Background: This study tested the hypothesis that childhood-onset schizophrenia (COS) is a variant of adult-onset schizophrenia (AOS) by determining if first-degree relatives of COS probands have an increased risk for schizophrenia and schizotypal and paranoid personality disorders.

Methods: Relatives of COS probands (n=148) were compared with relatives of attention-deficit/hyperactivity disorder (ADHD) (n=368) and community control (n=206) probands. Age-appropriate structured diagnostic interviews were used to assign DSM-III-R diagnoses to probands and their relatives. Family psychiatric history was elicited from multiple informants. Diagnoses of relatives were made blind to information about probands’ diagnoses. Final consensus diagnoses, which integrated family history, direct interview information, and medical records, are reported in this article.

Results: There was an increased lifetime morbid risk for schizophrenia (4.95%±2.16%) and schizotypal personality disorder (4.20%±2.06%) in the parents of COS probands compared with parents of ADHD (0.45%±0.45%, 0.91%±0.63%) and community control (0%) probands. The parents of COS probands diagnosed as having schizophrenia had an early age of first onset of schizophrenia. Risk for avoidant personality disorder (9.41%±3.17%) was increased in the parents of COS probands compared with parents of community controls (1.67%±1.17%).

Conclusions: The psychiatric disorders that do and do not aggregate in the parents of COS probands are remarkably similar to the disorders that do and do not aggregate in the parents of adults with schizophrenia in modern family studies. These findings provide compelling support for the hypothesis of etiological continuity between COS and AOS.

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Recall that interest in childhood-onset schizophrenia (COS) is sparked by the belief that COS may be a more homogeneous, severe form of schizophrenia than adult-onset schizophrenia (AOS). Many neurocognitive, linguistic, and psychophysiological impairments and changes in brain structure observed in AOS are present in COS, suggesting that COS and AOS may have a common neurobiological substrate. The present study provides an important further test of the hypothesis that COS is a variant of AOS.

Schizophrenia strongly aggregates in families. Twin and adoption studies suggest that genetic factors play a major role in the etiology of AOS. This study tested the hypothesis that first-degree relatives of COS probands, like relatives of AOS probands, have an increased risk for schizophrenia and schizophrenia-related personality disorders. If so, this would be further evidence for etiological continuity with AOS.

Two early studies found an aggregation of schizophrenia in relatives of COS probands comparable with that reported in relatives of AOS probands. In addition, in COS twins the concordance rates for schizophrenia were significantly higher in monozygotic than in dyzygotic twins, suggesting genetic transmission of COS. While these results are intriguing, neither study meets modern methodological standards. We employed modern family study methods to determine if there is an increased aggregation of schizophrenia in first-degree relatives of COS probands compared with first-degree relatives of community controls.

With only 1 exception, 10 prior studies that compared the prevalence of schizotypal personality disorder (SPD) in relatives of AOS probands with matched controls found substantial evidence for a familial relationship between schizophrenia and SPD. Familial relationships of schizophrenia to paranoid, schizoid, and avoidant personality disorders is
SUBJECTS AND METHODS

SUBJECTS

Ascertainment and Diagnosis of Probands

The UCLA Family Study involves parallel studies of the relatives of 3 child (principal investigator: R.F.A.) and 3 adult proband groups (principal investigator: K.H.N.). This report concerns the relatives of the 3 child proband groups: COS, ADHD, and community controls. We ascertained COS probands by identifying 12 Los Angeles County facilities that treated substantial numbers of these children. We screened 9 facilities by periodically reviewing cases with site clinicians to identify potential COS probands. Child-onset schizophrenia probands were also ascertained through the University of California, Los Angeles Neuropsychiatric Hospital and school-based programs for seriously emotionally disturbed children in Los Angeles County. Attention-deficit/hyperactivity disorder probands were ascertained through outpatient pediatric clinics and support groups for the families of children with ADHD (particularly the Children and Adults With Attention-Deficit/Hyperactivity Disorder group) located in Los Angeles County.

Lists of potential community controls living in the same ZIP codes as COS probands were obtained from a scientific survey research firm (Survey Sampling Inc, Fairfield, Conn). Parents of potential community control probands were contacted by telephone to explain the purpose of the study and to screen probands for schizophrenia and ADHD or placement in special classes for either exceptionally bright or learning-disabled children.

All participants in this study provided informed consent or assent (if a minor).

An experienced child clinical psychologist used the Schedule for Affective Disorder and Schizophrenia for School-Aged Children: Epidemiologic Version (K-SADS-E) to interview the best-informed parent about the proband’s history of psychiatric symptoms and then interviewed the proband. The K-SADS-E was used to diagnose schizophrenia, ADHD, and other Axis I disorders in COS, ADHD, and community control probands. Medical and school records were obtained. The clinician interviewing the parent and proband reviewed diagnostic interviews and ancillary information with an experienced child psychiatrist to reach a consensus diagnosis. Our earlier formal study of diagnostic reliability on 35 children with schizophrenia revealed satisfactory agreement ($k=0.88$). Our goal was to enroll 120 ADHD and 60 COS and community control families. Because a few proband diagnoses changed when additional diagnostic information became available and some families declined to participate in family interviews after the parents consented to diagnostic interviews of the proband, 118 ADHD probands, 51 COS, and 61 families of community control probands were entered into this study. Children with consensus diagnoses of DSM-III-R schizophrenia with first onset of psychosis before 13 years of age were the schizophrenia probands. Children with consensus diagnoses of DSM-III-R ADHD (at least 8 ADHD symptoms rated as definitely or probably present) were the ADHD probands. Of these, 106 had at least 8 ADHD symptoms rated as definitely present, while 12 children had at least 6 ADHD symptoms rated as definitely present.

Children were excluded from these proband groups if they had a full-scale IQ less than 70, had a history of central nervous system disease (eg, temporal lobe epilepsy), or had taken drugs that could have produced psychotic episodes. Children were excluded from the community control group for personal diagnoses of either schizophrenia or ADHD, but not for any other psychiatric diagnosis. More than 31% of the community control probands received at least 1 DSM-III-R diagnosis. The most frequent diagnoses were separation anxiety disorder ($n=3$), adjustment disorder ($n=4$), oppositional defiant disorder ($n=3$), overanxious disorder ($n=3$), and simple phobia ($n=3$).

Diagnosis of First-Degree Relatives

The diagnoses of 366 first-degree relatives were based on direct interview, family history, and ancillary information. The diagnoses of 156 additional first-degree relatives, who were not directly interviewed, were based on family history interviews and, when available, medical records.

First-degree relatives 16 years and older were interviewed to assess DSM-III-R Axis I diagnoses using the Diagnostic Interview Schedule, to which a time line for affective and psychotic symptoms was added. When subjects reported any experiences suggesting the presence of psychotic symptoms, the psychosis section of the Present State Examination was administered. Although the Diagnostic Interview Schedule has good reliability and validity, the modifications were designed to mitigate concerns about its sensitivity to schizophrenia. The structured Diagnostic Interview Schedule ensured that no areas of psychopathology were overlooked, while the additional semistructured Present State Examination probes and syndrome time line facilitated differential diagnosis of schizophrenia, schizoaffective disorder, and mood disorders.

Siblings aged 7 to 15 years were directly interviewed using the K-SADS-E, and the best-informed parent was also interviewed about the sibling. For children aged 5 to 6 years, diagnostic information was collected solely through parental interview with the K-SADS-E.

limited or mixed in studies of AOS probands. The present study tested the hypothesis that there is an increased aggregation of SPD, and of paranoid, schizoid, and avoidant personality disorders in relatives of COS probands. We examined the specificity of this familial relationship by determining if there was an increased risk of schizophrenia, SPD, paranoid, schizoid, and avoidant personality disorders in relatives of attention-deficit/hyperactivity disorder (ADHD) probands, another disorder with prominent cognitive features. We attempted to establish the outer boundaries of schizophrenia-spectrum personality disorders by examining one personality disorder, borderline personality disorder, which prior research suggested does not tend to aggregate in families of AOS probands.

Eliminating control probands with any psychiatric disorder (“supernormal controls”) may produce spurious evidence for coaggregation. Therefore, we used a case-control design in which community control probands with the index disorders (schizophrenia or ADHD)
The Structured Clinical Interview for DSM-III-R: Personality Disorders was used to assess 2 “narrow” schizophrenia-spectrum disorders (paranoid and SPD), and schizoid, avoidant, and borderline personality disorders. We modified the Structured Clinical Interview for DSM-III-R: Personality Disorders so that it could be used with adolescents.

Nine family interviewers were doctorate- or master’s degree–level clinicians, while 1 family interviewer had a bachelor’s degree and 4 years of experience in clinical interviewing. All interviewers were trained to criterion levels on the Diagnostic Interview Schedule by the person who trained the Los Angeles staff of the Epidemiologic Catchment Area project and on the Present State Examination by the diagnosis and psychopathology core of the University of California, Los Angeles, Clinical Research Center for Schizophrenia. One of us (R.F.A.) conducted K-SADS-E training. Our training procedures for the Structured Clinical Interview for DSM-III-R: Personality Disorders and its adequate reliability in the current study have been described elsewhere. Every family interviewer rated gold standard videotapes of each diagnostic interview, conducted “mock” interviews of other staff, and finally carried out at least 5 videotaped interviews of patient volunteers that were co-rated by training staff.

Family history information on all first- and second-degree relatives (including directly interviewed relatives) was typically obtained from 2 adult informants, the proband’s parents whenever possible. After the systematic generation of a genealogy, family history of major psychiatric illness was elicited using the National Institute of Mental Health Relative Psychiatric History interview format. Personality disorders were assessed using the Structured Clinical Interview for DSM-III-R: Personality Disorders adapted to a third-person format.

DIAGNOSTIC PROCEDURES FOR FIRST-DEGREE RELATIVES

To keep family interviewers blind to the proband’s diagnosis, diagnostic evaluations of probands and first-degree relatives were conducted by entirely different diagnostic teams, housed in separate buildings. Whenever feasible, first-degree relatives were directly interviewed by staff members who had not interviewed any other relatives within the same family. Information regarding other family members’ psychiatric histories was not considered in making a relative’s psychiatric diagnosis.

A 2-stage diagnostic process was used. In the first stage, interviewers made independent diagnoses for each first-degree relative based on 1 source of information (either direct interview or family history information). Two interviewers for each relative then met to make consensus diagnoses that integrated family history and direct interview information and medical records, if available. To further minimize any potential bias, cases with psychotic symptoms or potential schizophrenia-spectrum personality disorders were reviewed at a weekly project meeting by senior clinicians (D.F., K.L.S., K.H.N., and R.F.A.) blind at all stages of the diagnostic process to the diagnosis of probands and all other family members. For each diagnosis, interviewers assigned a confidence level (definite, probable, and possible). In this report, only definite diagnoses are considered.

The second stage of the diagnostic process was carried out immediately before data analysis. To ensure uniform application of DSM-III-R criteria over time, all cases with possible psychotic symptoms and/or with diagnoses of SPD or paranoid personality disorder (or who were 1 symptom short of receiving these diagnoses) were reviewed. Senior clinicians reached final consensus diagnoses after case presentation of all symptom and illness course information. The net effect of this final diagnostic review was to downrate the diagnoses of paranoid and SPD from definite to probable for a number of cases lacking clear examples of certain symptoms.

To permit the comparison of the results of this study to prior studies, the primary data analyses used a minor modification of the hierarchy employed by Kendler et al. That hierarchy was (1) schizophrenia; (2) schizoaffective disorder; (3) SPD; and (4) nonaffective psychoses (schizophreniform disorder and atypical psychosis). We placed paranoid personality disorder fifth in our hierarchy. When a relative received multiple diagnoses, the diagnosis highest in the hierarchy was used for analyses.

STATISTICAL ANALYSES

The Kaplan-Meier method of analyzing life tables, as operationalized in the LIFETEST procedure in SAS was used to calculate lifetime morbid risks. The age of onset for personality disorders was set at 18 years, except for relatives younger than 18 years at the time of the evaluation. In these instances, the age of onset was considered to be the age at evaluation. We tested for differences in life table curves between various groups using the log-rank statistic. We used 2-tailed tests for all comparisons between groups for morbidity risk. The α level was P < .05 for all analyses. Analyses of variance, followed up by Bonferroni protected post hoc t tests, were used to test between group differences on continuous demographic variables, while χ² analyses were used on dichotomous demographic variables.

RESULTS

CHARACTERISTICS OF SUBJECTS

There were no significant group differences in the mean age of parents at evaluation (Table 1). The 3 groups of siblings differed in age (F(2,272) = 17.29, P < .0001). The siblings of the schizophrenic probands were significantly older than the siblings of the ADHD (t(221) = 4.74, P = .00001) and community control probands (t(221) = 5.80, P = .00001), who did not differ from each other. The 3 groups of parents differed in education level (F(2,221) = 6.86, P < .001). Parents of COS probands completed significantly fewer years of school than parents of community control (t(221) = 3.56, P = .0007) and ADHD probands (t(221) = 2.97, P = .005), who did not differ from each other. More mothers than fathers were directly interviewed in all 3 groups (χ² = 15.35, P < .0001). The 3 groups were excluded, but community control probands were allowed to have any other psychiatric disorder.
did not, however, differ significantly in the percentage of parents directly interviewed who were mothers.

There were significant differences in ethnic backgrounds ($\chi^2=7.33, P=.02$) between the proband groups. The COS group contained relatively fewer white and relatively more Hispanic and African American children than the other 2 groups.

RISK FOR SCHIZOPHRENIA AND NARROW SCHIZOPHRENIA-SPECTRUM DISORDER

Parents

Risks of schizophrenia and schizophrenia-spectrum personality disorders are presented separately for parents and siblings because the vast majority of siblings have not yet entered the typical age of risk for schizophrenia (Table 1). The first set of analyses used the diagnostic hierarchy described above to ensure that no relative received more than 1 diagnosis.

There were no cases of schizophrenia or DSM-III-R Axis I diagnoses closely related to schizophrenia (schizotypal, schizoaffective disorder [depressed type], or atypical psychosis) among the parents of community control probands. The risk for schizophrenia in parents of COS probands (Table 2) was significantly greater than in parents of community control ($\chi^2=6.15, P=.01$) and ADHD probands ($\chi^2=7.69, P=.006$). The parents of ADHD and community control probands did not differ in the risk for schizophrenia or schizophrenia-related Axis I disorders.

There were 5 cases of schizophrenia and 1 case of schizoaffective disorder (depressed type) in the parents of COS probands. These parents have a rather early age of first onset of schizophrenia (mean [SD], 20.8 [4.5] years).

The risk for SPD was significantly greater in the parents of COS probands compared with parents of community control ($\chi^2=5.21, P=.02$) and ADHD probands ($\chi^2=3.91, P=.05$). There were no significant differences

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**Table 1. Demographic Characteristics of Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Probands</th>
<th></th>
<th></th>
<th></th>
<th>Siblings</th>
<th></th>
<th></th>
<th></th>
<th>Parents</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>ADHD</td>
<td>Community</td>
<td>Control</td>
<td>Schizophrenia</td>
<td>ADHD</td>
<td>Community</td>
<td>Control</td>
<td>Schizophrenia</td>
<td>ADHD</td>
<td>Community</td>
</tr>
<tr>
<td>Sample size</td>
<td>51</td>
<td>112</td>
<td>61</td>
<td>46</td>
<td>145</td>
<td>84</td>
<td>102</td>
<td>223</td>
<td>84</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Age at evaluation, y, mean (SD)</td>
<td>13.0 (3.4)</td>
<td>10.0 (2.6)</td>
<td>11.0 (2.6)</td>
<td>15.1 (6.0)</td>
<td>9.8 (5.1)</td>
<td>10.4 (5.3)</td>
<td>41.4 (7.4)</td>
<td>40.3 (6.6)</td>
<td>42.1 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex of subjects directly interviewed, % female</td>
<td>31.4</td>
<td>23.2</td>
<td>52.5</td>
<td>51.3</td>
<td>51.0</td>
<td>53.6</td>
<td>60.8</td>
<td>56.6</td>
<td>62.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, y, mean (SD)</td>
<td>7.1 (3.4)</td>
<td>4.5 (2.7)</td>
<td>5.7 (2.7)</td>
<td>8.9 (3.6)</td>
<td>5.9 (3.7)</td>
<td>6.2 (3.7)</td>
<td>13.4 (3.2)</td>
<td>14.9 (2.8)</td>
<td>15.5 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>49</td>
<td>70.5</td>
<td>67.2</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>13.7</td>
<td>8.9</td>
<td>6.6</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American, %</td>
<td>11.8</td>
<td>5.4</td>
<td>6.6</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Directly interviewed, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>82.6</td>
<td>71.0</td>
<td>72.6</td>
<td>77.5</td>
<td>84.8</td>
<td>77.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ADHD indicates attention-deficit/hyperactivity disorder; ellipses, not applicable.

---

**Table 2. Morbid Risk for Schizophrenia-Spectrum Disorders and 3 Other Personality Disorders as Determined by Life Table Analysis, in Parents and Siblings of 3 Groups of Child Probands**

<table>
<thead>
<tr>
<th></th>
<th>CC (n = 122)</th>
<th>ADHD (n = 223)</th>
<th>Schiz (n = 102)</th>
<th>Schiz vs CC</th>
<th>Schiz vs ADHD</th>
<th>ADHD vs CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>0</td>
<td>0.45% (0.45%)</td>
<td>4.95% (2.16%)</td>
<td>6.15‡</td>
<td>7.68‡</td>
<td>0.54</td>
</tr>
<tr>
<td>Schizoaffective (depressed type)</td>
<td>0</td>
<td>0.04% (0.03%)</td>
<td>1.04% (1.04%)</td>
<td>1.27</td>
<td>2.31</td>
<td>...</td>
</tr>
<tr>
<td>Schizotypal personality disorder</td>
<td>0</td>
<td>0.9% (0.63%)</td>
<td>4.21% (2.06%)</td>
<td>5.21‡</td>
<td>3.91</td>
<td>1.1</td>
</tr>
<tr>
<td>Schizophreniform and atypical psychosis</td>
<td>0</td>
<td>0.93% (0.66%)</td>
<td>0.03% (0.06%)</td>
<td>0.83</td>
<td>1.13</td>
<td>...</td>
</tr>
<tr>
<td>Paranoid personality disorder</td>
<td>0.82% (0.82%)</td>
<td>3.21% (0.19%)</td>
<td>4.4% (2.15%)</td>
<td>2.89</td>
<td>0.26</td>
<td>1.94</td>
</tr>
<tr>
<td>Narrow spectrum = any of the above diagnoses§</td>
<td>0.82% (0.82%)</td>
<td>5.4% (1.52%)</td>
<td>13.86% (3.44%)</td>
<td>14.96</td>
<td>6.76‡</td>
<td>4.52‡</td>
</tr>
<tr>
<td>Avoidant personality disorder</td>
<td>1.67% (1.17%)</td>
<td>4.76% (1.47%)</td>
<td>9.41% (3.17%)</td>
<td>6.40‡</td>
<td>2.23</td>
<td>2.08</td>
</tr>
<tr>
<td>Schizoid personality disorder</td>
<td>0.83% (0.82%)</td>
<td>0.47% (0.47%)</td>
<td>2.3% (1.61%)</td>
<td>0.76</td>
<td>2.05</td>
<td>0.16</td>
</tr>
<tr>
<td>Borderline personality disorder</td>
<td>1.69% (1.19%)</td>
<td>2.0% (0.99%)</td>
<td>2.60% (1.81%)</td>
<td>0.18</td>
<td>0.09</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; CC, community control; ADHD, attention-deficit/hyperactivity disorder; schiz, schizophrenia; and ellipses, not applicable.
† Includes subjects directly interviewed and subjects whose conditions were diagnosed via family history.
‡ P < .05.
§ Narrow spectrum includes schizophrenia, schizoaffective disorder (depressed type), schizotypal and paranoid personality disorder, and schizophreniform and atypical psychosis.
¶ P < .001.
|| P < .01.

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in risk for paranoid personality disorder between the 3 groups of parents. The parents of ADHD and community control probands did not differ significantly in risk for SPD or paranoid personality disorder.

Combining diagnoses of schizophrenia, schizoaffective, schizotypal, and paranoid personality disorders, the risk for narrow schizophrenia-spectrum disorders was significantly greater in parents of COS probands compared with parents of community control (χ² = 14.96, P = .0001) and ADHD probands (χ² = 6.76, P = .009). A greater risk for narrow schizophrenia-spectrum disorders in parents of ADHD probands compared with parents of community control probands (χ² = 4.52, P = .03) was almost entirely caused by paranoid personality disorder.

**Parents**

These analyses concern the risk for other personality disorders when they occur outside of the presence of narrow schizophrenia-spectrum disorders. Consistent with prior practice, we did not hierarchically organize avoidant, schizoid, and borderline personality disorders. The risk for avoidant personality disorder was significantly increased (χ² = 6.40, P = .01) in parents of COS probands compared with parents of community controls (Table 2). Consistent with prior research, there was no increased risk for borderline personality disorder in parents of COS probands compared with parents of community controls. The risk for schizoid personality disorder was quite low in all 3 groups, and group differences were not significant. Parents of COS and ADHD probands did not differ in risk for avoidant, schizoid, or borderline personality disorder.

Parents receiving personality disorder diagnoses typically received at least 1 other diagnosis (10 of 11 cases of borderline, 5 of 6 cases of schizotypal, and 5 of 7 cases of paranoid personality disorder). Avoidant personality disorder, however, appears 64% of the time (7 of 11 cases) outside the presence of narrow schizophrenia-spectrum disorders.

**Siblings**

No cases of schizophrenia were identified among siblings of COS, ADHD, or community control probands. One sibling of a COS proband received a diagnosis of schizoaffective disorder (mainly depressed type). The differences between 3 groups of siblings in risk for schizotypal or paranoid personality disorder were not significant.

**RISK FOR OTHER PERSONALITY DISORDERS**

### Parents

These analyses concern the risk for other personality disorders when they occur outside of the presence of narrow schizophrenia-spectrum disorders. Consistent with prior practice, we did not hierarchically organize avoidant, schizoid, and borderline personality disorders. The risk for avoidant personality disorder was significantly increased (χ² = 6.40, P = .01) in parents of COS probands compared with parents of community controls (Table 2). Consistent with prior research, there was no increased risk for borderline personality disorder in parents of COS probands compared with parents of community controls. The risk for schizoid personality disorder was quite low in all 3 groups, and group differences were not significant. Parents of COS and ADHD probands did not differ in risk for avoidant, schizoid, or borderline personality disorder.

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### Siblings

Differences between the 3 groups of siblings in the risk for avoidant, schizoid, and borderline personality disorders were not significant. However, a substantial percentage of siblings of COS probands received diagnoses of avoidant personality disorder.

### ANALYSES BY ETHNICITY, FAMILY DENSITY, AND DIAGNOSTIC METHODS

There were no significant differences between white and nonwhite parents of COS in morbid risk for schizophrenia or schizophrenia-spectrum disorders. The increased risk for schizophrenia and schizophrenia-spectrum disorders in parents of COS probands is not caused by an increased percentage of nonwhites, since the risk for schizophrenia-spectrum disorders tends to be slightly less in nonwhite than white parents of COS probands.

A few densely loaded families might have contributed disproportionately to the elevated risk of schizo-
phrenia-spectrum disorders in parents of COS probands. Thus, we conducted analyses in which the family was the unit of analysis by comparing the percentage of families containing 1 or more relatives with schizophrenia-spectrum diagnoses (Table 3). More than 33% of the families of COS probands had at least 1 first-degree relative with either a diagnosis of schizophrenia, or schizotypal or paranoid personality disorder. Consistent with studies of AOS families, the percentage of families with at least 1 relative receiving a narrow schizophrenia-spectrum disorder was significantly greater for families of COS probands than for families of ADHD (\( \chi^2 = 9.87, P < .001 \)) and community control probands (\( \chi^2 = 17.8, P < .001 \)).

Because diagnoses based on informants and medical history are less sensitive and may be more biased than diagnoses based on direct interviews,28-31 we compared morbid risks for diagnoses based on direct interview with diagnoses from family history interviews. Within each proband group, there were no significant differences in risk for schizophrenia, schizoaffective, schizophreniform, and schizotypal disorders, and borderline and avoidant personality disorders for those relatives who were directly interviewed vs those who were not. In contrast, the relatives of community control and ADHD probands who were not directly interviewed had a significantly greater risk (\( \chi^2 = 3.75, P < .05 \), and \( \chi^2 = 17.1, P < .0001 \), respectively) for paranoid and schizoid personality disorders (\( \chi^2 = 3.89, P < .05 \), and \( \chi^2 = 6.25, P < .01 \)) than did relatives of community control and ADHD probands who were directly interviewed. This may reflect a selection bias (more suspicious relatives not agreeing to be interviewed).

The surprising sensitivity of family history diagnoses may be attributable to the fact that diagnoses of relatives not directly interviewed were almost always based on information from 2 informants and sometimes included information from medical records. When information from multiple sources and specific diagnostic criteria are employed, the family history method can detect schizophrenia and schizophrenia-related personality disorders in relatives of schizophrenic patients.29,30,32

The results of the present study are consistent with recent AOS family studies, which indicate a clear familial aggregation of schizophrenia-spectrum disorders. There was an increased risk of schizophrenia in parents of COS compared with parents of community control probands. These findings replicate with a larger sample and more rigorous methods the results of 2 earlier family studies of COS probands. An interesting, but unexpected, finding was that the mean (SD) age of first onset of schizophrenia in parents of COS probands was 20.8 (4.5) years. This is considerably younger than the median age of onset of 24 to 28 years for males and 28 to 31 years for females.3,24 Age of onset is typically older in schizophrenic patients who are parents. Methodological differences, of course, might account for these differences in the estimates of age of onset.

None of the siblings of COS probands had developed schizophrenia. This is not surprising since the mean (SD) age of the siblings of COS probands is only 15.1 (6.0) years. Only 17.4% of these siblings were older than 20 years.

Consistent with 11 of the 12 most recent, methodologically rigorous AOS family studies, there was a significantly greater risk of SPD in parents of COS probands compared with parents of community control probands.5,10 These results extend support for a familial relationship between schizophrenia and SPD to instances in which the schizophrenic proband has an onset in childhood.

There was also an increased risk of avoidant personality disorder in parents of COS probands compared with parents of community control probands. This supports the hypothesis that the schizophrenia spectrum may include avoidant personality disorder, and underscores the importance of recent suggestions that avoidant personality disorder be evaluated in future family genetic studies of schizophrenia.

The parents of COS and community control probands did not significantly differ in their risk for borderline and schizoid personality disorders. Again, these findings are consistent with the results of most modern family genetic studies of AOS probands that have failed to find a consistent familial aggregation of borderline and, with 1 exception,13 schizoid personality disorders among relatives of AOS probands.

The psychiatric disorders that do and do not aggregate in parents of COS probands are remarkably similar to the disorders that do and do not aggregate in parents of AOS probands in modern family studies. These findings provide compelling support for the hypothesis of etiological continuity between COS and AOS.

Childhood onset of a disorder is frequently associated with increased familial aggregation compared with adult onset of a disorder.36 To determine if this is the case for COS, we compared the risk for schizophrenia in the cur-

### Table 3. Percentage of Families in Which at Least 1 First-Degree Relative Received a Schizophrenia-Spectrum Diagnosis

<table>
<thead>
<tr>
<th>Proband Diagnosis</th>
<th>Community Control (61 Families)</th>
<th>ADHD* (112 Families)</th>
<th>Schizophrenia (51 Families)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of first-degree relatives (excluding proband)</td>
<td>3.37</td>
<td>3.28</td>
<td>2.90</td>
</tr>
<tr>
<td>At least 1 first-degree relative with diagnosis of schizophrenia, schizoaffective disorder, %</td>
<td>0</td>
<td>0.9</td>
<td>13.7</td>
</tr>
<tr>
<td>At least 1 first-degree relative with a diagnosis of paranoid or schizotypal disorder, %</td>
<td>3.3</td>
<td>11.6</td>
<td>23.5</td>
</tr>
<tr>
<td>At least 1 first-degree relative with “narrow” spectrum disorder (any one of the 2 items above), %</td>
<td>3.3</td>
<td>11.6</td>
<td>33.3</td>
</tr>
</tbody>
</table>

*ADHD indicates attention-deficit/hyperactivity disorder.
rent study with rates observed in prior AOS family studies by comparing risk to relatives of schizophrenia probands with risk to relatives of community controls (relative risk [RR]). Relative risk is less affected by variations in interview methods, diagnostic practices, and criteria across studies than raw prevalence. However, a limitation of RR ratios is that they often have very large confidence intervals so the comparisons below are qualitative only and may not be statistically significant. Both classic second-generation family studies found significant differences in RR for schizophrenia between the siblings and parents of probands with AOS. Therefore, we examined the data from parents and siblings separately. The RR for schizophrenia in parents of COS probands is 17. This is considerably greater than the 6-fold and 3-fold, respectively, RR for schizophrenia between the siblings and parents of probands with AOS. None of the prior family studies, however, examined probands with onsets of schizophrenia before 15 years of age. Collectively, the present and prior studies suggest that an increase in familial liability to schizophrenia may be associated with very early (ie, preadolescent) onset of schizophrenia.

The only 2 prior studies that compared the risk for schizophrenia-spectrum personality disorders separately for parents and siblings of AOS probands found RRs for SPD and/or paranoid personality disorder of 6.69 and 3.05 in parents compared with 3.89 and 2.55 in siblings. The RR for SPD and/or paranoid personality disorder was 10.5 in parents of COS probands and 3.8 in siblings of COS probands. The RR for SPD and paranoid personality disorder is somewhat increased in parents and comparable in the siblings of COS probands compared with the parents of AOS probands. In the Roscommon Family Study, the RR of schizophrenia, SPD, or paranoid personality disorders in parents of AOS probands was 5.8% compared with 15.1% in parents of COS probands in this study.

Our blind diagnostic procedures yielded quite low rates of narrow schizophrenia-spectrum disorders in relatives of community control probands. The greater RR of schizophrenia-spectrum disorder in the parents and siblings of COS probands, however, is probably not attributable to our control group being a “super” normal control group. As noted above, 31% of the community control probands received a psychiatric diagnosis. Moreover, the rates of unipolar and bipolar disorder in the parents of the community control group are within the range reported in prior community samples.

The aggregation of schizophrenia-spectrum disorders in relatives of COS probands shows a considerable degree of diagnostic specificity when compared with relatives of ADHD probands. Schizophrenia occurs in parents of ADHD probands at the population base rate, and at a significantly lower rate than in the parents of COS probands. These findings are consistent with prior family studies of ADHD probands. Similarly, there were no significant differences between parents of ADHD and community control probands in risk for schizotypal and paranoid personality disorders.

The limitations of this study include the fact that the sample size in the COS group, while much larger than in prior COS family studies, was still relatively small. In addition, we cannot determine the extent to which the current sample is representative of children with a schizophrenia-spectrum disorder. Clearly, the current findings need to be replicated in another family study of children with schizophrenia.

The increase in RR of narrow schizophrenia-spectrum disorders in parents of COS probands compared with the rates observed in prior studies of AOS probands is based on studies that did not use wholly comparable interview methods and diagnostic procedures. While the result of this comparison is quite intriguing, a direct comparison of rates of disorder in relatives of COS and AOS probands diagnosed by identical methods is required before firm conclusions about differential aggregation can be reached.

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