The New York High-Risk Project:

Psychoses and Cluster A Personality Disorders in Offspring of Schizophrenic Parents at 23 Years of Follow-up

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Abstract

Background—We herein present lifetime prevalence rates of psychoses and *DSM-III-R* cluster A personality disorders in sample A of the New York High-Risk Project, a prospective study following offspring of parents with schizophrenia (HRSz subjects) and affective illness (HRAff subjects) and of psychiatrically normal parents (NC subjects) from midchildhood to adulthood.

Methods—We interviewed the offspring in adulthood with the Schedule for Affective Disorders and Schizophrenia, Lifetime Version, for Axis I disorders and the Personality Disorder Examination for Axis II disorders.

Results—Lifetime prevalence rates ($\pm$ SE) of schizophrenia and unspecified psychosis were $11.1\% \pm 4.3\%$ and $5.6\% \pm 3.1\%$, respectively, in the HRSz group and 0% in the HRAff and NC groups. Rates of schizoaffective disorder subclassified as mainly schizophrenic, however, were highest in the HRAff group. Rates of psychotic affective disorders did not differ between the HRSz and other groups. Age-corrected morbidity risks were similar to lifetime prevalence rates. Rates of the three cluster A personality disorders did not differ among the groups, but the combined rate was greater in the HRSz and HRAff groups than in the NC group.

Conclusions—Our data strongly support a specific familial liability to narrowly defined schizophrenia that is not shared by families of probands with affective disorder. Schizoaffective disorder and cluster A personality disorders, however, occur in families of both schizophrenic probands and probands with affective disorder. Psychotic affective disorders, which are not increased in HRSz subjects, do not appear to be an expression of the liability to schizophrenia.

From the first family study of schizophrenia conducted by Rüdin¹ early in this century, this illness has been shown to be significantly increased in first-degree relatives of schizophrenic probands,^{2–5} compared with a general population expectancy of about 1%. Although the older family studies have been faulted for reasons having to do with diagnosis, sampling, lack of blindness, and other design inadequacies, most studies of contemporary design^{6–13} have continued to display a significantly greater aggregation of schizophrenia in families of schizophrenic probands than in families of normal controls. Many of these later studies with comparatively narrow definitions of schizophrenia have also demonstrated an increased risk for certain other psychotic and nonpsychotic (personality) disorders in the relatives of schizophrenic probands,^{7–21} thus reinforcing the concept of a spectrum of deviant conditions sharing a common liability.^{22–26}

Because of relatively low reproductive rates in schizophrenic individuals,²⁷ one category of relatives—namely, offspring of schizophrenic parents—often have been sparsely represented in recent family studies. The offspring, however, were the focus of prospective studies started in the 1960s and 1970s with the goal of examining early characteristics of preschizophrenic individuals and the unfolding of the illness itself.²⁸ Those high-risk studies that have been able to follow the offspring into adulthood^{29–32} therefore present an opportunity to expand and update the limited prevalence and morbidity risk data on this group of relatives. Herein, we report lifetime diagnoses of psychoses and *DSM-III-R*³³ cluster A disorders in the New York High-Risk Project (NYHRP),³² in which we have followed offspring of schizophrenic parents from midchildhood to midadulthood.

SUBJECTS AND METHODS

SUBJECT SELECTION

The NYHRP consists of two independent samples of subjects selected in childhood because of their parents' psychiatric diagnoses or lack of psychiatric history as being at high risk for schizophrenia (the HRSz group) or affective disorders (the HRAff group) or at low risk for psychiatric disorders (the normal comparison, or NC, group). The first sample, sample A, entered the study in 1971 to 1972; the second, sample B, in 1977 to 1979. We limit this report to sample A, at the mean ($\pm$ SE) age of 31.11 ± 1.83 years in 1994.

We selected mentally ill parents by screening consecutive admissions at several state psychiatric facilities in the New York City metropolitan area to identify schizophrenic patients and patients with major affective disorders who (1) were white and English-speaking, (2) had at least one child aged 7 to 12 years, (3) were still married to the other biological parent of the target-age child (ren) at the time of ascertainment, and (4) did not have a diagnosis of chronic alcoholism, other drug addiction, brain trauma, or psychosis of toxic origin. In addition, we required the children to (1) have an IQ above 70, (2) show no overt signs of a major psychiatric disturbance, and (3) have received no treatment for psychiatric problems.

We identified the NC group through two large school districts, having selected the geographical areas for locating NC families to correspond to those in which most of the HRSz families resided. Parents in the NC families had to be free of any psychiatric

treatment history and meet the same background and marital criteria as parents in the HRSz and HRAff families. Children in the NC families were in the same age range and met the same inclusion or exclusion criteria as children in the groups at risk.

Table 1 shows the number of children at entry into the study and current follow-up, as well as age and gender compositions of the three groups. The numbers shown for HRSz and HRAff subjects at entry are those applicable after rediagnosis of the parents, as described below.

Informed consent was obtained from the parents for themselves and their minor children at the first contact with the family. Subsequently, informed consent was obtained from each individual participating in the study at each assessment phase.

PARENTS' DIAGNOSES

Initially, two senior psychiatrists independently made *DSM-III* diagnoses from the parents' hospital records, from which hospital diagnoses and medication histories had been removed. Only those patients for whom there was consensus agreement between the two psychiatrists were accepted for study.

Subsequently, at the third round of testing of sample A, all available parents were interviewed with the Schedule for Affective Disorders and Schizophrenia, Lifetime Version (SADS-L),³⁶ and were given new diagnoses with the Research Diagnostic Criteria (RDC),³⁷ based on the interview and hospital record materials. All diagnoses were reviewed at a meeting of senior consultants (I.I.G., Leonard L. Heston, MD, John D. Rainer, MD, and Jean Endicott, PhD), and those diagnoses that remained questionable or difficult to decide after applying the RDC rules were resolved by majority agreement. Further details of the initial sampling and the diagnostic procedures appear elsewhere.³²

Based on the RDC, 24% of the parents originally called schizophrenic received rediagnoses of a major affective disorder; no reclassifications occurred in the opposite direction. Further information about the effects of reclassification of the parental diagnoses is presented in the "Results" section of the text.

DIAGNOSTIC ASSESSMENTS OF THE OFFSPRING

We examined sample A subjects in six evaluation rounds (A-1 through A-6), at mean ($\pm$ SE) ages of 9.5 ± 1.70 , 11.5 ± 1.96 , 15 ± 1.94 , 20 ± 1.86 , 23.5 ± 2.03 , and 27.8 ± 1.95 years. Further, throughout the project, staff social workers conducted telephone interviews of the subjects and their parents at least once a year.

Clinical assessments in adolescence were based on results of the Minnesota Multiphasic Personality Inventory^{38–40} and a videotaped psychiatric interview rated on the Mental Health Assessment Form.^{41,42} Formal diagnostic assessment of *adulthood* disorders—the topic of this report—began in evaluation round A-4 with administration of the SADS-L interview to all subjects aged 18 years or older. In evaluation round A-5, we used an abbreviated version of the SADS-L, covering only the major Axis I disorders, and the Personality Disorder Examination (PDE),⁴³ a semi-structured clinical interview covering all *DSM-III-R* Axis II disorders. Assessments in evaluation round A-6 included both the full SADS-L interview and the revised PDE.⁴⁴

Interviewers were clinical psychologists or psychiatric social workers with previous experience with patients. We gave training workshops and individual supervision in the interview instruments at the beginning of each round. In the latest round (A-6), we also held refresher workshops in midround. The SADS-L workshops were conducted by expert diagnosticians from Dr Endicott's Department of Research Assessment and Training (DRAT) at the New York State Psychiatric Institute, New York City, where the interview schedule and RDC rules originated.^{36,37} Throughout the process, the interviewers were blind with respect to parental diagnostic group, but in evaluation round A-6, they learned the RDC diagnoses given the offspring in earlier clinical assessments. At completion of evaluation round A-6, one of us (U.H.A.), who has trained continuously with DRAT in the use of the SADS-L and application of RDC rules, assigned lifetime diagnoses based on the interviews in evaluation rounds A-4 through A-6 and other available clinical materials. In approximately 10% of cases, questions remained concerning differential diagnosis, subtype, or course (chronicity) after this final review. These cases were then referred to DRAT for additional review by two senior diagnosticians who have participated in that department's diagnostic and training services for many years; both raters were blind to parental diagnostic group and to the lifetime diagnosis given at the completion of evaluation round A-6. If the two DRAT raters did not fully agree, the case was reviewed by Dr Endicott to reach a final consensus diagnosis.

Reliability between the diagnoses given after evaluation round A-6 and by the DRAT raters was tested using 21 randomly selected cases that had not previously been referred to DRAT. Agreement between both diagnoses was 96% ($\kappa=0.91$).

We also used group workshops and supervised reviews to train the interviewers in administration of the PDE. In evaluation round A-6, the group workshops were conducted personally by Armand Loranger, PhD (the principal developer of the instrument).⁴⁴ The developers of the PDE reported high interrater reliabilities (intraclass correlations) for dimensional scores and moderately high κ s measuring diagnostic agreement; $\kappa=0.80$ was reported for schizotypal personality disorder (STPD) but could not be calculated for paranoid and schizoid personality disorders because of their rarity in the sample of Loranger et al.⁴⁴ No formal reliability assessment was undertaken in our study. As described in Squires-Wheeler et al,⁴⁵ interviews were audiotaped and reviewed by clinical supervisors. The diagnostic algorithm provided in the PDE was used, and the diagnosis of a definite personality disorder was assigned if the subject fulfilled the specified number of features to meet *DSM-III-R* criteria (eg, five or more features for STPD). Results of PDE evaluations in evaluation rounds A-5 and A-6 were combined, so that subjects received a lifetime diagnosis of a definite personality disorder if they met criteria for the given disorder on either or both assessment rounds.

SUBJECTS OF THIS REPORT

Because we have maintained continuous telephone contact with most families in the sample, we have been able to obtain information about the occurrence of major psychiatric disorders in the few subjects whose first episodes took place after evaluation round A-6 but prior to April 1994, the closing date for this report. The total number of

subjects with data available for lifetime Axis I diagnoses in this report was 188, as shown in Table 1; these subjects represent 86%, 95%, and 93% of the original numbers in the HRSz, HRAff, and NC groups, respectively. Five subjects (two HRSz subjects, one HRAff subject, and two NC subjects) did not have a PDE interview in any round and, thus, could not be assigned Axis II diagnoses.

OFFSPRING DIAGNOSES CONSIDERED IN THIS REPORT

Herein, we report on all diagnoses of psychosis—including schizophrenia, other nonaffective psychotic disorders, and psychotic affective illness—and definite cluster A personality disorders in the offspring. The other nonaffective psychoses are unspecified psychosis and schizoaffective disorder subclassified according to the RDC as mainly schizophrenic (SAS, ie, core schizophrenic symptoms were present for at least 1 week in absence of affective features, or features often associated with schizophrenia were present prior to onset of affective features).³⁷ The psychotic affective illnesses are bipolar I disorder with psychosis and schizoaffective disorder subclassified according to the RDC as mainly affective (SAA, ie, good premorbid social and occupational adjustment and schizophrenialike features developed simultaneously or followed affective symptoms and were never present for a period of at least 1 week in absence of affective features).³⁷ The cluster A personality disorders are schizotypal, paranoid, and schizoid.

No subject had more than one psychotic disorder, but several subjects had both a psychosis and one or more cluster A personality disorders. We used a diagnostic hierarchy in which subjects with schizophrenia or schizoaffective disorder were removed from the calculation of the rates of cluster A disorders. Subjects with more than one cluster A disorder were counted only once for the category as a whole.

STATISTICAL METHODS

We mainly present prevalence rates (mean±SE), not corrected for age, in this report. As the ages of the three subject groups fall within the same narrow range (currently 28 to 35 years) in the risk period for psychoses, age correction is not needed for comparisons between the groups. For comparisons with the literature on lifetime morbidity risks in first-degree relatives, however, we also calculated age-corrected morbidity risks using the Kaplan-Meier method.

We used one-tailed tests (treating *P* values of .10 or less as significant) for comparisons when we had a priori directional predictions. These predictions were that schizophrenia, other nonaffective psychotic disorders, and cluster A disorders would occur at higher rates among the HRSz subjects than in the other two groups and that psychotic affective disorders would occur most frequently among the HRAff subjects. We used two-tailed tests (treating *P* values of .05 or less as significant) for all other comparisons. Because we had hypotheses for most comparisons, we did not correct for multiple statistical tests.

For comparison of lifetime prevalences of disorders among the three subject groups, we used logistic regression⁴⁶ to calculate odds ratios and their significance. We also calculated χ^2 statistics⁴⁷ using Fisher's exact test when cell sizes were small.

We used the Mantel-Cox test of the Kaplan-Meier method of survival analysis⁴⁸ for comparison of risk of development of psychoses over time in the three groups. Onset age,

defined as the age at which a subject first met criteria for the disorder according to the rules of the RDC, was estimated for all Axis I disorders by one of us (U.H.A.). Agreement between these estimates of age at onset and the estimates made by DRAT raters was 95%, in line with previous calculations of high reliability of onset age estimates based on results of the SADS-L and RDC.^{49–51}

The NYHRP and other high-risk studies,^{29–31} in which longitudinal data have been collected prospectively in the offspring of schizophrenic probands, provide a “constructive replication”³⁴ of the usual retrospective and cross-sectional approach to family studies. In addition, because the NYHRP contains as a comparison group the offspring of parents hospitalized for major affective disorders, it offers, as have several recent family studies of schizophrenia,^{6–8,10,11,15,20} a contrast group of relatives presumably at risk for a different set of disorders. Inclusion of such a group may help to shed light on the specificity of conditions aggregating with schizophrenia and clarify the diagnostic boundaries separating schizophrenic and affective spectra.

We will report on nonpsychotic Axis I disorders in the NYHRP at a future date.

RESULTS

LIFETIME PREVALENCE OF PSYCHOSES AND CLUSTER A DISORDERS

Table 2 presents, for each subject group, the lifetime prevalence rates of the psychoses as a whole and separately and cluster A personality disorders as a whole and separately. The odds ratios and their statistical tests are from the logistic regression analyses.

Psychosis as a Whole—The prevalence of psychosis of any type was greater in the HRSz and HRAff groups than in the NC group, but the two risk groups did not differ from each other.

Schizophrenia-Related Psychoses—As shown in Table 2, combined lifetime prevalences for all schizophrenia-related psychoses (ie, schizophrenia, SAS, and unspecified psychosis) were, again, significantly greater in each risk group than in the NC group but did not differ between risk groups. Both schizophrenia and unspecified psychosis occurred only in the HRSz group. (The single case of completed suicide in this sample occurred in an HRSz subject who had received a diagnosis of schizophrenia.)

On the other hand, SAS occurred in four HRAff subjects ($9.8\% \pm 4.7\%$) but in only one subject each in the HRSz and NC groups ($1.9\% \pm 1.9\%$ and $1.1\% \pm 1.1\%$, respectively). Whereas the SAS rates of the two risk groups were not significantly different, the HRAff and NC groups did differ.

Affective and Other Psychoses—The psychotic affective illnesses—SAA and bipolar I disorder—occurred at low rates in all three subject groups, and acute drug-induced psychosis was diagnosed in one NC subject. There were no group differences in prevalence rates for these disorders.

Cluster A Personality Disorders—For cluster A personality disorders, prevalence rates (shown in Table 2, with subjects with schizophrenia and schizoaffective illnesses removed) were significantly greater in each risk group than in the NC group for the category as a whole but did not differ between groups for any of the component disorders considered separately.

DIAGNOSES IN THE HRAff GROUP AS A FUNCTION OF PARENTAL DIAGNOSES

Table 3 examines the diagnoses of psychotic disorders in HRAff subjects as a function of their parents' diagnoses and their parents' initial classification as having schizophrenia or affective illness. As can be seen, (1) more parents whose initial diagnosis was schizophrenia received a final diagnosis of psychotic disorder (SAA or psychotic bipolar) than parents whose initial diagnosis was affective illness (14/18 vs 3/25, respectively); (2) psychoses were more frequent in the offspring of parents with reclassified diagnoses (4/18) than in offspring of parents whose diagnosis was not changed (2/25); but (3) diagnoses of schizoaffective disorder in offspring did *not* occur in subjects whose parents received—either originally or at reclassification—a diagnosis of SAA.

LIFETIME MORBIDITY RISKS AND KAPLAN-MEIER SURVIVAL CURVES

We estimated cumulative hazard functions for the psychotic disorders using the Kaplan-Meier survival procedures. We found significant differences in the survival curves for the risk for (1) any psychosis ($P=.007$), (2) schizophrenia-related psychoses combined ($P=.003$), and (3) schizophrenia alone ($P=.001$) developing over time (Mantel-Cox test). The survival curves (Figure) illustrate the cumulative hazard functions for schizophrenia-related psychoses combined.

The hazard functions complement the prevalence rates and yield an approximate estimate of age-corrected lifetime morbidity risks. The lifetime morbidity risk estimates and SEs were as follows: (1) for all psychoses, $24.4\% \pm 7.1\%$ in the HRSz group, $22.5\% \pm 11.2\%$ in the HRAff group, and $2.2\% \pm 1.5\%$ in the NC group; (2) for schizophrenia, $14.1\% \pm 5.3\%$ in the HRSz group and 0% in the HRAff and NC groups; and (3) for schizophrenia-related psychoses combined, $20.5\% \pm 6.5\%$ in the HRSz group, $10.8\% \pm 5.4\%$ in the HRAff group, and $1.1\% \pm 1.1\%$ in the NC group. Thus, for sample A subjects at their current ages, most of the lifetime morbidity risks are very similar to the lifetime prevalences presented in Table 2. However, for psychotic affective disorders, the morbidity risks in the HRAff and NC groups differed at the .04 level, whereas the prevalence rates did not differ.

COMMENT

As expected, both HRSz and HRAff subjects had significantly elevated prevalence rates and age-corrected morbidity risks for psychotic disorders as a whole, compared with NC subjects. Also as expected, schizophrenia occurred at markedly higher rates in the HRSz group than in the other two groups, alone or in combination with unspecified psychosis ($11.1\% \pm 4.3\%$ and $16.7\% \pm 5.1\%$ prevalences, respectively, vs 0% in the HRAff and NC groups). The NYHRP is thus clearly in agreement with contemporary family studies,^{6–13} as well as recent reports^{30,31} from other longitudinal high-risk studies, in demonstrating that

narrowly defined or “classic” schizophrenia aggregates in families of schizophrenic probands and not in families of normal controls. Our findings are also consistent with those of most,^{10,11,52,53} although not all,⁵⁴ studies that have contrasted schizophrenia risks in relatives of schizophrenic probands vs relatives of probands with affective illness.

The rate of *all* schizophrenia-related psychoses together, however, did not differ between the HRSz and HRAff groups because of the higher rate of SAS in the latter.

Schizoaffective disorder, long recognized as a trouble-some diagnosis,^{9,55–57} certainly does not present a clear familial pattern in our sample or in many others.^{7,9,56,58} We had expected to find a higher prevalence in the HRSz group of a syndrome (SAS) that is mainly schizophrenialike in prominence of symptoms, premorbid functioning, and course and a greater frequency in the HRAff group of a syndrome (SAA) more similar to affective illness. Although earlier analyses using the Minnesota Multiphasic Personality Inventory data in the NYHRP generally supported a commonality between schizophrenia and SAS,^{38,39} our present findings are similar to those of other investigators^{7,9,56,58} who did not see clear familial relationships for the RDC³⁷ subclassifications of schizoaffective disorder. In our sample, SAS was less frequent in the HRSz group than in the HRAff group, while SAA occurred at essentially equal prevalence rates in both risk groups.

We explored the possibilities that the parents of our HRAff subjects might represent an atypical group of patients with affective illness or that schizoaffective disorders might occur mainly in the offspring of parents with SAA. Given that we identified HRAff parents through state hospitals and that 40% were psychotic (SAA or bipolar), the group undoubtedly was atypical as to severity, compared with the patients with affective illness identified in many epidemiological studies. The conjecture that schizoaffective disorders occurred chiefly in offspring of parents with schizoaffective diagnoses, however, was not borne out.

Rather than using a distinction between mainly schizophrenic and mainly affective, many investigators have subtyped schizoaffective disorder by polarity. Some,^{15,59–61} but not all,⁵⁶ have reported a familial relationship between unipolar schizoaffective disorder and schizophrenia and between bipolar schizoaffective disorder and affective (especially bipolar) illness. Other studies,^{9,10} although partially supporting a familial distinction between unipolar and bipolar schizoaffective disorder, have produced a more mixed picture. Splitting of schizoaffective disorder by polarity did not help to clarify our data: all three subjects with schizoaffective disorder in the HRSz group had the bipolar form and three of five subjects with schizoaffective disorder in the HRAff group had the unipolar form. Also, in a pair of HRAff monozygotic co-twins, one had the unipolar and the other the bipolar form, a complication similar to that noted in a review⁵⁷ of genetic relationships among the psychoses. We must, therefore, concur with the conclusion⁹ that no method of partitioning schizoaffective disorder to date produces subclasses that are clearly specific to a genetic liability to schizophrenia.

As could be expected, the HRAff group had significantly greater age-corrected risks for psychotic affective illness than the NC group. Neither the low prevalence rates nor age-

corrected risks of these disorders differed between the HRSz and NC groups; rates of nonpsy-chotic major affective disorders also did not differ between the groups. Our findings thus agree with those from the Copenhagen High-Risk Study³⁰ in showing no excess of psychotic or nonpsychotic affective disorders in offspring of schizophrenic parents. The NYHRP is also consistent with other recent family studies⁶² in showing no increase in affective illnesses as a whole among relatives of schizophrenic probands. Our study does not suggest, however, as some others do,^{10,11,62} that psychotic affective disorders may be included in the familial liability to schizophrenia.

CLUSTER A PERSONALITY DISORDERS

The Danish adoption studies^{14,63} substantiated historical observations^{64,65} that, besides schizophrenia, certain subsyndromal traits appear to aggregate in families of schizophrenic probands, thus suggesting expression of the genetic liability in a spectrum of disorders from full-blown manifestations of the illness to milder behavioral aberrations. The cluster A personality disorders proposed in *DSM-III*⁶⁶ and subsequent versions were considered to capture the essence of these subsyndromal traits.

Relatives of schizophrenic probands have been reported to show a higher prevalence of cluster A STPD than relatives of normal controls in several,^{11,21,30} but not all,^{67,68} recent family studies, as well as in the expanded adoption studies.^{12,14} Elevated rates of schizotypal personality features and disorder in HRSz compared with NC subjects in analyses combining both samples (A and B) at earlier testing rounds have been previously reported.^{45,69} In the present study, examining only sample A and removing subjects in whom schizophrenia had developed, we found a significant difference in HRSz vs NC subjects for cluster A as a whole, but not for STPD alone.

The prevalence of cluster A personality disorder in relatives of probands with affective disorder has been examined in a few studies.^{21,70} No differences have been found between the offspring of schizophrenic parents and parents with affective illness in the frequency of cluster A disorders.^{45,69} A recent Irish family study^{11,70} reported both significantly higher rates of STPD in relatives of schizophrenic probands than in relatives of affectively ill probands and no difference between the latter and relatives of controls. Other investigators, however, have obtained results more similar to ours, showing higher rates of STPD in families of probands with affective disorders than in families of controls²¹ and no differences between relatives of schizophrenic or affectively ill probands.^{12,25,71} Some investigators, observing an increased frequency of STPD in relatives of probands with non-schizophrenic disorders,^{72–75} have concluded that not all cases of STPD are genetically related to schizophrenia,^{76–78} a point made some years ago in a discussion of issues associated with defining the “extended” schizophrenia spectrum of disorders.⁷⁹

The NYHRP⁸⁰ and others⁸¹ have speculated about alternative constructions of a schizophrenia-spectrum dimension more specifically related to familial aggregation of schizophrenia.²⁴ One proposal, for example, has been that definitions of STPD limited to certain clinical symptoms (eg, negative features) may enhance specificity in relatives of schizophrenic probands vs relatives of probands with other psychiatric disorders.⁸¹ In another recent exploration of possible heterogeneity in STPD,⁷⁶ comorbid disorders were

found to differentiate schizotypal relatives of schizophrenic and affective probands. Similarly, the NYHRP42 has reported differences among the offspring groups in Axis I disorders later expressed by subjects who had schizotypal features in adolescence. Other evidence from the NYHRP also suggests that the accepted criteria for cluster A personality disorders may not be the best for identifying conditions with a familial relationship to schizophrenia. For example, using a latent structure analysis of the PDE data in our NC families, the NYHRP82 found both STPD and paranoid personality disorder to correlate highly with other personality disorders, indicating that these two conditions are not discrete personality variants. On the other hand, a distinct cluster of personality aberrations assessed by the Minnesota Multiphasic Personality Inventory clearly differentiated the HRSz group (23%) from the HRAff (7%) or NC (2%) groups.⁴⁰ Further pursuit of these different approaches to the subsyndromal signs of the familial liability to schizophrenia is needed.

LIMITATIONS AND ADVANTAGES

We note three limitations of this report. First, sample A, at the mean age of 31 years, has not completed the risk period for schizophrenia or other psychoses. It might seem, therefore, that new onsets of these disorders in the future could change the picture now seen in this sample. Important changes are not likely to take place in frequencies of schizophrenia-related psychoses, however, which are already as high in our subjects as previous literature would lead us to expect. In any event, *relative age-corrected* risks among the subject groups would not change.

A second limitation lies in the modest sizes of the two risk groups, which may tend to obscure the significance of differences between them. A positive note, however, is that those group differences that are seen can be considered to be robust. Nevertheless, the statistical power of future analyses of adulthood diagnoses in the NYHRP will be enhanced substantially by inclusion of recently collected Axis I and II diagnoses in our younger sample (sample B) and in the siblings of both samples.

Another important limitation for this and other high-risk or family studies has to do with diagnostic accuracy, given that a “gold standard” is unavailable.⁸³ Diagnoses of both probands and relatives—parents and offspring in high-risk studies—are subject to fallibility. Because of our unusual, but far from unique,^{12,21,25,71–75} lack of difference in rates of cluster A personality disorders between the HRSz and HRAff groups, as well as the mixed picture presented for schizoaffective disorders, one of us (E.S.-W.), along with Andrew Skodal, MD, again reviewed, blind as to information about the offspring, all available clinical material on the parents classified as having affective disorders. No misclassifications of the parents were identified in that review. Nevertheless, as part of the long-term plan for the project, we have begun a painstaking final review of the diagnoses of all parents, who are now between the ages of 50 and 74 years and whose lifetime histories of psychopathology may thus be considered to be completed.

There are at least two advantages of the longitudinal approach used in high-risk studies of psychiatric disorders. First, prospective follow-up, in a developmental genetic study such as the NYHRP, helps to ensure that all cases of emerging psychopathology will be detected in the relatives. Second, the opportunity to carry out repeated assessments at different times

during adulthood enhances the possibilities of making accurate differential diagnoses, in contrast to cross-sectional studies with single examinations of the relatives.

Compared with other prospective high-risk studies of schizophrenia, the NYHRP has the added advantages of including a group of relatives of probands with affective illness, thus allowing examination of nosological boundaries between the expressions of familial liability for the two disorders, and of containing an independent sample (B) for added statistical power and confirmatory analyses, as noted above.

CONCLUSIONS

A finding of an increased prevalence of schizophrenia in relatives of schizophrenic probands compared with relatives of the general population is, obviously, not new. It has been demonstrated, using cross-sectional family study methods, by numerous investigators in the past^{2–5} with varying definitions of the illness and by several recent investigators^{6–13} with narrow definitions and operationalized diagnostic tools. The results of our longitudinal, prospective study of offspring of schizophrenic parents strongly support these later, criterion-based family studies in finding a specific familial liability for narrowly defined schizophrenia.

Our results also clearly show that the offspring of schizophrenic parents and parents with affective illness do not share a liability for the same disorders. First, although rates of schizophrenia and unspecified psychosis are high in the HRSz group, these disorders do not occur at all in the HRAff group. Second, compared with NC subjects, HRAff subjects have an excess of psychotic affective disorders, whereas HRSz subjects do not. The NYHRP, therefore, shows some specificity for schizophrenia limited to offspring of schizophrenic parents and for the psychotic affective disorders limited to offspring of parents with affective illness. The results do not lend support to the hypothesis that these latter disorders are part of the liability to schizophrenia.

Schizoaffective disorder and cluster A personality disorders, however, present less clear boundaries between the two risk groups. Our present data, along with those of others,⁶² suggest that schizoaffective disorder shares a liability to both schizophrenia and affective illnesses and that current methods of partitioning schizoaffective disorder are not entirely effective in distinguishing between the two types of familial liability.^{9,10} The frequency of cluster A personality disorders, including STPD, also does not differ between offspring of probands with schizophrenia and affective illness, an increasingly common finding in studies comparing relatives of the two types of probands. Several studies^{76–78,80} have suggested that STPD observed in relatives of schizophrenic probands and probands with affective illness may not be the same clinical entity, the former being part of the genetic liability to schizophrenia and the latter, not.

Endophenotypic measures (eg, those tapping neurobehavioral functions) may help to discriminate individuals with STPD who have a disorder genetically related to schizophrenia from those whose disorder is not part of the same genetic spectrum.⁷⁶ One of the initial goals of high-risk studies such as the NYHRP was to identify endophenotypic “markers”

that flag the genetic liability to schizophrenia.⁸⁴ There has been considerable progress, both in these studies and in research on other relatives and population groups, toward establishing several such markers.^{85–88} In the NYHRP, for example, we have focused here to fore on childhood attentional dysfunctions and their association with certain psychiatric and psychological outcomes in adolescence and young adulthood in the different risk groups.⁸⁹ Future analyses of differential associations among early measures of endophenotypic dysfunctions and lifetime diagnoses of specific psychotic or personality disorders in our subject groups may help to distinguish more clearly between adulthood forms of psychopathology that are related to the genetic liability to schizophrenia and those that are not.

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References

1. Rüdin, E. Zur Vererbung und Neuentstehung der Dementia Praecox. New York, NY: Springer-Verlag NY Inc; 1916.
2. Zerbini-Rüdin, E. Endogene Psychosen. In: Becker, PE., editor. Humangenetik. Vol. 2. Stuttgart, Germany: Georg Thieme Verlag; 1967. p. 446-513.
3. Slater, E., Cowie, V. The Genetics of Mental Disorders. New York, NY: Oxford University Press; 1971.
4. Gottesman, Shields, J. Schizophrenia: The Epigenetic Puzzle. New York, NY: Cambridge University Press; 1982.
5. Gottesman II, McGuffin P, Farmer AE. Clinical genetics as clues to the “real” genetics of schizophrenia (a decade of modest gains while playing for time). *Schizophr Bull.* 1987; 13:23–47. [PubMed: 3474774]
6. Tsuang MT, Winokur G, Crowe RR. Morbidity risks of schizophrenia and affective disorders among first-degree relatives of patients with schizophrenia, mania, depression and surgical conditions. *Br J Psychiatry.* 1980; 137:497–504. [PubMed: 7214104]
7. Baron M, Gruen R, Asnis L, Kane J. Schizoaffective illness, schizophrenia and affective disorders: morbidity risk and genetic transmission. *Acta Psychiatr Scand.* 1982; 65:253–262. [PubMed: 7080847]
8. Frangos E, Athanassenas G, Tsitourides S, Katsanou N, Alexandrakou P. Prevalence of *DSM-III* schizophrenia among the first-degree relatives of schizophrenic probands. *Acta Psychiatr Scand.* 1985; 142:447–455.
9. Gershon ES, DeLisi LE, Hamovit J, Nurnberger JI, Maxwell ME, Schreiber J, Dauphanais D, Dingman CW, Guroff JJ. A controlled family study of chronic psychoses: schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry.* 1988; 45:328–336. [PubMed: 3355320]
10. Maier W, Lichtermann D, Minges J, Hallmayer J, Heun R, Benkert O, Levinson DF. Continuity and discontinuity of affective disorders and schizophrenia: results of a controlled family study. *Arch Gen Psychiatry.* 1993; 50:871–883. [PubMed: 8215813]

11. Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D. The Roscommon Family Study I: methods, diagnosis of probands, and risk of schizophrenia in relatives. *Arch Gen Psychiatry*. 1993; 50:527–540. [PubMed: 8317947]
12. Kety SS, Wender PH, Jacobsen B, Ingraham LJ, Jansson L, Faber B, Kinney DK. Mental illness in the biological and adoptive relatives of schizophrenic adoptees: replication of the Copenhagen Study in the rest of Denmark. *Arch Gen Psychiatry*. 1994; 51:442–455. [PubMed: 8192547]
13. Kendler KS, Gruenberg AM, Kinney DK. Independent diagnoses of adoptees and relatives as defined by *DSM-III* in the provincial and national samples of the Danish Adoption Study of schizophrenia. *Arch Gen Psychiatry*. 1994; 51:456–468. [PubMed: 8192548]
14. Kety, SS., Rosenthal, D., Wender, PH., Schulsinger, F. The types and prevalence of mental illness in the biological and adoptive families of adopted schizophrenics. In: Rosenthal, D., Kety, SS., editors. *Transmission of Schizophrenia*. Elmsford, NY: Pergamon Press; 1968. p. 345-362.
15. Scharfetter C, Nusperli M. The group of schizophrenias, schizoaffective psychoses, and affective disorders. *Schizophr Bull*. 1980; 6:586–591. [PubMed: 7444390]
16. Lowing PA, Mirsky AF, Pereira R. The inheritance of schizophrenic spectrum disorders: a reanalysis of the Danish adoptee study data. *Am J Psychiatry*. 1983; 140:1167–1171. [PubMed: 6614222]
17. Baron M, Gruen R, Rainer JD, Kane J, Asnis L, Lord S. A family study of schizophrenic and normal control probands: implications for the spectrum concept of schizophrenia. *Am J Psychiatry*. 1985; 142:447–455. [PubMed: 3976917]
18. Kendler KS, Gruenberg AM, Tsuang MT. Psychiatric illness in first-degree relatives of schizophrenic and surgical control patients: a family study using *DSM-III* criteria. *Arch Gen Psychiatry*. 1985; 42:770–779. [PubMed: 4015321]
19. Kendler KS, Gruenberg AM, Tsuang MT. A *DSM-III* family study of the non-schizophrenic psychotic disorders. *Am J Psychiatry*. 1986; 143:1098–1105. [PubMed: 3752293]
20. Maj M, Starace F, Pirozzi R. A family study of *DSM-III-R* schizoaffective disorder, depressive type, compared with schizophrenia and psychotic and non-psychotic major depression. *Am J Psychiatry*. 1991; 148:612–616. [PubMed: 2018162]
21. Maier W, Lichtermann D, Minges J, Heun R. Personality disorders among relatives of schizophrenic patients. *Schizophr Bull*. 1994; 20:481–493. [PubMed: 7973465]
22. Kety SS. Schizotypal personality disorders: an operational definition of Bleuler's latent schizophrenia? *Schizophr Bull*. 1985; 11:590–594. [PubMed: 4081652]
23. Kendler KS. Diagnostic approaches to schizotypal personality disorder: a historical perspective. *Schizophr Bull*. 1985; 11:538–553. [PubMed: 3909377]
24. Ingraham, LJ. Family-genetic research and schizotypal personality. In: Raine, A, Lencz, T., Mednick, S., editors. *Schizotypal Personality*. New York, NY: Cambridge University Press; In press
25. Ingraham, LJ., Kety, SS. Schizophrenia spectrum disorders. In: Tsuang, MD., Simpson, JC., editors. *Handbook of Schizophrenia: Nosology, Epidemiology and Genetics of Schizophrenia*. Vol. 3. New York, NY: Elsevier Science Publishing Co; 1988. p. 117-137.
26. Webb CT, Levinson DF. Schizotypal and paranoid personality disorder in the relatives of patients with schizophrenia and affective disorders: a review. *Schizophr Res*. 1993; 11:81–92. [PubMed: 8297808]
27. Erlenmeyer-Kimling, L. Fertility of psychotics: demography. In: Cancro, R., editor. *Annual Review of the Schizophrenic Syndrome, 1976–1977*. New York NY: Brunner/Mazel; 1978. p. 298-325.
28. Watt, NF, Anthony, EJ, Wynne, LC., Rolf, JE., editors. *Children at Risk for Schizophrenia: A Longitudinal Perspective*. New York, NY: Cambridge University Press; 1984.
29. Fish, B. Characteristics and sequelae of the neurointegrative disorder in infants at risk for schizophrenia: 1952–1982. In: Watt, NF, Anthony, EJ, Wynne, LC., Rolf, J., editors. *Children at Risk for Schizophrenia: A Longitudinal Perspective*. New York, NY: Cambridge University Press; 1984. p. 423-439.
30. Parnas J, Cannon TD, Jacobsen B, Schulsinger H, Schulsinger F, Mednick SA. Lifetime *DSM-III-R* diagnostic outcomes in the offspring of schizophrenic mothers: results from the Copenhagen High-Risk Study. *Arch Gen Psychiatry*. 1993; 50:707–714. [PubMed: 8357296]

31. Ingraham LJ, Kugelmass S, Frenkel E, Nathan M, Mirsky AF. Twenty-five year follow-up of the Israeli High-Risk Study: current and lifetime psychopathology. *Schizophr Bull.* 1995; 21:183–192. [PubMed: 7631166]
32. Erlenmeyer-Kimling L, Cornblatt B. The New York High-Risk Project: a follow-up report. *Schizophr Bull.* 1987; 13:451–463. [PubMed: 3629200]
33. American Psychiatric Association. . Diagnostic and Statistical Manual of Mental Disorders. 3. Washington, DC: American Psychiatric Association; 1987. Revised
34. Lykken DT. Statistical significance in psychological research. *Psychiatr Bull.* 1968; 70:151–159.
35. American Psychiatric Association. . Diagnostic and Statistical Manual of Mental Disorders. 2. Washington, DC: American Psychiatric Association; 1968.
36. Spitzer, RL., Endicott, J. Schedule for Affective Disorders and Schizophrenia, Lifetime Version (SADS-L). 3. New York: New York State Psychiatric Institute, Biometrics Unit; 1977.
37. Spitzer, RL., Endicott, J., Robins, E. Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders. 3. New York: New York State Psychiatric Institute, Biometrics Unit; 1978.
38. Moldin SO, Gottesman II, Erlenmeyer-Kimling L. Psychometric validation of psychiatric diagnoses in the New York High-Risk Study. *Psychiatry Res.* 1987; 22:159–177. [PubMed: 3685223]
39. Moldin SO, Gottesman II, Erlenmeyer-Kimling L. Searching for the psychometric boundaries of schizophrenia: evidence from the New York High-Risk Study. *J Abnorm Psychol.* 1987; 96:354–363. [PubMed: 3693687]
40. Moldin SO, Gottesman II, Erlenmeyer-Kimling L, Cornblatt B. Psychometric deviance in offspring at risk for schizophrenia, I: initial delineation of a distinct subgroup. *Psychiatry Res.* 1990; 32:297–310. [PubMed: 2388968]
41. Kestenbaum CJ, Bird HR. A reliability study of the Mental Health Assessment Form for school-age children. *J Am Acad Child Adolesc Psychiatry.* 1978; 17:338–347.
42. Squires-Wheeler E, Skodol AE, Erlenmeyer-Kimling L. The assessment of schizotypal features over two points in time. *Schizophr Res.* 1992; 6:75–85.
43. Loranger AW, Susman VL, Oldham JM, Russakoff LM. The Personality Disorder Examination: a preliminary report. *J Pers Disord.* 1987; 1:1–13.
44. Loranger AW. The impact of *DSM-III* on diagnostic practice in a university hospital: a comparison of *DSM-II* and *DSM-III* in 10914 patients. *Arch Gen Psychiatry.* 1990; 47:672–675. [PubMed: 2360860]
45. Squires-Wheeler E, Skodol AE, Adamo UH, Bassett AS, Gewirtz GR, Honer WG, Cornblatt BA, Roberts SA, Erlenmeyer-Kimling L. Personality features and disorder in the subjects in the New York High-Risk Project. *J Psychiatr Res.* 1993; 27:379–393. [PubMed: 22287799]
46. SPSS Reference Guide. Chicago III: SPSS Inc; 1990. Logistic regression; p. 312-322.
47. SPSS Reference Guide. Chicago, Ill: SPSS Inc; 1990. Crosstabs; p. 98-108.
48. Dixon, WJ., editor. BMDP Statistical Software Manual. Vol. 2. Berkeley, Calif: University of California Press; 1992. Life tables and survivor functions; p. 795-824.
49. Andreasen NC, Grove WM, Shapiro RW, Keller MB, Hirschfeld RM, McDonald-Scott P. Reliability of lifetime diagnosis: a multicenter collaborative perspective. *Arch Gen Psychiatry.* 1981; 38:400–405. [PubMed: 7212970]
50. Egeland JA, Blumenthal RL, Nee J, Sharpe L, Endicott J. Reliability and relationship of various ages of onset criteria for major affective disorder. *J Affect Disord.* 1987; 12:159–165. [PubMed: 2955008]
51. Blumenthal RL, Egeland JA, Sharpe L, Nee J, Endicott J. Age of onset in bipolar and unipolar illness with and without delusions or hallucinations. *Compr Psychiatry.* 1987; 28:547–554. [PubMed: 3691078]
52. Maier, W., Hallmayer, J., Mingos, J., Lichtermann, D. Affective and schizoaffective disorders: similarities and differences. In: Marneros, A., Tsuang, MT., editors. *Morbid Risks in Relatives of Affective, Schizoaffective and Schizophrenia Patients: Results of a Family Study.* New York, NY: Springer-Verlag NY Inc; 1990. p. 201-207.

53. Onstad S, Skre I, Edvardsen J, Torgersen S, Kringlen E. Mental disorders in first-degree relatives of schizophrenics. *Acta Psychiatr Scand Suppl.* 1991; 83:463–467.
54. Taylor MA, Berenbaum SA, Jampala VC, Cloninger CR. Are schizophrenia and affective disorder related? preliminary data from a family study. *Am J Psychiatry.* 1993; 150:278–285. [PubMed: 8304989]
55. Angst J, Felder W, Lohmeyer B. Schizoaffective disorders: results of a genetic investigation, I. *J Affect Disord.* 1979; 1:139–153. [PubMed: 162495]
56. Angst J, Felder W, Lohmeyer B. Are schizoaffective psychoses heterogeneous? results of a genetic investigation, II. *J Affect Disord.* 1979; 1:155–165. [PubMed: 162496]
57. Propping, P. Genetic relationship between the psychoses: implications for genetic modeling. In: Marneros, A., Tsuang, MT., editors. *Affective and Schizoaffective Disorders*. New York, NY: Springer-Verlag NY Inc; 1990. p. 195–200.
58. Kendler KS, McGuire M, Gruenberg AM, Spellman M, O'Hare A, Walsh D. The Roscommon Family Study, II: the risk of nonschizophrenic nonaffective psychoses in relatives. *Arch Gen Psychiatry.* 1993; 50:645–652. [PubMed: 8343035]
59. Rice JP, Reich T, Andreasen NC, Endicott J, Van Eerdewegh M, Fishman P, Hirschfeld RMA, Klerman GL. The familial transmission of bipolar illness. *Arch Gen Psychiatry.* 1987; 44:441–447. [PubMed: 3579495]
60. Andreasen NC, Rice J, Endicott J, Coryell W, Grove WM, Reich T. Familial rates of affective disorder: a report from the National Institute of Mental Health Collaborative Study. *Arch Gen Psychiatry.* 1987; 44:461–469. [PubMed: 3579497]
61. Maier W, Lichtermann D, Minges J, Heun R, Hallmeier J, Benkert O. Schizoaffective disorder and affective disorder with mood-incongruent psychotic features: keep separate or combine? evidence from a family study. *Am J Psychiatry.* 1992; 49:1666–1673.
62. Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D. The Roscommon Family Study, IV: affective illness, anxiety disorders, and alcoholism in relatives. *Arch Gen Psychiatry.* 1993; 50:952–960. [PubMed: 8250681]
63. Kety, SS., Rosenthal, D., Wender, PH., Schulsinger, F., Jacobsen, B. Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic: a preliminary report. In: Fieve, RR., Rosenthal, D., Brill, H., editors. *Genetic Research in Psychiatry*. Baltimore, Md: Johns Hopkins University Press; 1975. p. 147–165.
64. Kraepelin, E., Barclay, RM., translators. *Dementia Praecox*. Edinburgh, Scotland: E & S Livingstone; 1919.
65. Bleuler, E., Zinkin, J., translators. *Dementia Praecox or the Group of Schizophrenias*. New York, NY: International Universities Press Inc; 1950.
66. American Psychiatric Association. . *Diagnostic and Statistical Manual of Mental Disorders*. 3. Washington, DC: American Psychiatric Association; 1980.
67. Coryell W, Zimmerman M. The heritability of schizophrenia and schizoaffective disorder: a family study. *Arch Gen Psychiatry.* 1988; 45:323–327. [PubMed: 3355319]
68. Ritsner M, Karas S, Ginath Y. Relatedness of schizotypal personality to schizophrenic disorders: multifactorial threshold model. *J Psychiatr Res.* 1993; 27:27–38. [PubMed: 8515386]
69. Squires-Wheeler E, Skodol A, Friedman D, Erlenmeyer-Kimling L. The specificity of *DSM-III* schizotypal personality traits. *Psychol Med.* 1988; 18:757–765. [PubMed: 3186874]
70. Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D. The Roscommon Family Study, III: schizophrenia-related personality disorders in relatives. *Arch Gen Psychiatry.* 1993; 50:781–788. [PubMed: 8215802]
71. Ingraham, LJ., Kety, SS. Schizophrenia spectrum disorders: exclusively related to schizophrenia?. In: Schulz, SC., Tamminga, CA., editors. *Schizophrenia: Scientific Progress*. New York, NY: Oxford University Press; 1989.
72. Schulz PM, Schulz SC, Goldberg SC, Ettigi P, Resnick RJ, Friedel RO. Diagnoses of the relatives of schizotypal outpatients. *J Nerv Ment Dis.* 1986; 174:457–463. [PubMed: 3734768]
73. Dahl AA. The personality disorders: a critical review of family, twin and adoptive studies. *J Pers Disord.* 1993; 7(suppl):86–99.

74. Silverman JM, Siever LH, Horvath TB, Coccaro EF, Klar H, Davidson M, Pinkham L, Apter SH, Mohs RC, Davis KL. Schizophrenia-related and affective personality disorder traits in relatives of probands with schizophrenia and personality disorders. *Am J Psychiatry*. 1993; 150:435–442. [PubMed: 8434659]
75. Yeung AS, Lyons MJ, Waternaux CM, Faraone SV, Tsuang MT. A family study of self-reported personality traits and *DSM-III-R* personality disorders. *Psychiatry Res*. 1993; 48:243–255. [PubMed: 8272446]
76. Lyons MJ, Toomey R, Faraone SV, Tsuang MT. Comparison of schizotypal relatives of schizophrenia versus affective probands. *Am J Med Genet*. 1994; 54:279–285. [PubMed: 7810589]
77. Thaker G, Moran M, Casidy S. Normal smooth pursuit eye-movements in volunteer subjects meeting schizotypal personality disorder criteria. *Am J Psychiatry*. 1991; 148:1096–1097.
78. Siever LJ, Keefe R, Bernstein DP. Dr Siever and colleagues reply. *Am J Psychiatry*. 1991; 148:1097.
79. Shields, J., Heston, LL., Gottesman. Schizophrenia and the schizoid: the problem for genetic analysis. In: Fieve, RR, Rosenthal, D., Brill, H., editors. *Genetic Research in Psychiatry*. Baltimore, Md: Johns Hopkins University Press; 1975. p. 167-197.
80. Squires-Wheeler E, Skodol A, Bassett A, Erlenmeyer-Kimling L. *DSM-III-R* schizotypal personality traits in offspring of schizophrenic disorder, affective disorder, and normal control parents. *J Psychiatr Res*. 1989; 23:229–239. [PubMed: 2635220]
81. Torgersen S, Onstad S, Skre I, Edvardsen J, Kringlen E. True' schizotypal personality disorder: a study of co-twins and relatives of schizophrenic probands. *Am J Psychiatry*. 1993; 150:1661–1667. [PubMed: 8214174]
82. Moldin S, Rice J, Erlenmeyer-Kimling L, Squires-Wheeler E. Latent structure of *DSM-III-R* Axis II psychopathology in a normal sample. *J Abnorm Psychol*. 1994; 103:259–266. [PubMed: 8040495]
83. Faraone SV, Tsuang MT. Measuring diagnostic accuracy in the absence of a 'gold standard'. *Am J Psychiatry*. 1994; 151:650–657. [PubMed: 8166304]
84. Erlenmeyer-Kimling L, Cornblatt B. High-risk research in schizophrenia: a summary of what has been learned. *J Psychiatr Res*. 1987; 21:401–411. [PubMed: 3326935]
85. Erlenmeyer-Kimling, L. Biological markers for the liability to schizophrenia. In: Helmchen, H., Fenn, FA., editors. *Biological Perspectives of Schizophrenia: Dahlem Konferenzen*. New York, NY: John Wiley & Sons; 1987. p. 33-56.
86. Matthyse S, Levy DL, Kinney D, Deutsch D, Lajonchere C, Yurgelun-Todd D, Woods B, Holzman PS. Gene expression in mental illness: a navigation chart to future progress. *J Psychiatr Res*. 1992; 26:461–473. [PubMed: 1491362]
87. Moldin S, Erlenmeyer-Kimling L. Measuring liability to schizophrenia. *Schizophr Bull*. 1994; 20(special issue):25–29. [PubMed: 8197419]
88. Erlenmeyer-Kimling L, Cantoni G, Kety S. Genetics and gene expression in mental illness. *J Psychiatr Res*. 1992; 26(special issue):221–224. [PubMed: 1362774]
89. Erlenmeyer-Kimling L, Cornblatt B. A summary of attentional findings in the New York High-Risk Project. *J Psychiatr Res*. 1992; 26:405–426. [PubMed: 1491360]

Figure.

Kaplan-Meier survival curves for the risks for schizophrenia-related psychoses combined (schizophrenia, unspecified functional psychosis, or schizoaffective disorder, subclassified as mainly schizophrenia) developing in the three subject groups. NC indicates offspring of normal comparison subjects; HRSz, offspring of schizophrenic parents; and HRAff, offspring of parents with major affective illness.

Table 1

Number, Age, and Sex Ratio of Subjects at Recruitment and Follow-up

Parents' Diagnoses [†]	Group Label [‡]	At Recruitment*			At Follow-up		
		No. of Subjects	Mean (±SD) Age, y	Male:Female Ratio	No. of Subjects	Mean (±SD) Age, y	Male:Female Ratio
Schizophrenia	HRSz	63	9.68±1.65	51:49	54	31.48±1.80	50:50
Major affective disorder (unipolar or bipolar)	HRAff	43	9.30±1.77	40:60	41	31.22±1.84	37:63
No psychiatric disorder identified	NC	100	9.43±1.70	59:41	93	30.84±1.83	57:43
Total	...	206	9.48±1.70	52:48	188	31.11±1.83	50:50

* Two offspring of a parent with a nonschizophrenic, nonaffective current diagnosis or rediagnosis are excluded. Prior to parents' diagnoses, 83 offspring were in the HRSz group and 25 in the HRAff group.

[†] Based on Research Diagnostic Criteria.³⁷

[‡] HRSz indicates offspring at high risk for schizophrenic disorders; HRAff, offspring at high risk for affective disorders; and NC, offspring of normal comparison subjects.

Table 2
Lifetime Prevalences of Psychoses and Probable Cluster A Disorders in the Three Subject Groups

Diagnosis	Prevalence, % ($\pm$ St) [*]			P		
	HRSz (n=54)	HRAff (n=41)	NC (n=93)	HRSz vs HRAff	HRSz vs NC	HRAff vs NC
All psychoses	22.2 $\pm$ 5.7	14.6 $\pm$ 5.6	2.2 $\pm$ 1.5	.35	.001	.01
Schizophrenia-related psychoses	18.5 $\pm$ 5.3	9.8 $\pm$ 4.7	1.1 $\pm$ 1.1	.24	.004	.04
Schizophrenia	11.1 $\pm$ 4.3	0.0	0.0	.03	.002	[†]
Schizoaffective, mainly schizophrenic, disorder	1.9 $\pm$ 1.9	9.8 $\pm$ 4.7	1.1 $\pm$ 1.1	.12	.70	.04
Unspecified functional	5.6 $\pm$ 3.1	0.0	0.0	.42	.05	[†]
Affective and other psychoses	3.7 $\pm$ 2.6	4.9 $\pm$ 3.4	1.1 $\pm$ 1.1	.77	.31	.12
Bipolar I	0.0	2.4 $\pm$ 2.4	0.0	.43	[†]	.31
Schizoaffective, mainly affective	3.7 $\pm$ 2.6	2.4 $\pm$ 2.4	0.0	.73	.85	.85
Acute drug-induced	0.0	0.0	1.1 $\pm$ 1.1	[†]	<.99	.69
Cluster A disorders [‡]	15.9 $\pm$ 5.6	11.1 $\pm$ 5.3	2.2 $\pm$ 1.6	.54	.01	.06
Schizotypal	4.5 $\pm$ 3.2	2.8 $\pm$ 2.8	0.0	.58	.11	.29
Paranoid	6.8 $\pm$ 3.8	8.3 $\pm$ 4.7	1.1 $\pm$ 1.1	.19	.11	.07
Schizoid	6.8 $\pm$ 3.8	0.0	1.1 $\pm$ 1.1	.16	.10	.71

^{*} HRSz indicates offspring at high risk for schizophrenic disorders; HRAff, offspring at high risk for affective disorders; and NC, offspring of normal comparison subjects.

[†] No test was possible because of empty cells.

[‡] Forty-four subjects were interviewed in the HRSz group, 36 in the HRAff group, and 90 in the NC group. Schizophrenic and schizoaffective subjects were excluded. In addition, five subjects were not interviewed for personality disorders, including two in the HRSz group (one was psychotic), one in the HRAff group (psychotic), and two in the NC group.

Table 3

Psychoses in HRAff Subjects by Specific Affective Disorder Diagnoses in Their Parents *

Parental Diagnoses [†]	Offspring (n=43)	
	No. of Subjects	No. of Psychotic Subjects
Originally classified as affective illness [†]		
Unipolar, not psychotic	15	2 (SAS)
Bipolar, not psychotic	4	0
Bipolar, psychotic	1 [‡]	...
SAA	2	0
Both parents affective (1 unipolar, 1 bipolar)	3	0
Reclassified from schizophrenia to affective illness [‡]		
Unipolar, not psychotic	1	0
Bipolar, not psychotic	0	...
Bipolar, psychotic	9	2 (1 SAS, 1 SAA)
SAA	5	0
Both parents affected (1 unipolar, 1 bipolar)	3 [§]	2 (1 Bipolar I, 1 SAS)

* HRAff indicates subjects at high risk for affective disorders; SAS, schizoaffective disorder subclassified as mainly schizophrenic; and SAA, schizoaffective disorder subclassified as mainly affective.

[†] n=25.

[‡] n=18.

[§] One subject was not assessed at follow-up.