British Journal of Psychiatry (1987), **151**, 753–757

The Copenhagen High-Risk Project
The Diagnosis of Maternal Schizophrenia and its Relation to Offspring Diagnosis

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The Copenhagen longitudinal high-risk study of offspring of 129 schizophrenic mothers commenced in 1962. At that time, the mothers were diagnosed according to contemporary Danish criteria. We have re-examined all of the hospital records of these mothers: 108 (84%) fulfil present-day DSM-III criteria for schizophrenia and 95 (74%) were diagnosed as paranoid schizophrenic according to ICD-8 criteria. In a follow-up at mean age 24, the offspring of the paranoid schizophrenic mothers were themselves found to be less frequently schizophrenic (5%) than were the offspring of non-paranoid schizophrenic mothers (29%).

Longitudinal high-risk studies have long been advocated in the investigation of the aetiology and pathogenesis of schizophrenia (Mednick & McNeil, 1968), and a number of such studies are now under way (Watt *et al*, 1984). The earliest of these was initiated in Copenhagen by Mednick & Schulsinger (1965) in 1962 and is still continuing. The high-risk group of this study comprises children of schizophrenic mothers.

Strauss (1984) has observed that rigorous diagnosis of parental schizophrenia is critical to high-risk longitudinal research. Diagnostic uncertainty could compromise many years of work. A particular problem facing longitudinal studies is that of changing diagnostic criteria through time. In the years since the 1962 inception of the Copenhagen study, several systems of diagnostic criteria for schizophrenia have been proposed, with the aim of increasing the reliability of the schizophrenia diagnosis. Thus, according to the criteria listed in ICD-8 (World Health Organization, 1967), the diagnosis of schizophrenia is based on the presence of described typical symptoms and symptom patterns but it is not clearly operationalised. In contrast, DSM-III (American Psychiatric Association, 1980) does provide clear operational criteria for schizophrenia. The concept of schizophrenia in DSM-III is rather conservative, with emphasis on duration.

The purpose of the present study has been to perform DSM-III and ICD-8 rediagnoses of maternal schizophrenia in the Copenhagen high-risk study, and to examine the association of these maternal diagnoses with the diagnostic outcome of the offspring for whom follow-up diagnoses according to ICD-8 have already been made (Schulsinger, 1976).

Method

The high-risk sample was initially derived by identifying all women who were admitted to hospital for severe psychosis within the vicinity of Copenhagen, and who had children in the age range 10–18. Their hospital records were read by one of us (FS), who selected those meeting diagnostic criteria of schizophrenia. The criteria at that time followed those of the Danish Psychiatric Association and were not precisely operationalised, but they were anchored in the Bleulerian concept of schizophrenia; thus they relied heavily on the presence of autism and formal thought disorder. In addition to these psychopathological criteria, it was required that the mothers should have had either at least five years in hospital; or at least three separate periods in hospital, each of at least three months' duration, with no sign of improvement during discharge; or an extended period in hospital plus a certified State Invalid Pension for schizophrenia.

The present rediagnosis of the 129 mothers according to the criteria of DSM-III and ICD-8 was carried out in connection with an extensive collection of data concerning the mothers. Employing information from the Danish central psychiatric register (Dupont *et al*, 1974), available case records from all admissions of the mothers to psychiatric hospitals and departments up to 1975 were obtained. The median number of admissions was 6.3 and the median total time in hospital was 28 months. In almost all cases this constituted considerably more record information on the mothers than had been available at the inception of the project in 1962.

The records were read by the senior author, who completed a precoded data schedule while remaining blind with respect to the diagnosis of the offspring. The schedule contained items covering the following areas: family history of mental illness; childhood background; premorbid personality traits; social adjustment and psychopathology; course of disease; social adjustment during disease; treatment; response to treatment, including side-effects; and maternal functioning. The Syndrome Check List (Wing

TABLE I
ICD-8 and DSM-III diagnoses for the mothers

ICD-8 diagnosis	*DSM-III schizophrenia*		
	Positive	*Negative*	*Total*
Schiz. simplex	2	0	2
Schiz. hebephrenic	13	0	13
Schiz. paranoid	84	11	95
Schiz. catatonic	5	0	5
Schiz. pseudoneurotic	0	2	2
Schizoaffective	3	5	8
Schizophreniform psychosis	1	0	1
Other psychoses	0	3	3
Total	108	21	129

et al, 1974) was used for scoring the psychopathology at each admission separately.

The mothers were diagnosed as schizophrenic according to DSM-III and/or ICD-8 if, at some time during their lives, they fulfilled the criteria of these diagnostic systems. For the ICD-8 diagnoses we used the *Glossary of Mental Disorders and Guide to Their Classification for Use in Conjunction with ICD-8* (World Health Organization, 1974). With respect to schizophrenia, such diagnoses are thereby equivalent to ICD-9. The ICD-8 diagnosis of schizophrenia was supplemented by a subtype diagnosis based on the symptomatology of the first phase of the schizophrenic disease.

In 1972–1974, a ten-year follow-up psychiatric assessment was undertaken of the 207 high-risk offspring of the 129 mothers, together with a matched control group comprising 104 subjects in whom neither the parents nor the grandparents were known to be psychiatric patients (Schulsinger, 1976). At that time, these offspring were between 18 and 30 years old (mean 24 years). On the basis of this assessment a clinical diagnosis was made by one of us (HS) according to the ICD-8 criteria. Since our present concern is with the relationship of the offspring diagnoses to the maternal diagnoses, the control group is not used here. For the purpose of statistical analysis the high-risk offspring diagnoses have been grouped into the following four categories: schizophrenia, borderline schizophrenia (corresponding to the DSM-III schizotypal personality disorder), other mental illnesses, and no mental illness. A total of 173 of the high-risk offspring completed the 1972–1974 assessment. To the 13 children diagnosed as schizophrenic on the basis of this assessment we have added two subjects who were already deceased at that time, but who could be posthumously diagnosed as schizophrenic on the basis of hospital record information.

Results

Table I shows the distribution of DSM-III (positive or negative for schizophrenia) and ICD-8 subtype diagnoses for the 129 mothers. Three mothers did not fulfil the schizophrenia diagnostic criteria of either DSM-III or ICD-8. According to the latter criteria, two of these suffered from paranoid states, while the third had a paranoid psychosis subsequent to amphetamine intoxication. On DSM-III criteria they were diagnosed as schizophreniform disorder, paranoid disorder followed by major depressive disorder at a later admission, and paranoid disorder respectively.

TABLE II
Maternal DSM-III schizophrenia diagnosis by offspring diagnosis

Offspring diagnosis (grouped)	*Maternal DSM-III diagnosis of schizophrenia*				
	Positive		*Negative*		*Total*
	n	*%*	*n*	*%*	
Schizophrenic	14	(9)	1	(4)	15
Borderline	25	(17)	4	(16)	29
Other	70	(46)	6	(25)	76
Not ill	42	(28)	13	(54)	55

A further 18 mothers fulfilled the ICD-8 criteria, but not those of DSM-III. Of these, ten were diagnosed as atypical psychoses, with an onset of disease later than 44 years; but, this criterion apart, they all fulfilled the other DSM-III criteria for schizophrenia. The DSM-III diagnoses for the remaining eight mothers were: two schizophreniform disorders, two schizoaffective disorders, schizoaffective disorder followed by major depressive disorder, paranoid disorder, obsessive-compulsive disorder followed by atypical personality disorder, and schizotypal personality disorder. It is noteworthy that, according to the ICD-8 criteria, 74% of the mothers were paranoid schizophrenics.

The mean age at first admission to hospital for the 108 DSM-III-positive mothers was 31.4 years (s.d. 7.6), which was, not unexpectedly, earlier than for the 21 DSM-III-negative mothers (mean 39.8, s.d. 8.5) ($t(127)=4.5$, $P=0.001$). Similarly, the mean age at first admission to hospital for all ICD-8 non-paranoid schizophrenic mothers (simplex, hebephrenic, and catatonic) was 23.3 years (s.d. 4.04) which, again as would be expected, is very much lower than that for paranoid schizophrenic mothers (mean 34.4, s.d. 7.9).

Table II shows the relationship between maternal DSM-III diagnosis (positive/negative for schizophrenia) and diagnosis, grouped as described above, among the 175 offspring. The offspring of mothers diagnosed as schizophrenic according to DSM-III criteria were not themselves significantly more often diagnosed as schizophrenic (9%) than were the offspring of mothers not so diagnosed (4%) (Fishers Exact Probability = 0.70). This lack of significance may, however, be the result of the small numbers involved. The proportion of individuals free from mental illness among the offspring of the DSM-III-positive mothers (28%) is significantly lower than that among the offspring of DSM-III-negative mothers (54%) (Fisher's Exact Probability = 0.02).

Table III shows the distribution of offspring diagnoses as a function of maternal ICD-8 diagnosis. The offspring of non-paranoid schizophrenic mothers (i.e., simplex, hebephrenic, and catatonic) had the highest rate of schizophrenia (29%) and borderline schizophrenia (21%);

https://doi.org/10.1192/bjp.151.6.753 Published online by Cambridge University Press

TABLE III
Maternal ICD–8 diagnosis by offspring diagnosis

Offspring diagnosis (grouped)	*Maternal ICD–8 diagnosis (grouped)*								
	Schiz. paranoid		*Schiz. non-paranoid*		*Schizo-affective*		*Other*		*Total*
	n	%	*n*	%	*n*	%	*n*	%	
Schizophrenic	6	5	8	29	1	8	0	0	15
Borderline	20	16	6	21	2	17	1	13	29
Other	60	47	9	32	4	33	3	37	76
Not ill	41	32	5	18	5	42	4	50	55

that is, 50% of all of these offspring were diagnosed within what may be called a 'schizophrenia spectrum' (Kety *et al*, 1978). Only 18% were free of mental illness. A much smaller proportion of the offspring of paranoid mothers were schizophrenic (5%). This number is significantly less than the corresponding rate among the offspring of non-paranoid schizophrenic mothers (Fisher's Exact Probability < 0.001).

There was no detectable tendency for the ICD–8 subtypes to 'breed true' between mothers and offspring. Of the 13 diagnostically interviewed schizophrenic offspring, only four were paranoid schizophrenics, and of these only one had a paranoid schizophrenic mother, compared with three among the remaining nine non-paranoid schizophrenic offspring (Fisher's Exact Probability = 1.00).

As mentioned above, maternal diagnosis is strongly related to age at first admission to hospital. We have previously shown early age of maternal admission to hospital to be predictive of poorer diagnostic outcome in offspring (Parnas *et al*, 1985). In order to explore the independence of the contributions of diagnostic subtype and age at admission to hospital, we have conducted a series of logistic regression analyses (Fleiss *et al*, 1986) employing diagnostic outcome in the offspring as a dependent variable, and maternal age at first admission to hospital and maternal diagnostic subtype (paranoid *v.* non-paranoid) as independent variables.

In the first analysis the offspring diagnoses were dichotomously grouped into schizophrenic plus borderline ($n = 44$) and other diagnoses ($n = 131$). In this analysis, both maternal age at first admission to hospital and maternal diagnosis subtype have significant chi-squared to-enter values ($\chi^2 = 6.77$, $P = 0.009$, and $\chi^2 = 10.13$, $P = 0.002$). Following forced entry, however, neither variable remained significant after the prior entry of the other. This indicates that the contributions of the variables are not statistically independent of each other.

In a second analysis we compared the contribution of the same two maternal independent variables with offspring diagnoses within the 'schizophrenia spectrum', by comparing the 15 schizophrenic offspring with the 29 borderline schizophrenic offspring. In this comparison neither predictor was significant.

Discussion

In the present study the rediagnoses of the mothers are based on hospital records; i.e. on information collected for clinical rather than research purposes. Hospital records are usually less structured and less comprehensive than information gathered for psychopathological research purposes. In fact, it is not infrequent that clinical information, including discharge diagnosis, is based on the immediate presenting picture at admission, rather than a thorough and comprehensive evaluation of the psychopathology (Parnas & Teasdale, 1987). This might call into question the reliability of the rediagnoses presented here.

Counter to these considerations, however, in 1962 the sample of 129 mothers was selected precisely because their hospital records contained sufficient information to confidently diagnose schizophrenia according to a rather narrow concept of the disease, with emphasis on chronicity. In addition, from 1962 to 1975 the great majority of mothers had several further admissions, often for long periods of time and to different psychiatric departments, yielding a fuller psychopathological picture.

For the diagnosis of schizophrenia, DSM–III requires that the patient's age at onset should be less than 45 years and that the duration of the illness should be more than six months. Estimation of disease onset and duration is necessarily made retrospectively. In the present study, however, no seriously problematic cases were encountered. The very large majority of the mothers were admitted to hospital with a schizophrenic breakdown before the age of 45, and the disease had a chronic course. In view of the potential diagnostic difficulties to be encountered by longitudinal high-risk studies (Strauss, 1984), it is reassuring to find that so high a proportion of the mothers meet the DSM–III criteria now widely used for research. Indeed, among the 21 who did not do so, ten fell only on the criterion of latest age of onset (i.e. 45 years). In the proposed revision of DSM–III, this limit has been raised to 50 years, which would have included nine of these ten mothers. The high level of agreement between the diagnoses made 24 years ago and the present-day DSM–III diagnoses is probably to be attributed to the joint emphasis placed by both diagnostic procedures on both psychopathological and social functioning criteria.

Epidemiological evidence suggests that paranoid schizophrenia is less common than non-paranoid forms (Fuller Torrey, 1981). There may be two reasons why, in the present study, almost three-quarters of the mothers were of the paranoid subtype. Firstly, perhaps because of the later age of onset, the reproductive capacity of this subtype is higher than for all other subtypes, except the

https://doi.org/10.1192/bjp.151.6.753 Published online by Cambridge University Press

schizoaffective (Reisby, 1967; Larson & Nyman, 1973; Erlenmeyer-Kimling, 1978). Consequently, in a sample of schizophrenics selected as being mothers, the paranoid subtype would be particularly well represented. Secondly, the diagnosis of schizophrenia based on hospital records might favour the selection of patients with reliably identifiable productive paranoid symptoms.

Our difficulty in distinguishing the relative influences on offspring outcome of maternal schizophrenia subtype and age at onset arises from the well-established strong association between these two. It is conceivable that the disintegration and disruption of psychic structures seen in non-paranoid schizophrenics (Meissner, 1981) arise precisely because the schizophrenic process afflicts the individual early in his or her life.

The disparity in the prevalence of schizophrenia among the offspring of non-paranoid early-onset mothers versus late-onset paranoid mothers – 29% versus 5% – is surprisingly high compared with that reported elsewhere (Kendler & Davis, 1981). The offspring were diagnosed at a mean age of 24 years, which is rather early in the risk period for schizophrenia, and further schizophrenic cases are to be expected. However, it seems unlikely that such a disparity will be evened out, given that the overall morbidity risk for schizophrenia in the offspring of a schizophrenic parent is estimated to be 10–15% (Gottesman & Shields, 1982).

Based upon earlier findings from our study, we suggest that the disparity could be due to: (a) a greater specific genetic loading for schizophrenia in the offspring of early-onset non-paranoid mothers (Parnas *et al*, 1985), further compounded by assortative mating with schizotypal fathers (Parnas, 1985), and (b) both non-specific genetic and environmental factors effecting the penetrance of the specific genetic loading; for example, birth complications (Parnas *et al*, 1982), early rearing experiences (Parnas *et al*, 1985), and other maternal personality and social characteristics (Talovic *et al*, 1980).

Familial homotypy for schizophrenia subtype has been found by Kallmann (1938), Ödegaard (1963), Farmer *et al* (1983), and Scharfetter & Nüsperli (1980), although not by Tsuang *et al* (1980). Irrespective of how many more schizophrenia cases ultimately manifest themselves in our study in future follow-ups, we anticipate that some degree of homotypy will emerge and that those with paranoid schizophrenic mothers will themselves principally develop paranoid schizophrenia.

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https://doi.org/10.1192/bjp.151.6.753 Published online by Cambridge University Press