–M26	DAS–M27	DAS–M28	DAS–M3
AFS	0.39	–0.43	–0.42	–0.34	–0.44
<i>p</i>	0.005	0.002	0.002	0.012	0.001
AFPS	–0.31	–0.30	–0.31	–0.35	–0.39
<i>p</i>	0.019	0.024	0.021	0.009	0.005

Note.—DAS–M14 = communication deficit/social withdrawal; DAS–M26 = working behavior; DAS–M27 = interest in work and occupation; DAS–M28 = interests/need for information, DAS–M3 = global social adaptation. Disability Assessment Schedule–Mannheim (Jung et al. 1989).

Table 4. Analysis of variance of age group differences at manifestation of first psychiatric symptoms (AFS)

	DAS–M14	DAS–M26	DAS–M27	DAS–M28	DAS–M3
AFS < 12 years (<i>n</i> = 14)	3.9	4.4	4.3	3.5	3.7
AFS ≥ 12 years (<i>n</i> = 30)	2.7	2.8	2.7	2.6	2.3
<i>F</i>	3.8	6.0	5.4	1.7	6.6
<i>p</i>	0.0556	0.0183	0.0239	0.0192	0.0134

Note.—DAS–M14 = communication deficit/social withdrawal; DAS–M26 = working behavior; DAS–M27 = interest in work and occupation; DAS–M28 = interest/need for information, DAS–M3 = global social adaptation. DAS–M = Disability Assessment Schedule–Mannheim (Jung et al. 1989).

Patient Age and Gender. Eleven (25%) of the 44 patients in our followup study showed first signs of psychological abnormality at or before age 10. The earliest onset was at 6 years (one girl). It must be remembered that relatives' subjective reactions (i.e., when their child's behavioral abnormalities start to worry them) undoubtedly vary from case to case. It is easier to assess information about the first appearance of productive psychotic symptoms, which are alarming for both relatives and hospital staff. It seems sensible to consider this time as the real onset of disease. The first inpatient admission often comes later; in only 3 patients did the first definitely psychotic symptoms occur after their first hospital stay (0.3 to 3 years).

The first inpatient admission is also not a reliable

sign of the beginning of the manifestation of psychosis because its timing may depend on several factors, including relatives' tolerance of the child's behavioral abnormalities, how close they live to a psychiatric hospital, and the attitude of the relatives toward psychiatric inpatient admission. Experience suggests a source of further uncertainty: unproductive, negative symptoms, such as social withdrawal, deteriorating school performance, loss of interest, apathy, and fears only mildly alarm observers and are often interpreted as naughtiness or laziness.

Confirmed, diagnostically unequivocal schizophrenic psychoses are extremely rare before the age of 10, becoming more common after age 12 (Makita 1966; Kolvin 1971; Eggers 1973, 1978; Werry 1992; Remschmidt et al.

1994; Russell 1994; Werry et al. 1994). Galdos et al. (1993) studied 103 adolescent psychotic patients and found no case of a schizophrenic or schizoaffective psychosis that began before age 12. These patients ranged in age from 12 to 18 at onset. However, of the 44 patients we studied, the first definitely productive psychotic symptoms (acoustic, optic, haptic, and coenesthetic hallucinations, ideas of persecution, and poisoning) were at the age of 7½ years. Three other patients had prominent positive psychotic symptoms at age 10.

For a long time, there was debate as to whether schizophrenic symptoms analogous to those in adults already appear in childhood. Schizophrenic psychoses can now be reliably diagnosed in children using adult criteria from *DSM-III-R*, *DSM-IV*, or *ICD-10* (Eggers 1973, 1978; Asarnow and Ben-Meir 1988; Watkins et al. 1988; Russell et al. 1989; Green et al. 1992; Werry 1992). We agree with Reiser (1963), Kolvin et al. (1971), Strömngren (1968), and Watkins et al. (1988) that a schizophrenic psychosis cannot be diagnosed with sufficient certainty before age 5 or 6 because, up to this age, important psychobiological maturation is occurring that must be complete for psychotic symptoms to develop (Eggers 1973). Our results confirm those of Garralda (1984) and Watkins et al. (1988) that, in general, individual experiences that can be unequivocally diagnosed as delusions and hallucinations generally do not occur before age 9.

On the other hand, our observation that childhood-onset psychoses begin with a relatively broad spectrum of uncharacteristic behavioral disorders at an earlier age, before the emergence of true psychotic first-rank symptoms, also agrees with the findings of other authors. However, in our study group, the time span between the occurrence of first psychological abnormalities and the manifestation of unmistakable productive psychotic symptoms was relatively small (a little more than 1 year). The average age at which children were noticed to be behaving abnormally was also quite high (11.8 years) compared with other studies.

With respect to gender differences, many authors argue that male patients show psychotic symptoms at an earlier age than females (Angermeyer and Kühn 1988; Lewine 1988; Castle and Murray 1991; Häfner et al. 1991; DeLisi 1992). A predominance of male patients has also been reported for childhood-onset schizophrenia, especially in schizophrenic psychoses of very early onset (Bettes and Walker 1987; Russell et al. 1989; Green et al. 1992; Werry et al. 1994). We are unable to confirm this finding, probably because the patients with very early onset of psychosis reported in the literature (e.g., Watkins et al. 1988) include some with infantile autism and childhood-onset pervasive developmental disorders, in which a

male predominance is known. At the first followup study (Eggers 1973), the male-female ratio was 26:31, or 0.84:1. At the second followup, the male-female ratio in the remaining 44 patients was 0.76:1.

We found no significant gender difference in the morbidity risk by the survival analysis. However, the time at which psychotic symptoms first occurred reveals that all the girls (100%) were psychotic by the age of 15.0 years, but it took until 18 years of age for 100 percent of the boys to be psychotic (figure 3). Similar results have been reported by Galdos and van Os (1995). When assessing gender differences in the onset of psychosis, therefore, the cumulative prevalence over a wide age range (e.g., early school age to late adolescence) should be investigated.

Attempts to explain the gender differences must take into account that estrogens, which are released at the onset of female puberty, have been shown to exert an antidopaminergic, and therefore probably an antipsychotic, effect (Seeman and Lang 1990). This effect might explain the predominance of male patients in early adolescence and adolescence, after the peak of puberty. The antipsychotic action of estrogens is probably not effective until puberty is under way. In general, even girls do not reach the peak of puberty before age 12; the protective antipsychotic action of gonadal steroids, especially estrogens, will therefore not be effective at this age. In addition, 15 of the female patients in this study suffered disease onset before 1950, and a positive secular growth shift only became evident after World War II as a result of improved nutrition (van Wieringen 1978). Unfortunately, the patient registers do not record any clinical determination of pubertal stage according an objective measure, so we are confined to theoretical remarks on this topic.

Estrogens not only exert antidopaminergic effects, they also have neurotrophic functions. Gonadal steroids, particularly estradiol, act as neurotrophic substances and stimulate the growth of neuronal processes, especially during psychosexual development. It has been proved experimentally that estradiol exerts protective effects on dendritic spine density in adult female rats via *N*-methyl-D-aspartate receptor activity (Woolley and McEwen 1994). Therefore, estrogens may counteract the reduction in synaptic density that takes place during late puberty and early adolescence (Hüttenlocher 1979).

The drop in synaptic density during this period of life, especially in the area of limbic structures and the prefrontal cortex, has been suggested to be related to the first peak of schizophrenic psychoses. Some results have indicated that the reduction in dopaminergic receptors in the corpus striatum and the frontal cortex proceeds differently in male and female subjects (Wong et al. 1984). Also, experimental findings support the assumption of a neu-

rotrophic function of gonadal steroids. Attella et al. (1987) found that gonadal steroids may exert a protective influence on the cognitive impairment caused by prefrontal brain lesions in pseudopregnant rats. Attella and colleagues (1987) also report more rapid recovery in female animals after limbic and striatal damage.

Prenatal or perinatal neuroanatomical lesions of this kind may play an important role in the etiology of schizophrenia. They could also be responsible for preexisting cognitive dysfunctions and for premorbid behavioral abnormalities in young individuals vulnerable to schizophrenic psychoses. A protective effect of estrogens would explain why fully pubertal girls are protected during this stage of development from the effects of existing prenatal or perinatal brain lesions.

These interesting results, together with the theory of Gorski (1985), which postulates a neurotrophic function of gonadal steroids, not only allow an explanation of these gender-specific differences in age at manifestation, but also explain why these differences are not effective before the peak of puberty when its accompanying estrogen production is reached. In accordance with these considerations, as many girls as boys become psychotic, if not more, up to age 15 (Forrest and Hay 1971; Eggers 1973, 1978; Goldstein and Link 1988; Galdos et al. 1993; Lewine 1994), and between the ages of 15 and about 24 years there is a clear and statistically significant majority of males among first-break schizophrenia patients. Our finding that there was no difference between boys and girls in average age at first manifestation of productive first-rank psychotic symptoms is not adequately explained by the fact that estradiol does not exert its protective effects before puberty has completely set in. It should be remembered at this point that the pubertal growth spurt starts much earlier in girls than in boys (at about 10.5 compared with 12.5 years). Brain maturation induced by pubertal influences may be initiated earlier in girls than in boys. If so, this could lead to earlier psychotic breakdown in predisposed female individuals. The above-mentioned neurotrophic function of estradiol might then later, during early adolescence, counteract these neuronal changes (e.g., myelination of corticolimbic circuits [Benes 1989] or developmental regression of synaptic density in the frontal cortex [Hüttenlocher 1979]). However, the affected girls may have intrinsically reduced estrogen concentrations. This possibility is supported by the endocrinological findings made by Oades and Schepker (1994) in adolescent female inpatients with schizophrenic psychoses: The psychotic patients had significantly lower 17β -estradiol (E2) levels than matched healthy cycling controls. Of course, precisely during puberty (between the ages of 10 and 12) the gonadal steroids are subject to wide fluctuations, so

transient drops in steroid concentrations may occur, reducing the dopamine-antagonizing effect of the steroids and thus increasing the subject's vulnerability to the manifestation of schizophrenic psychoses.

Course and Prognosis. Schizophrenia in general is a serious condition with a poor prognosis. Only about 20 to 25 percent of adult schizophrenia patients achieve a complete recovery (Tsuang and Winokur 1975; Ciompi and Müller 1976; Bleuler 1978; Huber et al. 1979; Westermeyer and Harrow 1988). We found a similar rate of complete recovery in 57 patients with a history of childhood onset of psychosis (ages 7 to 14; Eggers 1973, 1978). Our second followup study, 27 years after the first one and an average of 42 years after disease onset, confirms these figures: 25 percent of the 44 patients had achieved complete remission, which agrees with the results of Asarnow et al. (1994), who found "substantial recovery" in 22 percent of their 20 patients. These authors based their assessment on the Children's Global Assessment Score (Shaffer et al. 1983), which is as suitable for the assessment of post-psychotic social, intentional, and emotional deficiencies as the DAS-M that we used.

If we compare our results with longitudinal studies of adult-onset schizophrenia, we are close to the findings of Bleuler (1978; 208 patients), Tsuang et al. (1979a, 1979b; 186 patients), Ciompi (1980; 289 patients), and Huber et al. (1980; 758 patients) who report complete recovery in 20 to 27 percent of their cases. Harding et al. (1987; 269 patients), Mason et al. (1995; 58 patients), and Shepherd et al. (1989; 107 patients) report better recovery rates with about 50 percent complete recovery or significant improvement (no or mild impairment). These differences probably have their origin in varying numbers of patients, different followup periods, and different criteria for outcome measures.

In childhood-onset schizophrenia, it is important to compare different age groups; we found a significant positive correlation between early onset and severe impairment at followup. The unfavorable prognostic significance of onset at an early age is probably determined by two features: (1) the immaturity of the central nervous system, especially a dysfunction of cortico-subcortical pathways like the dorsolateral prefrontal cortex and its connection with mesolimbic structures, and (2) the chronic-insidious type of childhood schizophrenia is more common in young children before the age of 11 or 12 than in older children. Schizophrenia with a chronic-insidious course has a worse prognosis than acute-recurrent, a fact that was proved true in our study: 33.3 percent of those with an acute course were in complete remission and only 40 percent had a poor remission; among those with an insidious course, there

was not a single case of complete remission and 82 percent showed poor remission.

Because it was impossible to rate retrospectively the intensity of the PANSS symptoms, a qualitative measure was used (absence/presence of a PANSS symptom). A comparison of the complete, partial, and poor remitted groups with respect to the distribution of positive, negative, and global symptoms observed during their initial episode showed no differences. We can conclude that the symptomatology of the first psychotic episode assessed this way had a small prognostic value for the outcome. Although unfavorable and benign courses differ in the average length of all episodes, we do not deduce from this result that similarities in initial symptomatology and differences in course and outcome are caused by different nosological entities.

Type of Onset. In the first followup, we found that an insidious onset was more common in patients who became ill before age 10 ($n = 11$: onset acute in 4, insidious in 7), whereas in those with onset between ages 10 and 13, an acute onset was more common (38 acute, 8 insidious). This constituted a statistically significant difference according to Fisher's exact test (Eggers 1973). We could replicate this finding in our selected sample at the second followup. Our observation that the insidious type of onset of psychosis predominates in the younger age group agrees with earlier findings (Eggers 1973, 1978) and with the experience of others (Kolvin et al. 1971;

Asarnow and Ben-Meir 1988; Green et al. 1992; Werry 1992; Asarnow et al., 1994; Russell 1994; see also table 5). However, the number of patients in the studies by other authors is much higher and the age of onset lower than in our sample (see table 6).

The differences between the various studies are partly due to heterogeneous use of terms and definitions. Russell et al. (1989), for instance, characterize as "insidious" a course where unspecific psychopathological symptoms and behavioral disturbances occur before the acute onset of psychosis. Some authors (Kolvin et al. 1971; Green et al. 1992) not only distinguish between acute and insidious onset, but also have a further category of "insidious onset with acute exacerbation," so that the figures in table 6 are not comparable in all cases. A further confounding factor is the inclusion by the authors of very young children with onset at 5 or 6 years of age.

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Table 5. Selective review of studies: Onset pattern of childhood schizophrenia

Study	# of patients (age < 12 yrs)	Acute onset n (%)	Insidious onset n (%)
Kolvin et al. 1971	33	4 (12)	29 (88)
Green et al. 1992	38	8 (21)	30 (79)
Asarnow and Ben-Meir 1988	17	1 (6)	16 (94)
Russell et al. 1989	35	5 (14)	30 (86)
Asarnow et al. 1994	21	1 (5)	20 (95)
Eggers and Bunk 1996	14	5 (36)	9 (64)

Table 6. Selective review of studies: Age at onset of childhood schizophrenia

	Eggers and Bunk (1996)	Green et al. (1992)	Russell et al. (1989)
Mean age at onset of nonpsychotic symptoms	11.8	6.4	4.6
Mean age at onset of psychotic symptoms	13.0	8.6	6.9
Mean age of first hospitalization	13.4	9.6	9.5

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