Specificity of Familial Transmission of Schizophrenia Psychosis Spectrum and Affective Psychoses in the New England Family Study’s High-Risk Design

Jill M. Goldstein, PhD; Stephen L. Buka, ScD; Larry J. Seidman, PhD; Ming T. Tsuang, MD, PhD

**Context:** There is a long history of research on the familial transmission of schizophrenia and other psychoses. However, few studies have investigated the specificity of the transmission of schizophrenia-psychosis spectrum (SPS) disorders and affective psychoses (APs) or observed high-risk offspring into mid-adulthood.

**Objectives:** To investigate the transmission of psychoses from parents to their offspring and the specificity of transmission across psychosis subtypes.

**Design:** High-risk follow-up study.

**Setting:** New England Family Study’s High-Risk Study, with population-based community sampling from Boston, Massachusetts, and Providence, Rhode Island.

**Participants:** A total of 203 high-risk offspring of 159 parents with diagnoses of psychoses (SPS and AP) and 147 control offspring of 114 control parents.

**Main Outcome Measures:** Systematically assessed research DSM-IV psychiatric diagnoses for adult offspring.

**Results:** Compared with those of control parents, offspring of parents with SPS had a significant, almost 6-fold elevated risk of SPS disorders and a nonsignificant doubling of risk for AP. Offspring of parents with AP had a significant 14-fold elevated risk for AP compared with offspring of controls; for SPS disorders, the risk doubled but was not significant.

**Conclusion:** Having a parent with psychosis significantly increased the risk for psychosis among offspring and demonstrated specificity for the transmission of SPS disorders and APs within families.

Arch Gen Psychiatry. 2010;67(5):458-467

---

**ORIGINAL ARTICLE**

ONE ESTABLISHED METHOD of inquiry into the etiology of schizophrenia has been the familial high-risk study design. It consists of enriched samples of subjects at greater-than-normal risk for schizophrenia defined by the presence of a first-degree, biological relative with the disorder. Most commonly, the index case has been a parent, and the persons considered at high risk are offspring, as initiated with the New York Infant Development Study in the 1950s.1 A longitudinal, prospective cohort design within the high-risk framework allows identification of premorbid characteristics, possible predictors of psychosis, rates of disorders, and other features of normal and abnormal development. Studies of this type may evaluate high-risk offspring beginning in early life, during the mother’s pregnancy,2-20 during infancy,1,4,21-27 or during childhood and adolescence.6-7

The available prospective development data on these high-risk offspring have allowed for the identification of preillness characteristics and eliminated the potential of reporting bias that can occur in retrospective studies of illness among family members.58 Many of these studies prospectively observed cohorts of offspring into early adulthood.9 However, fewer have observed offspring through the extensive period of disease onset,† undoubtedly in large part because of the difficulty of carrying out a long-duration follow-up. The age at onset of schizophrenia peaks between 18 and 30 years but may continue with a decelerating rate into a person’s 30s and 40s, and thus a follow-up into that age range allows a better estimate of rates of psychiatric disorders and other characteristics than a study that terminates with high-risk participants in their 20s.

Despite variations in their methods (eg, differences in age at study entry, age at study follow-up, matching variables, and diagnostic criteria), these longitudinal high-

---

†References 19, 21, 22, 31, 32, 42, 45, 49, 56.
risk studies have consistently reported a higher risk of psychoses among offspring of parents with psychosis than among offspring of unaffected controls. Table 1 presents the prevalence of adult psychoses (schizophrenia-psychosis spectrum [SPS], affective psychosis [AP], and any psychoses) among the offspring of parents with psychoses from classic high-risk studies that observed offspring at least into their 20s. The differences in methods...
across studies likely contribute to some of the variability in rates across studies, which ranged from 4.0% to 22.2%. The latter of which included affective disorders (regardless of presence of psychosis) in the parent high-risk group.

The specificity of transmission of schizophrenia and spectrum psychoses compared with APs has only been partially investigated in a few high-risk studies. The Copenhagen Perinatal Cohort, Helsinki High-Risk Study, and New York High-Risk Project have examined rates of APs among offspring of parents with broadly defined schizophrenia. With the exception of the Copenhagen Perinatal Cohort, which identified no cases of AP in their sample, these studies reported rates of APs that were higher, but not significantly so, among offspring of parents with psychosis than among those of healthy controls. Although the prevalence of APs among high-risk children of parents with affective disorders in general (2.2% to 3.7%) is greater than that found among healthy control children (0.0% to 0.6%), our knowledge no study has estimated the rates of APs among high-risk children of parents with APs alone. Two studies reported rates of APs among offspring, although they defined parental illness by combining nonpsychotic and psychotic affective disorders. The Finnish Adoptive Family Study combined APs among parental schizophrenia spectrum disorders.

Using data from the High-Risk Study of the New England Family Study (NEFS), we investigated the transmission of psychoses from parents to their offspring and the specificity of transmission across psychosis subtypes. The NEFS High-Risk Study represents one of the few epidemiologically representative cohorts studied that has prospectively observed offspring from their mothers’ pregnancy to their adulthood (age ≥40 years); through rigorous tracing and interviewing methods, the study provides DSM-IV diagnoses for both parents and adult offspring by assessing a range of psychopathology. Herein we present rates of psychoses among offspring of parents with SPS disorders and APs and those of healthy controls, then test for the specificity of the transmission of SPS disorders and AP diagnoses among the adult offspring.

**METHODS**

**THE NATIONAL COLLABORATIVE PERINATAL PROJECT SAMPLE**

Participants for this study were selected from the Boston, Massachusetts, and Providence, Rhode Island, cohorts of the Collaborative Perinatal Project (CPP), also known as the NEFS. The CPP of the National Institute of Neurological and Communicative Disorders and Stroke was initiated more than 40 years ago to investigate prospectively the prenatal and familial antecedents of pediatric, neurologic, and psychological disorders of childhood. The CPP prospectively observed and examined more than 50,000 pregnancies from 12 university-affiliated medical centers through the first 7 years of the offspring’s lives. Pregnant women (generation 1) were recruited between 1959 and 1966. Women in the study were largely representative of the patients receiving prenatal care at each participating center. Extensive data on gestation, labor, and delivery were collected, along with neonatal data and repeated medical, neurologic, and psychological examinations of the children (generation 2) at 4 and 8 months and 1, 4, and 7 years of age. At the conclusion of the study, a total of 55,908 pregnancies had been recorded nationally, of which 17,741 (of 13,464 generation 1 mothers) were from the New England cohorts of Boston and Providence.

**HIGH-RISK FOLLOW-UP STUDY**

Using the NEFS sample, we initiated a follow-up study of the high-risk families. The details of generation 1 ascertainment and diagnoses have been described by us (S.L.B., L.J.S., M.T.T., and J.M.G., unpublished data, 2009). Briefly, the study goal was to ascertain approximately 200 psychotic generation 1 parents, half with schizophrenia and half with APs, and a comparable group of normal control parents. Generation 1 parents were contacted between 1994 and 2002. Parents with a history of psychiatric treatment were identified by the following sources: (1) record review (previously published); (2) subsequent record linkages with private and public psychiatric treatment facilities in Rhode Island and Massachusetts; (3) information provided by mothers during the original study (eg, psychiatric hospitalization at study enrollment, psychiatric treatment at the 7-year assessment, or history of treatment with antipsychotic medication); and (4) family member reports from recent follow-up studies with the CPP cohort. Through these efforts, from a total pool of 26,928 generation 1 parents, we identified 839 persons with indications of potential psychosis. This represents a rate of approximately 3.2% to 4.2% of the pool of parents whose data we were able to review, which is consistent with current estimates of the lifetime prevalence of psychotic disorders. Of these parents, 755 were eligible for follow-up (S.L.B., L.J.S., M.T.T., and J.M.G., unpublished data, 2009). Parents were considered eligible if at least 1 generation 2 offspring was assessed after 4 months of age.

Control parents were selected to be comparable to parents with psychotic disorders on the basis of the number of offspring enrolled in the CPP, patient status (public or private), parent’s age, ethnicity (Caucasian or other), study site, and the offspring’s age, sex, and history of chronic hypoxia (given that we wanted to test for the interaction of genetic vulnerability and this obstetric condition). Eligible controls included all members of the CPP who were not identified as potential psychotic parents and whose records did not indicate a history of psychiatric treatment. Healthy control parents did not have spouses, parents, siblings, or any second-degree relatives with psychoses, recurrent major depressive disorder (MDD), suicide, or psychiatric hospitalizations.

**GENERATION 1 FOLLOW-UP AND PSYCHIATRIC ASSESSMENT**

Subjects were located through a variety of methods, including thorough searches of credit bureaus, address directories, death certificates, motor vehicle reports, and home visits. The located subjects were invited to participate in a 2-part interview. The first interview screened for potential psychoses, and the second was a full diagnostic interview using the Structured Clinical Interview for DSM-IV and assessing Axis I diagnoses of any form of psychotic, major affective, and bipolar disorders, as well as substance abuse or dependence (alcohol and drug). The clinical interview was conducted by systematically trained master’s-level clinical interviewers. Medical records were obtained with subject consent. Family history of psychiatric disorders was evaluated by means of the Family Interview for Genetic Studies. Expert diagnosticians (including J.M.G., L.J.S., and June Wolf, PhD) reviewed all the information collected from both interviews and medical records, if available, to determine the final best-estimate diagnoses. If there was any evidence of mental illness in the spouse, we interviewed the spouse or, if the spouse had died, searched for medical records. Spouses’ names were subjected to the linkage procedures used for the mothers. There were only 6 spouses of case parents who had a diagnosis of some form of psychosis.
FINAL GENERATION 1 SAMPLE

Of the 755 eligible generation 1 parents, 212 with confirmed DSM-IV psychotic disorders were identified; they were 139 mothers (72.2%) and 99 fathers (27.8%). On the basis of past literature on familial transmission of schizophrenia and APs,6,46,% parents with schizophrenia, schizoaffective disorder of depressed type, delusional disorder, brief psychosis, schizophreniform disorder, and psychosis not otherwise specified (NOS) were classified into one higher-order group (SPS disorders), and schizoaffective disorder of bipolar type, bipolar disorders with psychosis, and MDD with psychosis were classified into a second group (the APs). Parents with a history of psychotic diagnoses that were brief compared with other psychiatric disorders (eg, MDD or substance disorders) were also categorized as having a psychotic diagnosis.

GENERATION 2 SAMPLE

The sample of 212 parents with psychosis and 132 nonpsychotic parents had a total of 467 pregnancies: 167 offspring among parents with APs, 114 offspring among parents with SPS disorders, and 186 offspring among nonpsychotic parents (Figure). Of note, among the 344 final generation 1 parents, there were six “2-parent families” in which both parents were diagnosed as having some form of psychosis, resulting in a sample size of 338 unduplicated families. Of the 467 pregnancies, 22 (4.7%) resulted in an offspring who was stillborn, did not live past early childhood, was lost to follow-up before age 7 years, or was adopted or placed in foster care and thus ineligible for this adult follow-up study. Of the 445 eligible individuals in generation 2, 428 (96.2%) were located of whom 344 (80.4%) were interviewed, for an overall interview rate of 77.3%. In addition to the 344 generation 2 subjects with diagnostic information, this reflects a completed diagnostic rate of 78.7%, quite successful for a 30- to 40-year follow-up study.

STATISTICAL ANALYSES

Data analyses examined rates of generation 2 psychopathology in relation to generation 1 diagnostic status. Psychopathological diagnoses for both generation 1 and generation 2 were categorized as SPS and AP and as any psychosis (both SPS and AP). Additional psychopathology groups of interest for the generation 2 subjects were (1) all schizophrenia spectrum disorders (including nonpsychotic disorders) (schizophrenia, schizoaffective disorder, schizophreniform disorder, psychosis NOS, delusional disorder, brief psychosis, and schizotypal personality disorder (SPD)); (2) affective spectrum disorders (bipolar disorder with psychosis, schizoaffective bipolar disorder, MDD with psychosis, bipolar disorder without psychosis, and recurrent MDD); and (3) any psychopathology (schizophrenia, schizoaffective depressive disorder, schizophreniform disorder, psychosis NOS, delusional disorder, brief psychosis, schizotypal personality disorder, bipolar disorder with psychosis, SPD, bipolar disorder, MDD with psychosis, bipolar disorder without psychosis, recurrent MDD, and schizoid and paranoid personality disorders).

Least-squares means and standard errors for continuous variables were calculated with mixed linear models accounting for intrafamilial correlation. For count variables (ie, number of pregnancies and number of children), the means and standard errors were calculated with Poisson regression based on a generalized estimating equations model to account for the intrafamilial correlation. Risk ratios were calculated by regression analyses modeled with generalized estimating equations. For models with a small number of offspring in a cell (ie, 5 or less), the generalized estimating equations approach is a statistically inappropriate model. Thus, exact methods were used to calculate the relative risks (RRs) and corresponding 95% confidence intervals (CIs). The comparison group was composed of generation 2 offspring of unaffected generation 1 parents. The following potential confounders were examined: socioeconomic status (SES), maternal ethnicity, maternal marital status, study site,
offspring sex, parity, gravity, maternal education, offspring year of birth, and maternal age. Parental SES and maternal ethnicity were identified as statistically significant confounders in univariate analyses in several models, in particular the SPS and psychosis models. All models were adjusted for these 2 covariates for consistency. The models for offspring recurrent MDD and affective spectrum disorder additionally controlled for generation 2 sex, which was significant in the multivariate models.

### RESULTS

The final analytic sample included 350 generation 2 subjects who were the offspring of 273 generation 1 families. Of these families, there were 114 healthy control parents and 159 parents with psychosis. The 159 generation 1 subjects with psychosis, 59 had SPS disorders (schizophrenia in 36, schizoaffective depressed disorder in 5, delusional disorder in 4, schizophreniform disorder in 1, psychosis NOS in 12, and history of psychosis not otherwise due to organicity in 1). The remaining 100 parents with psychosis had APs (schizoaffective bipolar type in 9, bipolar disorder with psychotic features in 41, MDD with psychosis in 40, history of MDD with psychosis in 6, and history of bipolar disorder with psychosis in 4).

Among the 350 generation 2 subjects, 28 (8.0%) developed psychosis in adulthood. The numbers of SPS disorders and APs among these offspring were as follows: 12 offspring with SPS (schizophrenia in 4, delusional disorder in 2, brief psychosis in 2, and psychosis NOS in 4) and 16 offspring with APs (schizoaffective bipolar type in 3, bipolar disorder with psychotic features in 12, and MDD with psychosis in 1).

The demographic features of the final analytic sample are presented in Table 2. Of the offspring, 92.0% were born to Caucasian mothers and 90.9% were born to mothers who were married. The majority of the study offspring were from the Boston site (73.4%). The mean age of the mothers at pregnancy was 26.4 years. They had a mean education of 11.1 years in school, a mean of 2.2 pregnancies and 1.9 children, and a roughly uniform SES distribution.

Among the offspring born to parents with SPS disorders, 114 of 159 offspring (71.7%) had an Axis I diagnosis (SPS = 51, and any psychosis not otherwise specified = 63) and 46 (28.3%) had no genetic risk. Among the offspring born to parents with APs, 100 of 159 offspring (63.0%) had an Axis I diagnosis (AP = 38, and any psychosis not otherwise specified = 62) and 54 (35.0%) had no genetic risk. The offspring with any psychosis had a significantly lower maternal age at pregnancy (26.4 [0.1] years) compared with the offspring without any psychosis (26.7 [0.2] years, P = .01).

### Table 2. Parent Demographic and Diagnostic Information Among the 350 High-Risk Offspring

<table>
<thead>
<tr>
<th>Offspring Among All Parents (N=350)</th>
<th>Offspring Among Healthy Control Parents (N=147)</th>
<th>Any Psychosis (N=203)</th>
<th>SPS (N=71)</th>
<th>AP (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical Variables, No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Categorical Variables, No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Categorical Variables, No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Categorical Variables, No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Categorical Variables, No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Ethnicity, mother</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>322 (92.0)</td>
<td>137 (93.2)</td>
<td>185 (91.1)</td>
<td>62 (87.3)</td>
</tr>
<tr>
<td>African American</td>
<td>26 (7.4)</td>
<td>8 (5.4)</td>
<td>18 (8.9)</td>
<td>9 (12.7)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.6)</td>
<td>2 (1.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Socioeconomic status, quartile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>96 (27.4)</td>
<td>35 (23.8)</td>
<td>61 (30.0)</td>
<td>24 (33.8)</td>
</tr>
<tr>
<td>Lower middle</td>
<td>74 (21.1)</td>
<td>29 (19.7)</td>
<td>45 (22.2)</td>
<td>18 (25.4)</td>
</tr>
<tr>
<td>Upper middle</td>
<td>81 (23.1)</td>
<td>36 (24.5)</td>
<td>45 (22.2)</td>
<td>15 (21.1)</td>
</tr>
<tr>
<td>Highest</td>
<td>90 (25.7)</td>
<td>43 (29.3)</td>
<td>47 (23.2)</td>
<td>11 (15.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (2.6)</td>
<td>4 (2.7)</td>
<td>5 (2.5)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td><strong>Marital status, mother</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>14 (4.0)</td>
<td>4 (2.7)</td>
<td>10 (4.9)</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td>Married</td>
<td>318 (90.9)</td>
<td>137 (93.2)</td>
<td>181 (89.2)</td>
<td>60 (84.5)</td>
</tr>
<tr>
<td>Separated</td>
<td>5 (1.4)</td>
<td>3 (2.0)</td>
<td>2 (1.0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Single</td>
<td>13 (3.7)</td>
<td>3 (2.0)</td>
<td>10 (4.9)</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td><strong>Sex of offspring</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>165 (47.1)</td>
<td>69 (46.9)</td>
<td>96 (47.3)</td>
<td>40 (56.3)</td>
</tr>
<tr>
<td>Female</td>
<td>185 (52.9)</td>
<td>78 (53.1)</td>
<td>107 (52.7)</td>
<td>31 (43.7)</td>
</tr>
<tr>
<td><strong>Study site</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston, MA</td>
<td>257 (73.4)</td>
<td>116 (78.9)</td>
<td>141 (69.5)</td>
<td>46 (64.8)</td>
</tr>
<tr>
<td>Providence, RI</td>
<td>93 (26.6)</td>
<td>31 (21.1)</td>
<td>62 (30.5)</td>
<td>25 (35.2)</td>
</tr>
<tr>
<td><strong>Continuous and Count Variables, Mean (SE)&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>26.4 (0.4)</td>
<td>26.9 (0.5)</td>
<td>26.0 (0.5)</td>
<td>26.6 (0.8)</td>
</tr>
<tr>
<td>Education, y</td>
<td>11.1 (0.2)</td>
<td>11.4 (0.2)</td>
<td>11.0 (0.2)</td>
<td>11.0 (0.3)</td>
</tr>
<tr>
<td>No. of pregnancies</td>
<td>2.2 (1.1)</td>
<td>2.2 (1.1)</td>
<td>2.2 (1.1)</td>
<td>2.1 (1.1)</td>
</tr>
<tr>
<td>No. of children</td>
<td>1.9 (1.1)</td>
<td>1.8 (1.1)</td>
<td>1.9 (1.1)</td>
<td>1.8 (1.1)</td>
</tr>
<tr>
<td>Offspring’s year of birth</td>
<td>1962.7 (0.1)</td>
<td>1962.7 (0.2)</td>
<td>1962.7 (0.1)</td>
<td>1962.7 (0.2)</td>
</tr>
</tbody>
</table>

Abbreviations: AP, affective psychosis; SPS, schizophrenia-psychosis spectrum.

<sup>a</sup>High-risk offspring were children of parents with psychosis. The SPS group includes offspring of parents with schizophrenia, schizoaffective depressed disorder, psychosis not otherwise specified (NOS), delusional diagnosis, delusional diagnosis, schizophrenia, delusional disorder, history of psychosis NOS, or history of psychosis NOS due to organicity. The AP group includes offspring of parents with schizoaffective bipolar disorder, bipolar disorder with psychosis, major depressive disorder with psychosis, bipolar disorder with psychosis unknown, history of major depressive disorder with psychosis, and history of bipolar disorder with psychosis. “Any psychosis” includes offspring of parents with SPS and AP diagnoses. The comparison group consists of offspring of healthy parents, ie, parents who had no Axis I diagnosis and no Axis II disorders found to be genetically related to psychoses.

<sup>b</sup>Because of rounding, percentages may not total 100.

<sup>c</sup>Least-squares means and standard errors for continuous maternal variables were calculated by means of mixed linear models accounting for intrafamilial correlation. For count variables (ie, number of pregnancies and number of children), the means and standard errors were calculated by Poisson regression based on a generalized estimating equations model.
significantly fewer had mothers who were married compared with offspring of healthy control parents (84.5% [SPS] vs 93.2% [control]; \( \chi^2 = 4.2, P = .04 \)). Furthermore, there were significantly fewer offspring of parents with SPS disorders in the highest SES quartile than offspring of healthy control parents (15.5% vs. 29.3%; \( \chi^2 = 4.9, P = .03 \)). In general, there were few sociodemographic differences between offspring of parents with psychosis and offspring of healthy control parents except for lower SES and being married, which is typical for individuals with psychosis. Findings controlled for sociodemographic characteristics did not change the relative risks.

Table 3 and Table 4 provide the frequency and relative risks for offspring adult psychopathology in relation to parent psychoses. Having a parent with psychosis (“any psychoses”) increased the offspring’s risk of psychosis 5-fold compared with offspring of healthy control parents (adjusted RR, 5.4; 95% CI, 1.7-17.6) (Table 3). The rate of psychosis in generation 2 was 12.3% for offspring of parents with a psychotic disorder vs 2.0% for offspring of healthy control parents. However, psychosis subtype (ie, APs vs SPS disorders) among the offspring was specific to the psychosis subtype of the parent. That is, although having a parent with AP increased the risk of AP in offspring 14-fold (RR, 14.0; 95% CI, 1.8-106.3), the risk for SPS disorders in their offspring was not significantly elevated (RR, 2.2; 95% CI, 0.4-12.0). The rate of generation 2 AP was 10.6% for offspring of parents with AP vs 3.0% for generation 2 SPS in offspring of such parents. Alternatively, although having a parent with an SPS disorder increased the risk of SPS in their offspring almost 6-fold (RR, 5.5; 95% CI, 1.2-26.0) compared with offspring of healthy controls, there was a lack of significant risk for AP in their offspring (RR, 2.1; 95% CI, 0.1-32.6). The rate of generation 2 SPS was 8.5% for offspring of parents with SPS disorders vs 1.4% for generation 2 AP in offspring of healthy control parents.

These results did not change if we excluded schizoaffective disorder, depressed type (SAD), from the SPS parental group. There were only 5 parents with SAD. Of their 7 offspring, 6 had Axis I diagnoses of substance use disorders or personality disorders unassociated with the genetic spectrum of schizophrenia or AP. One had no Axis I or II disorders. Thus, removing the SAD group from the nonaffective psychoses group and adding them to the AP group did not change the results.

In terms of the spectrum disorders, parental AP significantly increased the offspring’s risk for affective spectrum disorder compared with offspring of healthy control parents (RR, 1.6; 95% CI, 1.0-2.6) (Table 4). Compared with risk among offspring of healthy control parents, parental psychosis did not significantly increase the offspring’s risk for SPD or recurrent MDD. Of note, SPD showed greater association with the AP than the SPS phenotype (5.3% vs 1.4%). To understand this issue further, we analyzed the symptoms of SPD in association with the AP and SPS parental status. Results showed that APs were associated with SPD interpersonal traits (ie, excessive social anxiety, no close friends, inappropriate or constrained affect, and suspiciousness or paranoid ideation) and not the SPD cognitive-perceptual items.

Psychoses, and particularly AP in the parent, significantly increased the rate of diagnosis of any psychopathology in the offspring (AP: RR, 1.3; 95% CI, 1.1-2.2). Schizophrenia-psychosis spectrum disorders in the parent were not significantly associated with general psychopathology in the offspring, but rather the transmission of SPS in the parent appeared specific to SPS in the offspring (Table 3).
In this new NEFS high-risk study of psychoses, we demonstrated an increased risk of psychoses among the offspring of parents with psychoses. Consistent with rates reported in the high-risk literature (Table 1), there was a prevalence of 9.9% for psychoses and 8.5% for SPS disorders among offspring of parents with SPS disorders, representing an approximately 6-fold increased risk for SPS disorders among offspring of parents with SPS disorders. Among offspring of parents with APs, 13.6% developed psychoses and 10.6% developed AP, representing a 14-fold increased risk of APs among offspring of parents with APs.

The magnitude of risk estimates in this study is similar to that in a number of reports of other high-risk studies (Table 1), in particular studies that clinically interviewed subjects by using current diagnostic criteria and used similar inclusion criteria for the definition of psychoses for both offspring and parents. Furthermore, there were differences in control for potential confounders and age at follow-up assessment across studies. The risk estimates (in the following studies, represented by odds ratios [ORs]) for the Helsinki High-Risk Project31 (OR, 8.6), the Finnish Adoptive Family Study32 (OR, 4.9), and the Copenhagen Perinatal Project38 (OR, 4.5) are similar to our relative risk for psychosis of 5.4. In each of these studies, the offspring were assessed at 34 to 48 years of age and diagnoses were made on the basis of personal interviews and medical record information, similar to our study. In contrast, for example, the Helsinki High-Risk Project31 and Swedish registry study by Lichtenstein and colleagues36 resulted in higher risks (OR, 12.9 and 10.3, respectively). These 2 studies included schizoaffective disorder, bipolar type, in the definition of SPS. Finally, they used clinical diagnoses, which we know may...
be accurate with regard to “presence of psychosis” but not necessarily with regard to type of psychosis. The highest risk estimate was the study in Myles-Worsley et al. However, there is substantial use of betel nut (a muscarinic agonist) chewing in the healthy population as well as in patients with schizophrenia, particularly high in women, which may contribute to the substantially high rate of psychosis in the high-risk offspring, a hypothesis that warrants investigation.

However, a rate of SPS of 8.5% among offspring of parents with SPS is still on the lower side of the high-risk study literature. The lower rate of psychoses may be partially accounted for by nonparticipation among study offspring in general. Our design required location, interview, and diagnosis of offspring of both healthy and affected parents and, as in all such studies, we did not have complete participation (although our response rate of approximately 79% is excellent for a 40-year follow-up study). It may be the case that we were less successful in enrolling offspring with psychotic disorders either because they were more transient and difficult to locate and/or because of a lack of willingness to participate in this research project. Both of these methodologic points would result in a reduced estimate of the rate of psychosis among the offspring generation in general. However, there is little reason to expect that this reduction would be greater among high-risk offspring vs healthy control offspring. In other words, irrespective of the parental diagnosis, one might anticipate lower participation rates among offspring with psychoses. This “nondifferential attrition” is well recognized in the epidemiologic literature and is likely to generate lower absolute estimates of the rate of offspring psychoses in both the high-risk and healthy control groups, but would not alter the relative risk comparing the rates of these 2 groups.

Family history diagnostic information, obtained by using the Family Interview for Genetic Studies from first-degree relatives, was used to assess psychosis or other major psychopathology in non-CPP siblings. Of the non-CPP siblings, 5 were diagnosed as having psychoses. However, for the current analytic sample we included only offspring who participated in the CPP because of the rich amount of early-life data available for these subjects that were not available for their non-CPP siblings. This would not bias our RR estimates because CPP offspring represented both high-risk and healthy control groups, but would not alter the relative risk comparing the rates of these 2 groups.

In this study, we demonstrated specificity of risk by psychosis subtype (SPS vs AP), a relationship that has not been previously reported, to our knowledge. In previous literature, the affective high-risk groups included offspring of subjects with both psychotic and nonpsychotic affective disorders, and in some studies it was not clear whether psychosis in the parent was included at all. The Finnish Adoptive Family Study, the New York High-Risk Project, and Helsinki High-Risk Project examined APs in the offspring but did not explore the rates of APs in the offspring of parents with such disorders. The affective high-risk groups in the latter 2 studies were based on offspring of parents with unipolar disorder and bipolar disorder with and without psychosis. The Finnish Adoptive Family Study, combined APs among parental schizophrenia spectrum disorders. Thus, our study findings are unique because we investigated specificity of transmission of illness in offspring of parents with SPS disorders compared with APs.

These findings must be replicated because, owing to sample size, we have limited power to test whether the 2-fold RRs we found for these “cross-disorder rates” (ie, AP in offspring among parents with SPS and vice versa) are in fact significant compared with the 6-fold increased risk of SPS in offspring of parents with SPS and the 14-fold increased risk of AP in offspring of parents with AP. However, the magnitude of the risks within each diagnostic grouping (ie, RRs of 5.5 and 14.0) are much higher than the cross-disorder risk estimates for both groups (ie, RRs of 2.1 and 2.2). This suggests, at least, that there is some cross-disorder risk but not as high as within psychosis type.

The reason for the specificity of the transmission of SPS disorders and APs found in our study is currently unknown. In fact, recent molecular studies suggested nonspecificity of transmission by psychosis type or some common genetic susceptibility genes for both classes of psychoses. However, the results of this study indicating relative specificity of transmission for type of psychosis must be seen in a larger context of an increasing focus on identifying similarities and differences between schizophrenia and APs. This effort includes identifying commonalities and dissimilarities in endophenotypes, such as auditory P300 and P50, brain volumes, neuropsychological function, and other measures. An emerging model suggests that there is an overlapping genetic background to psychosis, but that schizophrenia, more than bipolar psychosis, is likely to be associated with additional neurodevelopmental insults. Our high-risk study suggests that clinical phenotypes (operationalized as lifetime diagnoses of these disorders in adult offspring and their parents) are relatively specifically linked within families to type of psychosis. This does not rule out the possibility that there will be overlapping neural phenotypes in our study, a question that is under active investigation by our group.

Recent molecular studies identifying unique and shared genes and environmental factors will help to elucidate mechanisms. The NEFS sample also provides a unique opportunity to contribute to this because we have stored prenatal and adult blood from these subjects to assess prenatal risk factors and genotyping in our family-based strategy. Furthermore, the sample has enriched childhood environmental variables to assess gene-environment interactions in our ongoing work with these cohorts.

Our family high-risk (FHR) study, along with other studies focused on offspring of parents with psychoses, provides an understanding of the transmission of psychosis from parents to their offspring. In addition, clinical high-risk (CHR) studies are based on enriched samples of adolescents or young people with prodromes for psychosis, individuals who already exhibit subthreshold symptoms and who are likely to develop psychosis within a relatively short time. This popular design provides an efficient approach to prospectively investigate the transmission of high-risk persons from the prodromal state to disease onset and potentially allows for targeted interventions during a treatment-seeking
phase with a favorable risk to benefit ratio. Thus, CHR studies have a number of strengths not found in FHR studies, which have a lower rate of conversion to psychosis over longer periods.

However, we would argue that CHR studies complement but should not supplant the FHR design because each approach has strengths and weaknesses. For example, the FHR design enables investigators to study early precursors to illness, beginning with fetal life, thus enabling the identification of premorbid characteristics that may ultimately lay the foundation for early interventions and prevention strategies. In addition, assessment at earlier ages in FHR studies typically allows for evaluation without the potential confounding effects of medication use, which is far more common in treatment-seeking CHR individuals. The FHR studies tend to allow for more homogeneous cases, at least with respect to family diagnosis, whereas CHR studies include a mix of families in which there may be only 1 or multiple members with psychoses. Thus, the FHR studies, such as the one presented herein, have considerable value for understanding the developmental course of these illnesses given that there are few FHR-based studies in the literature, including the NEFS, with the potential for studies of lifelong development.

Submitted for Publication: December 2, 2008; final revision received July 27, 2009; accepted September 6, 2009.

Correspondence: Jill M. Goldstein, PhD, 1 Bigham Cir, Division of Women’s Health, Brigham and Women’s Hospital, 1620 Tremont St, Third Floor, Boston, MA 02120 (jill.goldstein@hms.harvard.edu).

Financial Disclosure: None reported.

Funding/Support: This work was funded primarily by grant RO1 MH50647 from the National Institute of Mental Health (1999-2003, principal investigator Dr Tsuang; 2003-2006, principal investigator Dr Goldstein). Additional funding included National Institute of Mental Health grant RO1 MH63951 (Dr Seidman), Stanley Medical Research Institute (Drs Buka and Seidman), and NARSAD (Dr Seidman).

Additional Contributions: Sara Cherkzerian, ScD, June Wolf, PhD, Anne Peters-Remington, BA, CM, and JoAnn Donatelli, PhD, contributed tirelessly over several years with regard to the recruitment and diagnoses of subjects and data analyses. Their efforts have been (and continue to be) invaluable to the success of this study. We also appreciate the efforts of a number of research assistants over the years and a previous project coordinator, Lisa Denny, MD, for their contributions to the study at an earlier stage of the work and Ronald O. Rieder, MD, for access to his earlier 1975 study of some of the Boston mothers in our parental case group.

REFERENCES

32. Ingraham LJ, Kugelmasi S, Frenkel E, Nathan M, Mirsky AF. Twenty-five-year fol-