Independent Diagnoses of Adoptees and Relatives As Defined by *DSM-III* in the Provincial and National Samples of the Danish Adoption Study of Schizophrenia

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Background: This report describes the independent application of *DSM-III* criteria to the adoptees and relatives in the Provincial sample of the Danish Adoption Study of Schizophrenia of Kety and colleagues. We report these results and combine them with those reported previously for the Copenhagen sample to form the National sample.

Methods: Personal interviews and institutional record summaries of adoptees and biological and adoptive relatives were "blindly" diagnosed using *DSM-III* criteria. "Schizophrenia spectrum" was a priori defined as schizophrenia; schizoaffective disorder, mainly schizophrenic subtype; and schizotypal and paranoid personality disorders.

Results and Conclusion: In the Provincial sample, the prevalence of "spectrum" disorders was significantly greater in biological relatives of schizophrenia spectrum vs control adoptees. The results were also consistent with the genetic transmission of individual diagnoses within the spectrum. When combined into the National sample, the results provided strong evidence for (1) the genetic transmission of *DSM-III* schizophrenia; (2) a genetic relationship between *DSM-III* schizophrenia, mainly schizophrenic schizoaffective disorder, and schizotypal personality disorder; and (3) the absence of a significant genetic relationship between the schizophrenia spectrum and either psychotic nonspectrum disorders, major depression, or anxiety disorders. We found no evidence for the familial environment transmission of schizophrenia spectrum disorders. These results are consistent with the findings reported by Kety and coworkers from their diagnostic review.

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OF THE numerous twin and adoption studies of schizophrenia performed during the past 60 years,[1,2] one of the most influential has been the investigation of biological and adoptive relatives of schizophrenic and control adoptees carried out in Denmark by Kety and coworkers.[3-7] This landmark study has gone through four phases. First, in 1968, Kety et al[3] reported results from blinded abstracts of hospital records on the biological and adoptive relatives of 34 pairs of matched schizophrenic and control individuals placed for adoption through the courts in the greater Copenhagen area. Second, in 1975, they published preliminary results of diagnoses based on a "blind" review of personal interviews with relatives from this "Copenhagen sample."[4] Third, in 1978, they published results of "blinded" abstracts of hospital records from relatives of 42 pairs of schizophrenic and control adoptees ascertained in the rest of Denmark, termed the "Provincial sample."[5] Combining the Copenhagen and Provincial samples produced the first results of a "National sample" of schizophrenic and matched control adoptees.[5] Finally, in the fourth phase, Kety and coworkers initially reported their blind diagnostic review of interviews with relatives in the Provincial and National samples in a preliminary form[6,8] and then, in the preceding article, more completely.[7]

Since this adoption study began in

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MATERIALS AND METHODS

CONDUCTING THE INDEPENDENT REVIEW

We undertook a diagnostic review of interviews from the Provincial sample with the understanding that it would be completely independent from the review of these same interviews conducted by the original investigative team of Dr Kety and Paul Wender, MD. Therefore, aside from receiving copies of the same diagnostic material (interviews, institutional record summaries, and hospital abstracts), no conversation regarding the substance of the work took place between the two research groups until the first draft of manuscripts, including all results based respectively on final and independent diagnoses by the two groups, had been prepared. Thus, our diagnostic review, decisions about the sources of diagnostic information to be used, the inclusion vs exclusion of specific relatives, data analysis, and the initial written version of this article were conducted without knowing the specific decisions or results by Kety and Wender. A description of the method of the Provincial sample of the Danish Adoption Study has been described in a previous report.[7]

DIAGNOSTIC REVIEW

As in our review of the Copenhagen sample, blinded personal interviews and institutional record summaries with index adoptees were reviewed by one of two experienced psychiatric diagnosticians (K.S.K. or A.M.G.). The institutional record summaries, which are exhaustive abstracts of hospital records on index adoptees recorded on interview forms, were sufficiently different in format from the true interviews that we always knew that they were from an index adoptee. Otherwise, we were unaware whether personal interviews were from index or control adoptees or from their biological or adoptive relatives.

Individuals who had been personally contacted were placed into one of two categories: completed interviews and partial reports. Partial reports were prepared from those individual contacts in whom completed interviews could not be obtained. As with the Copenhagen sample, we reviewed these reports, which varied widely in the amount of information they contained, and classified them as adequate (n=9) or inadequate (n=20). Relatives with adequate partial reports were treated like relatives with completed interviews (and both are included when we refer to "interviewed relatives"), whereas relatives with inadequate reports were excluded from further analysis.

As in our analysis of the Copenhagen sample, the diagnoses presented here were based only on information from personal interviews and/or institutional record summaries in adoptees and interviews only from relatives. Hospital abstracts were not used and noninterviewed relatives were excluded from all analyses.

For two index adoptees, paternity could not be unambiguously assigned, as the biological mothers had indicated that there were two possible biological fathers. We chose to exclude their three possible paternal half siblings from analysis. In addition, one full sibling of an index adoptee was adopted together with the index adoptee into the same adoptive home. Again, we chose, a priori, to eliminate this individual (who was both a biological and adoptive relative) from all analyses.

Although we had the thorough interview from the Danish Adoption Study and the Schedule for Affective Disorders and Schizophrenia-Lifetime Version interview, information was not always available to rate each *DSM-III* criterion. Therefore, diagnoses were made nonhierarchically with three levels of certainty. *Definite* diagnoses were made when all diagnostic criteria could be met with a high degree of confidence. *Probable* diagnoses were given when we were confident of the diagnosis but, owing to a lack of information or ambiguity in the available information, we could not be certain that every single criterion was met. *Possible* diagnoses were made when we were reasonably confident of the clini-

Continued on next page

the 1960s, the approach to psychiatric diagnosis has moved from global descriptive criteria that characterized *DSM-II*[9] to the operationalized diagnostic criteria of *DSM-III*[10] and *DSM-III-R*.[11] The concept of schizophrenia has narrowed and a new diagnosis of possible relevance, schizotypal personality disorder (SPD), was created. To see whether the changes in diagnostic criteria would produce any substantial changes in the results of the Danish study, two of us (K.S.K. and A.M.G.), who had no previous role in the Danish Adoption Study, undertook in 1979, with the consent and support of the original investigative team, an independent review of all interviews with relatives and adoptees in the Copenhagen sample.

The *DSM-III* criteria for schizophrenia defined a narrower group of adoptees than those diagnosed as "chronic schizophrenia" by Kety and coworkers.[4,12] Compared with the "spectrum" diagnoses of Kety and coworkers of borderline and uncertain schizophrenia, the *DSM-III* criteria for SPD were more specific but less sensitive.[13] The substantive findings from this independent review confirmed the results of the original diagnostic review by Kety and coworkers.[4,12-17]

Interviews with probands and relatives from the Provincial sample were collected and edited by a team of colleagues in Denmark and the United States under the supervision of Seymour Kety, MD. When these interviews became available, it was decided that two of us (K.S.K. and A.M.G.), who had *no prior involvement* with the Provincial study, should complete an independent diagnostic review on this sample of interviews as had been done with the Copenhagen sample. In this

cal diagnosis but, owing to a lack of or ambiguity of available data, we could not be certain that diagnostic criteria were met. Diagnoses made at the probable or definite level were considered "narrow" diagnoses, whereas those made at the possible, probable, or definite level were considered "broad" diagnoses. As in our previous report,[14] the *DSM-III* diagnoses of generalized anxiety disorder and panic disorder were combined into a single category termed "anxiety disorder." Similarly, alcohol abuse and alcohol dependence were combined into a single category termed "alcoholism."

To assess interrater reliability, we diagnosed, "blind" each one to the other, 40 randomly chosen interviews. Using the broad diagnostic categories used in this report, diagnostic agreement was found in 38 (95%) of 40 cases ($\kappa[\pm SE]=.908\pm.047$).[18]

SCHIZOPHRENIA SPECTRUM

As in our previous report,[12] we defined, a priori, a schizophrenia spectrum consisting of the following *DSM-III* categories: schizophrenia, schizoaffective disorder (meeting Research Diagnostic Criteria[19] for the mainly schizophrenic subtype), SPD, and paranoid personality disorder. Although the Research Diagnostic Criteria provide two criteria with which to diagnose the mainly schizophrenic subtype of schizoaffective disorder, in this study, as in the Copenhagen sample, we only used the second criterion: the presence, for at least 1 week, of psychotic symptoms in the absence of prominent affective symptoms. This criterion is nearly identical with that found for schizoaffective disorder in *DSM-III-R*.[11]

DIAGNOSTIC HIERARCHIES AND THE CONTROL GROUP

Diagnostic hierarchies can complicate the interpretation of family/genetic studies.[20] Therefore, in the Provincial sample, multiple diagnoses were permitted and our analysis of nonschizophrenia spectrum diagnoses is initially presented without hierarchy. However, for schizophrenia spectrum disorders, there is an implicit hierarchy that is assumed in our analyses: schizophrenia, schizoaffective disorder, SPD, and paranoid personality disorder. Kendler and Gruenberg,[12] as well as Kety and colleagues[3,4,7] have previously reported results from this study using "supernormal" control adoptees—removing control adoptees with any major psychopathologic condition. However, this procedure is not without difficulty and can, by producing supernormal relatives of controls, give rise to spurious evidence for coaggregation.[21] Therefore, we take the conservative position and herein only report results for the unscreened control adoptees and their relatives.

STATISTICAL TESTS

For contingency tables where the expected values in all cells exceed 1 and the total number exceeds 20, an uncorrected χ^2 test is used[22,23]; otherwise, a modified Fisher's Exact Test is reported.[24] One-tailed *P* values are reported when there is a strong a priori prediction from our previous work[12-17] or from the literature.[1,2] Biological relatives in this sample are of two different types: first-degree relatives (parents and full siblings) and second-degree relatives (maternal and paternal half siblings). Because the percentage of first- and second-degree relatives is similar in the biological relatives of the index and control adoptees, collapsing the two together into a single contingency table for statistical analysis can be justified. As this approach is not ideal, we also performed logistic regression analyses in which proband status, relative type (first- vs second-degree), and their interaction could be separately tested, by a likelihood ratio χ^2 test (two-tailed *P* values), for their ability to predict diagnosis in relatives.[25]

article, we first report the results of that review and then combine those results with our earlier findings from the Copenhagen sample to present *DSM-III* diagnoses in adoptees and interviewed relatives from the national Danish Adoption Study.

RESULTS

THE PROVINCIAL SAMPLE

Index Adoptees

Adequate diagnostic information was available for all 42 index adoptees, who were assigned the following primary *DSM-III* diagnoses: schizophrenia in 19, schizoaffective disorder (mainly schizophrenic type) in two, SPD in 10, atypical psychosis in two, major depression in three (two with and one without psychotic features), atypical bipolar disorder in two, and obsessive-compulsive disorder, antisocial personality disorder, borderline personality disorder, and no psychiatric diagnosis in one each. By our a priori criteria, 31 of the index adoptees were in the schizophrenia spectrum and 11 were not.

Control Adoptees

The interview status of the 42 control adoptees was as follows: completed interview in 37, inadequate interview report in three, and no personal interview in two. Of the 37 control adoptees with adequate interview information, 25 had no psychiatric diagnosis, while the remaining 12 had the following primary diagnoses: major depression in six, anxiety disorder in five, and SPD in one.

Biological Relatives

The 42 index adoptees had 178 interviewed biological relatives of whom 38 were parents, 22 were full siblings, 63 were paternal half siblings, and 55 were maternal half siblings. The 42 control adoptees had 162 interviewed biological relatives of whom 42 were parents, 18 were full siblings, 51 were paternal half siblings, and 51 were maternal half siblings. Compared with the biological relatives of the control adoptees, the percentage of first- vs second-degree relatives did not differ significantly in the biological relatives of all index adoptees (χ^2=0.41) or in only the schizophrenia spectrum index adoptees (χ^2=0.01). The mean (±SD) age at interview of all biological relatives of control adoptees did not differ significantly from that for the biological relatives of index adoptees (43.9±15.4 vs 46.6±14.1 years, respectively; *t*=1.68).

Adoptive Relatives

The 42 index adoptees had 41 interviewed adoptive relatives of whom 26 were parents and 15 were siblings. The 42 control adoptees had 54 interviewed adoptive relatives of whom 34 were parents and 20 were siblings. The mean (±SD) age at interview of the adoptive relatives of the control adoptees did not differ significantly from that found for the adoptive relatives of all the index adoptees (62.7±19.2 vs 63.3±16.6 years, respectively; *t*=0.16).

Distribution of Schizophrenia Spectrum Disorders in Biological Relatives

The distribution of schizophrenia spectrum disorders in all biological relatives of the spectrum and nonspectrum *index* adoptees is seen in **Table 1**. At a trend level, the prevalence of schizophrenia spectrum disorders is higher in the biological relatives of spectrum adoptees than in the biological relatives of nonspectrum index adoptees (10.7% vs 2.6%, respectively; χ^2=2.39; *P*=.06; one-tailed). Of the nonspectrum adoptees, three had psychotic disorders, all diagnosed as atypical psychosis. No schizophrenia spectrum disorders were found in the 16 biological relatives of these "psychotic nonspectrum" index adoptees (vs biological relatives of spectrum adoptees; χ^2=1.90; *P*=.08; one-tailed).

The distribution of schizophrenia spectrum disorders in the biological relatives of the schizophrenic and spectrum index adoptees and the biological relatives of all control adoptees is compared in **Table 2**. A trend is seen toward a higher prevalence of schizophrenia spectrum disorders in the biological relatives of the schizophrenic adoptees vs in the biological relatives of all control adoptees (8.0% vs 3.7%, respectively; χ^2=2.09; *P*=.07; one-tailed). Although not shown, the prevalence of schizophrenia spectrum disorders in the biological relatives of the adoptees with schizoaffective disorder, mainly schizophrenic type, and SPD are both significantly greater than that found in the biological relatives of all control adoptees (χ^2=4.90, *P*=.01 and χ^2=7.03, *P*=.004, respectively, both one-tailed). Taken all together, the prevalence of schizophrenia spectrum disorders in the biological relatives of *all* the spectrum adoptees vs *all* control adoptees is highly significantly different (10.7% vs 3.7%, respectively; χ^2=5.70; *P*=.008; one-tailed).

The distribution of broadly defined schizophrenia spectrum disorders in only the first-degree and only the second-degree biological relatives of the schizophrenic and spectrum index adoptees and the biological relatives of all control adoptees is compared in **Table 3**. Several results are noteworthy. First, the prevalence of spectrum disorders is much greater in the first-degree than in the second-degree biological relatives of schizophrenic and of spectrum adoptees. For example, the rate of spectrum disorder in first-degree biological relatives of spectrum adoptees is 19.6% vs 5.6% in second-degree relatives (χ^2=6.63, *P*=.01, two-tailed). Unexpectedly, a

Table 1. Schizophrenia Spectrum Disorders in *All* Interviewed Biological Relatives of *Index* Adoptees From the *Provincial* Sample*

Adoptee's Diagnosis	No. of Subjects	Relative's Diagnosis, No. (%) Schizophrenia	SAD, MS	SPD	Schiz Spectrum
Schizophrenia Spectrum					
Schizophrenia	88	2 (2.3)	1 (1.1)	4 (4.5)	7 (8.0)
SAD, MS	11	1 (9.1)	0 (0)	1 (9.1)	2 (18.2)
SPD	41	0 (0)	1 (2.4)	5 (12.2)	6 (14.6)
Total	**140**	**3** (2.1)	**2** (1.4)	**10** (7.1)	**15** (10.7)
Nonspectrum					
Total	38	0 (0)	0 (0)	1 (2.6)	1 (2.6)

**SAD, MS indicates schizoaffective disorder, mainly schizophenic subtype; SPD, schizotypal personality disorder; and schiz spectrum, schizophrenia spectrum.*

Table 2. Schizophrenia Spectrum Disorders in *All* Interviewed Biological Relatives of Schizophrenic, Spectrum, and *All* Control Adoptees From the *Provincial* Sample*

Adoptee's Diagnosis	No. of Subjects	Relative's Diagnosis, No. (%) Schizophrenia	SAD, MS	SPD	Schiz Spectrum
Schizophrenia	88	2 (2.3)†	1 (1.1)	4 (4.5)‡	7 (8.0)§
Schiz spectrum	140	3 (2.1)‖	2 (1.4)	10 (7.1)¶	15 (10.7)#
Controls	162	1 (0.6)	0 (0)	5 (3.1)	6 (3.7)

**Abbreviations are explained in the footnote to Table 1.*
†*Versus controls, χ^2=1.32; P=.13.*
‡*Versus controls, χ^2=0.34; P=.27.*
§*Versus controls, χ^2=2.09; P=.07.*
‖*Versus controls, χ^2=1.34; P=.12.*
¶*Versus controls, χ^2=2.62; P=.05.*
#*Versus controls, χ^2=5.70; P=.008.*

Table 3. Schizophrenia Spectrum Disorders in Interviewed *First- and Second-Degree* Biological Relatives of Schizophrenic, Spectrum, and *All* Control Adoptees From the *Provincial* Sample*

Adoptee's Diagnosis	No. of Subjects	Degree of Relationship	Relative's Diagnosis, No. (%)			
			Schizophrenia	SAD, MS	SPD	Schiz Spectrum
Schizophrenia	28	1st	2 (7.1)†	0 (0)	3 (10.7)‡	5 (17.9)§
	60	2nd	0 (0)	1 (1.7)	1 (1.7)‖	2 (3.3)¶
Schiz spectrum	51	1st	2 (3.9)#	1 (2.0)	7 (13.7)**	10 (19.6)††
	89	2nd	1 (1.1)	1 (1.1)	3 (3.4)‡‡	5 (5.6)§§
Controls	60	1st	1 (1.7)	0 (0)	3 (5.0)	4 (6.7)
	102	2nd	0 (0)	0 (0)	2 (2.0)	2 (2.0)

**Abbreviations are explained in the footnote to Table 1.*
†χ^2=1.74; P=.09, vs relatives of controls within same degree of relationship.
‡χ^2=0.98; P=.16, vs relatives of controls within same degree of relationship.
§χ^2=2.60; P=.05, vs relatives of controls within same degree of relationship.
‖χ^2=0.02, P=,89, vs relatives of controls within same degree of relationship.
¶χ^2=0.30; P=.29, vs relatives of controls within same degree of relationship.
#χ^2=0.53; P=.23, vs relatives of controls within same degree of relationship.
***χ^2=2.56; P=.05, vs relatives of controls within same degree of relationship.*
††χ^2=4.19; P=.02, vs relatives of controls within same degree of relationship.
‡‡χ^2=0.37, P=.54, vs relatives of controls within same degree of relationship.
§§χ^2=1.80; P=.09, vs relatives of controls within same degree of relationship.

similar but nonsignificant trend is seen in the biological relatives of control adoptees.

Second, when examining only first-degree biological relatives, we find considerable evidence for the genetic transmission of spectrum disorders, in particular, (1) schizophrenia aggregates in relatives of schizophrenic adoptees (*P*=.09), (2) spectrum disorders aggregate in relatives of schizophrenic adoptees (*P*=.05), (3) SPD aggregates in relatives of spectrum adoptees (*P*=.05), and (4) spectrum disorders aggregate in relatives of spectrum adoptees (*P*=.02). A considerable portion of the evidence for genetic transmission of spectrum conditions is a result of the significant increased prevalence of SPD in the first-degree biological relatives of adoptees with a diagnosis of SPD (4 [19%] of 21) vs first-degree relatives of all controls (5.0%; χ^2=3.89, *P*=.02, one-tailed).

Third, there is only a weak and nonsignificant trend for increased rates for spectrum disorders in second-degree biological relatives of schizophrenic vs control adoptees and only modest evidence for an increased rate for spectrum disorders in second-degree biological relatives of all spectrum adoptees (*P*=.09, one-tailed).

It is of interest to compare the pattern of disorders in the two classes of first-degree relatives, parents, and full siblings because of the empirical finding, predicted by the decreased fitness of schizophrenic individuals, that schizophrenia is much less common in parents than in siblings of schizophrenic probands.[1,26] These results are replicated in the Provincial sample. Of the three cases of schizophrenia or schizoaffective disorder (mainly schizophrenic type) seen in the first-degree biological relatives of the spectrum adoptees, all three are in the 22 full siblings and none in the 29 parents (23.6% vs 0%, respectively; χ^2=4.20; *P*=.02; one-tailed).

The frequencies of spectrum disorders in the relatives of index and control probands were also analyzed by logistic regression. Examining schizophrenia spectrum disorders in the biological relatives of *schizophrenic* vs all control adoptees, we found a highly significant effect of "degree" (first vs second) (χ^2=7.54, *P*=.006), a marginal effect for proband status (schizophrenic vs control) (χ^2=2.65, *P*=.10), and no significant interaction (χ^2=0.21). Examining schizophrenia spectrum disorders in the biological relatives of *schizophrenia spectrum* vs all control adoptees, we found a highly significant effect of "degree" (first vs second) (χ^2=8.96, *P*=.003), a significant effect for proband status (schizophrenic vs control) (χ^2=5.97, *P*=.01), and no significant interaction (χ^2=0.02).

Narrowly Defined Diagnoses

Up until now, results were presented using broadly defined diagnoses. Using more narrowly defined diagnoses (ie, those made at only the definite or probable level), the prevalence of spectrum conditions in all biological relatives of schizophrenic, spectrum, and all control adoptees was five (5.7%) of 88, 10 (7.1%) of 140, and three (1.9%) of 162, respectively (relatives of schizophrenic vs control adoptees: χ^2=2.70, *P*=.05, one-tailed; relatives of spectrum vs control adoptees: χ^2=5.10, *P*=.01, one-tailed). Thus, the percentages of broadly defined schizophrenia spectrum disorders that met narrow criteria in the biological relatives of the schizophrenic, schizophrenic spectrum, and control adoptees were 71%, 67%, and 50%, respectively. In general, using narrower diagnostic criteria modestly increased the evidence for the genetic transmission of spectrum disorders.

Table 4. Nonschizophrenia Spectrum Disorder in *All* Interviewed Relatives of Schizophrenia Spectrum and *All* Control Adoptees From the *Provincial* Sample*

Adoptee's Diagnosis	No. of Subjects	Relative's Diagnosis, No. (%) Major Depression	Anxiety Disorder	Alcoholism
1st- and 2nd-Degree Relatives				
Schizophrenia	88	13 (14.8)	10 (11.4)	9 (10.2)†
Schizophrenia spectrum	140	15 (10.7)	18 (12.9)	11 (7.9)
Controls	162	18 (11.1)	19 (11.7)	6 (3.7)
1st-Degree Relatives				
Schizophrenia	28	7 (25.0)	5 (17.9)	3 (10.7)
Schizophrenia spectrum	51	9 (17.6)	10 (19.6)	4 (7.8)
Controls	60	6 (10.0)	11 (18.3)	2 (3.3)

**Diagnoses made nonhierarchically.*
†Significantly different at P<.05 from prevalence in the relatives of control adoptees.

Morbid Risk for Schizophrenia

Since schizophrenia has a variable age at onset, for many purposes lifetime prevalence is not as useful as morbid risk (MR). We present, calculated using the abridged Weinberg method (age of risk of 15 to 39 years), the MRs (±SE) for schizophrenia in all biological relatives of the following proband groups: all index adoptees—3 of 145=2.1%±1.2%; all control adoptees—1 of 120=0.8%±0.8%; schizophrenia spectrum adoptees—3 of 112.5=2.7%±1.5%; and schizophrenic adoptees—2 of 69.5=2.9%±2.0%. The MR (±SE) for schizophrenia in the first-degree biological relatives of the schizophrenia spectrum and schizophrenic adoptees was, respectively, 2 of 49.5=4.0%±2.8% and 2 of 26.5=7.5%±5.1%. In second-degree biological relatives of the schizophrenia spectrum adoptees, the MR for schizophrenia was 1 of 63=1.6%±1.6%.

Nonspectrum Diagnoses in Biological Relatives

The lifetime prevalence of major depression, anxiety disorder, and alcoholism diagnosed nonhierarchically in all relatives and in only first-degree relatives of the schizophrenic, schizophrenia spectrum, and all control adoptees is seen in **Table 4**. No significant differences are seen in the rates of either major depression or anxiety disorder in relatives of schizophrenic or schizophrenia spectrum vs control adoptees. However, the prevalence of alcoholism (alcohol abuse and alcohol dependence) is significantly greater in all biological relatives of schizophrenic adoptees (10.2%±3.2%) than in all biological relatives of controls (3.7%±1.5%) (χ^2=4.30, *df*=1, *P*=.04). A similar trend is seen in comparing all relatives of schizophrenia spectrum adoptees and controls or just first-degree relatives of schizophrenic and control adoptees, but these differences did not reach statistical significance.

Adoptive Relatives

No schizophrenia spectrum diagnosis was given to any interviewed adoptive relative in the Provincial sample. In the interviewed adoptive relatives of schizophrenic, schizophrenia spectrum, and control adoptees, no significant differences were seen in the prevalence rates of major depression (11.1%, 13.3%, and 7.4%, respectively), anxiety disorders (11.1%, 6.7%, and 5.6%, respectively) or alcoholism (5.6%, 3.3%, and 3.7%, respectively).

THE NATIONAL SAMPLE

Because our diagnostic reviews of the Copenhagen and Provincial samples were carried out by the same diagnosticians (K.S.K. and A.M.G.) using the same criteria (*DSM-III*), it is appropriate to combine results into a single National sample. Before this, however, it is of interest to examine the possible differences in the two samples.

The rates for schizophrenia, SPD, and total spectrum disorders were lower in the biological relatives of the schizophrenic and schizophrenia spectrum adoptees in the Provincial than in the Copenhagen sample. For the individual schizophrenia spectrum diagnoses, the only significant difference was a higher frequency of SPD in second-degree relatives of schizophrenic adoptees in the Copenhagen sample (χ^2=4.20, *df*=1, *P*=.04). However, examining together all the schizophrenia spectrum diagnoses produced significantly higher rates in the Copenhagen vs Provincial sample for all the biological relatives of the schizophrenic adoptees (χ^2=6.98, *df*=1, *P*=.01) and of the schizophrenia spectrum adoptees (χ^2=4.57, *df*=1, *P*=.03). Interestingly, no significant difference for total spectrum disorders was found in first-degree biological relatives in the two samples; but in second-degree relatives, all spectrum disorders were significantly more common in relatives of the schizophrenic (χ^2=6.49, *df*=1, *P*=.01) and the schizophrenia spectrum adoptees (χ^2=5.02, *df*=1, *P*=.03) in the Copenhagen vs Provincial sample.

Biological Relatives—Schizophrenia Spectrum Disorders

Table 5 presents the frequency of broadly defined schizophrenia spectrum disorders in all biological relatives of schizophrenic, schizophrenia spectrum, and control adoptees in the National sample. This table also reports traditional χ^2 analysis of differences in frequency of disorders in the various groups of relatives. In the National sample, the percentage of first- vs second-degree relatives is similar for control adoptees and schizophrenia spectrum adoptees (χ^2=0.58, not significant); therefore, combining results from both groups of relatives is probably appropriate.

Table 5. Schizophrenic Spectrum Disorders in *All* Interviewed Biological Relatives of Schizophrenic Spectrum and Control Adoptees From the *National* Sample*

Adoptee's Diagnosis	No. of Subjects	Relative's Diagnosis, No. (%)				
		Schizophrenia	SAD, MS	SPD	PPD	Schiz Spectrum
Schizophrenia Spectrum						
Schizophrenia	123	4 (3.3)†	1 (0.8)	9 (7.3)†	2 (1.6)	16 (13.0)‡
SAD, MS	39	2 (5.1)†	0 (0)	3 (7.7)§	0 (0)	5 (12.8)†
SPD	47	0 (0)	1 (2.1)	7 (14.9)‡	1 (2.1)	9 (19.1)‡
Total	**209**	**6** (2.9)†	**2** (1.0)	**19** (9.1)‡	**3** (1.4)	**30** (14.4)‡
Controls						
Total	299	1 (0.3)	0 (0)	7 (2.3)	1 (0.3)	9 (3.0)

**Abbreviations are explained in the footnote to Table 1. In addition, PPD indicates paranoid personality disorder.*
†P<.01, vs controls (one-tailed).
‡P<.0001, vs controls (one-tailed).
§P<.05, vs controls (one-tailed).

Because of the larger available sample size, we present results separately for relatives of index adoptees with schizophrenia, schizoaffective disorder (mainly schizophrenic type), and SPD, as well as for all of these together.

Compared with biological relatives of control adoptees, biological relatives of schizophrenic, schizoaffective disorder (mainly schizophrenic), and all schizophrenia spectrum adoptees have a significantly greater prevalence of schizophrenia (Table 5). Biological relatives of adoptees with schizophrenia, SPD, and all spectrum disorders also have, compared with biological relatives of controls, a significantly elevated risk for SPD. The prevalence of SPD is more than twice as high in biological relatives of schizotypal adoptees than in biological relatives of schizophrenic adoptees (14.9% vs 7.3%, respectively), although this difference is not statistically significant (χ^2=2.29, *df*=1).

In addition, logistic regression was used in the National sample to examine separately the impact of degree of relationship and adoptee status (index vs control) on risk for schizophrenia or schizophrenia spectrum in relatives (all *df*=1; all *P* values two-tailed). Predicting risk for schizophrenia in relatives of schizophrenic vs control adoptees, degree of relationship (χ^2=5.49, *P*=.02) and adoptee status (χ^2=7.26, *P*=.007) were significant, but their interaction was not (χ=0.24). A similar pattern was found in predicting spectrum disorders in these relatives: degree (χ^2=6.84, *P*=.009), adoptee status (χ^2=17.09, *P*<.0001), interaction (χ^2=0.22, not significant).

Examining relatives of schizophrenia spectrum vs control adoptees, the risk for schizophrenia was only predicted by adoptee status (χ^2=6.09, *P*=.01), as the effect of degree of relationship and the interaction were both nonsignificant (χ^2=1.89 and 0.76, respectively). The risk for schizophrenia spectrum in these relatives was significantly predicted by degree of relationship (χ^2=8.41, *P*=.04) and adoptee status (χ^2=23.65, *P*<.0001). Again, their interaction was nonsignificant (χ^2=0.06).

Results for only first-degree and only second-degree biological relatives in the National sample are seen in **Table 6**. Compared with relatives of controls, first-degree relatives of schizophrenic adoptees are at significantly increased risk for schizophrenia, SPD, and all spectrum disorders. First-degree relatives of schizotypal adoptees are at significantly increased risk for SPD and all spectrum disorders. The prevalence of spectrum disorders in first-degree relatives of all spectrum adoptees is highly significantly greater than in first-degree relatives of control adoptees (23.5% vs 4.7%, respectively; χ^2=15.00; *df*=1; *P*=.00005; one-tailed).

Compared with second-degree relatives of control adoptees, second-degree relatives of schizophrenic adoptees are at significantly increased risk only for all spectrum disorders. Second-degree relatives of adoptees with a diagnosis of schizoaffective disorder (mainly schizophrenic subtype) are, by contrast, at significantly increased risk for schizophrenia, SPD, and all spectrum disorders. Second-degree relatives of schizotypal adoptees are at significantly increased risk for SPD and all spectrum disorders. The prevalence of spectrum disorders in second-degree relatives of all spectrum adoptees is also highly significantly greater than in the second-degree relatives of control adoptees (9.9% vs 2.1%, respectively; χ^2=13.04; *df*=1; *P*=.0002; one-tailed).

Comparing the risk in maternal vs paternal half siblings may provide information regarding the possibility of intrauterine or early postnatal effects in the transmission of schizophrenia spectrum disorders. A modest trend was found for the prevalence of schizophrenia spectrum disorders to be greater in the maternal vs paternal half siblings of the schizophrenic adoptees (5 of 37 vs 2 of 48, respectively; χ^2=2.42; not significant). However, this trend disappeared when the sample was expanded to consider maternal vs paternal half siblings of all schizophrenia spectrum adoptees (8/65 vs 6/76, respectively; χ^2=0.76; not significant).

Table 6. Schizophrenia Spectrum Disorders in Interviewed *First- and Second-Degree* Biological Relatives of Schizophrenic, Spectrum, and *All* Control Adoptees From the *National* Sample*

Adoptee's Diagnosis	No. of Subjects	Degree of Relationship	Relatives Diagnosis, No. (%)				
			Schizophrenia	SAD, MS	SPD	PPD	Schiz Spectrum
Schizophrenia Spectrum							
Schizophrenia	38	1st	3 (7.9)	0 (0)	5 (13.2)	1 (2.6)	9 (23.7)‡
	85	2nd	1 (1.2)	1 (1.2)	4 (4.7)	1 (1.2)	7 (8.2)‡
SAD, MS	7	1st	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	32	2nd	2 (6.3)	0 (0)	3 (9.4)‡	0 (0)	5 (15.6)†
SPD	23	1st	0 (0)	1 (4.3)	5 (21.7)‡	1 (4.3)	7 (30.4)§
	24	2nd	0 (0)	0 (0)	2 (8.3)‖	0 (0)	2 (8.3)‖
Totals	**68**	1st	**3** (4.4)	**1** (1.5)	**10** (14.7)‡	**2** (2.9)‖	**16** (23.5)§
	141	2nd	**3** (2.1)‖	**1** (0.7)	**9** (6.4)	**1** (0.7)	**14** (9.9)†
Controls							
Totals	107	1st	1 (0.9)	0 (0)	4 (3.7)	0 (0)	5 (4.7)
	192	2nd	0 (0)	0 (0)	3 (1.6)	1 (0.5)	4 (2.1)

*Abbreviations are explained in the footnote to Table 1. In addition, PPD indicates paranoid personality disorder.
†P<.001, vs relatives of controls within same degree of relationship (one-tailed).
‡P<.01, vs relatives of controls within same degree of relationship (one-tailed).
§P<.0001, vs relatives of controls within same degree of relationship (one-tailed).
‖P<.05, vs relatives of controls within same degree of relationship (one-tailed).

Using the abridged Weinberg method, the MRs (±SEs) for schizophrenia in the first- and second-degree relatives of the schizophrenic adoptees in the National sample equal, respectively, 3 of 36=8.3%±4.6% and 1 of 58=1.7%±1.7%. The MRs (±SEs) for schizophrenia in the first- and second-degree relatives of all spectrum adoptees in the National sample are, respectively, 3 of 65.5=4.6%±2.6% and 3 of 91.5=3.3%±1.9%.

Each index adoptee selected by Kety et al[4] was matched to a control adoptee. It can be argued that this matching should be used in the statistical analysis. The National sample contained 26 matched index-control biological families in which the index adoptee had a diagnosis of schizophrenia and in which at least one biological relative was interviewed. One or more cases of schizophrenia spectrum disorder were diagnosed in 10 of the index biological families vs in two of the control biological families (McNemar's χ^2=5.33, df=1, P=.01, one-tailed). There were 44 index-control pairs in which the index adoptee had a schizophrenia spectrum diagnosis. One or more cases of schizophrenia spectrum disorder were found in 20 of the index vs in six of the control biological families (McNemar's χ^2=8.91, df=1, P=.001, one-tailed).

In the National sample, there were 13 index adoptees with a nonaffective psychosis that did not meet criteria for a schizophrenia spectrum disorder (atypical psychosis in six; schizophreniform disorder in five; delusional disorder in one; schizoaffective disorder, other subtype in one). These "psychotic nonspectrum" adoptees had 47 biological relatives in whom only one (2.1%±2.1%) had a schizophrenia spectrum disorder. This prevalence is similar to that found in the biological relatives of controls and significantly lower than that found in the relatives of schizophrenia spectrum adoptees (χ^2=5.39, P=.01, one-tailed).

Biological Relatives—Nonschizophrenia Spectrum Disorders

Alcoholism was not recorded as a diagnosis in the Copenhagen sample, so our comparison is restricted to anxiety disorders and major depression. The prevalence rates (±SE) of major depression in all biological relatives of controls in the National sample (30 of 299=10.0%±1.7%) does not differ significantly from that found in all biological relatives of schizophrenic (15 of 123=12.2%±3.0%; χ^2=0.43) or schizophrenia spectrum adoptees (18 of 209=8.6%±1.9%; χ^2=0.30). The prevalence of major depression in the biological relatives of the mainly schizophrenic schizoaffective disorder adoptees (1 of 39=2.6%±2.6%) was nonsignificantly lower than that found in biological relatives of controls (χ^2=2.31).

For anxiety disorders, the rates were also quite similar in all biological relatives of controls (40 of 299=13.4%±2.0%) vs relatives of schizophrenic adoptees (14 of 123=11.4%±2.9%; χ^2=0.31, not significant) and schizophrenia spectrum adoptees (26 of 209=12.4%±2.3%; χ^2=0.10, not significant).

Adoptive Relatives

Only two cases of schizophrenia spectrum disorders were diagnosed in adoptive relatives in the National sample and

both of these were personality disorders (one paranoid and one schizotypal). The prevalence rates (±SE) of schizophrenia spectrum disorders in the adoptive relatives of all control adoptees (1 of 102=1.0%±1.0%) was not different from that found in the adoptive relatives of schizophrenic (0 of 30) or schizophrenia spectrum adoptees (1 of 51=2.0%±2.0%). There were 15 adoptive siblings of schizophrenia spectrum adoptees and eight adoptive siblings of schizophrenic adoptees in the National sample; none of them was given a schizophrenia spectrum diagnosis.

The prevalence rates (±SE) of major depression in the adoptive relatives of all control adoptees (8 of 102=7.8%±2.7%) did not differ significantly from that found in the adoptive relatives either of the schizophrenic (2 of 30=6.7%±4.6%; χ^2=0.05) or of the schizophrenia spectrum adoptees (4 of 51=7.8%±3.8%; χ^2=0.00). The prevalence rates (±SE) of anxiety disorder in the adoptive relatives of all control adoptees (13 of 102=12.7%±3.3%) did not differ significantly from that found in the adoptive relatives either of the schizophrenic (5 of 30=16.7%±6.8%; χ^2=0.30) or of the schizophrenia spectrum adoptees (8 of 51=15.7%±5.1%; χ^2=0.25).

COMMENT

In this study, we blindly applied *DSM-III* criteria to adoptees and their interviewed biological and adoptive relatives in the Provincial sample of the Danish Adoption Study of Schizohrenia conducted by Kety et al.[7] We reported these results and then, combining them with those reported previously for the Copenhagen sample, examined the results on *DSM-III* diagnoses in the adoptees and interviewed relatives in the National adoption sample.

THE SCHIZOPHRENIA SPECTRUM

Schizophrenia

In the Provincial sample, the frequency of schizophrenia was greater in the biological relatives of the schizophrenic and schizophrenia spectrum adoptees than in the biological relatives of the control adoptees, but these differences were not statistically significant. Power calculations suggest, however, that nonsignificant results are not unexpected. If the risks for schizophrenia in first- and second-degree relatives of the schizophrenic and control adoptees were 4.0% and 1.0%, respectively, the power of this sample to show a significant difference ($P<.05$, one-tailed) is only 48%.[27]

When the Provincial and Copenhagen samples are combined into the National sample, however, the frequency of *DSM-III* schizophrenia in the biological relatives of schizophrenic adoptees is significantly greater than in the biological relatives of the control adoptees. These results strongly support the hypothesis that the vulnerability to *DSM-III* schizophrenia is genetically transmitted. No significant difference was found in the risk of maternal and paternal half siblings of the schizophrenic or schizophrenia spectrum adoptees, although the statistical power to detect such a difference is modest in this sample. This result suggests that the transmission of *DSM-III* schizophrenia is due to genetic factors rather than shared maternal influences on the intrauterine or early postnatal environment.

Schizoaffective Disorder

In the Provincial sample, the prevalence of schizophrenia spectrum disorders in the biological relatives of the adoptees with schizoaffective disorder, mainly schizophrenic subtype, significantly exceeded that found in the biological relatives of control adoptees. Combining results to form the National sample, schizophrenia alone, as well as all schizophrenia spectrum disorders, but not major depression, were significantly more common in the biological relatives of adoptees with mainly schizophrenic schizoaffective disorder vs control adoptees.

Similar to *DSM-III-R*,[11] our diagnostic approach to schizoaffective disorder emphasizes the chronologic relationship between affective and psychotic features, this disorder being diagnosed only when psychotic symptoms are present for at least 1 week, when the patient is no longer suffering from prominent affective features. Our results, as well as those of a number of recent family studies,[26,28-32] suggest that, when so diagnosed, schizoaffective disorder has a close familial/genetic relationship with schizophrenia and the schizophrenia spectrum. In accord with some,[30] but not other recent family studies,[28,31,33] we failed to find evidence for a familial/genetic relationship between mainly schizophrenic schizoaffective disorder and unipolar affective illness.

Schizotypal Personality Disorder

The original Copenhagen Danish adoption studies were the first controlled blind investigation to report an excess of nonpsychotic schizophrenialike syndromes (termed "latent," "borderline," and/or "uncertain" schizophrenia) in the biological relatives of schizophrenic adoptees.[3,4] Based in large measure on these studies, and using criteria derived from interviews from the Copenhagen sample, Spitzer et al[34] proposed criteria for a new diagnostic entity: SPD.

Our analysis of the Copenhagen sample found, using *DSM-III* criteria, that SPD strongly aggregated in the biological relatives of schizophrenic and schizophrenia spectrum adoptees.[12,13] Most,[31,35-38] but not all,[39] family studies that have examined this question have also found evidence for a familial/genetic link between schizophrenia and SPD.

In the Provincial sample, we found higher rates for SPD in the biological relatives of schizophrenic and schizophrenia spectrum adoptees. However, this difference only

reached statistical significance for relatives of schizotypal and all schizophrenia spectrum adoptees. Interestingly, the excess risk for SPD in the relatives of the index adoptees in the Provincial sample was restricted to first-degree relatives. Only minor differences in risk for SPD were found in second-degree relatives.

While the results of the Provincial sample are consistent with previous studies suggesting a genetic relationship between SPD and schizophrenia, the findings are less striking than those of the Copenhagen sample or several recent family studies. Nonetheless, when the results of the Provincial and Copenhagen samples are combined into the National sample, the results show a highly significant increased risk for SPD in the relatives of the schizophrenic adoptees.

One unexpected result, seen in the Provincial and Copenhagen samples,[12] was the higher prevalence of SPD in the biological relatives of schizotypal adoptees than in the biological relatives of schizophrenic adoptees. This finding, although falling short of statistical significance, is contrary to the popular conceptual model in which SPD represents a "less severe" variant of schizophrenia. This model predicts that the rate for SPD should be *greater* in relatives of schizophrenic vs schizotypal probands. These results, consistent with findings from twin and family studies suggesting substantial heritability for schizotypal traits,[40-44] suggest that the genetic liability to schizotypal traits may in part be transmitted independently of the vulnerability to schizophrenia.

Schizophrenia Spectrum

Results from the application of *DSM-III* criteria to the Provincial and National samples provide strong support for the hypothesis of a genetic "schizophrenia spectrum." Specifically, these findings suggest that mainly schizophrenic schizoaffective disorder and SPD have a strong genetic relationship with schizophrenia. The results for paranoid personality disorder, although suggestive, are less clear. Our findings confirm, using a different diagnostic system, a key finding from the original analysis of the Copenhagen sample by Kety and coworkers[3,4] and support the wisdom of their sampling strategy for probands, in which they included a wide variety of schizophrenia-like syndromes.

NONSPECTRUM DISORDERS

Nonspectrum Psychotic Disorders

In the Copenhagen and Provincial samples, index adoptees were found with a nonaffective psychotic disorder that did not meet criteria for schizophrenia or schizoaffective disorder (mainly schizophrenic subtype). The rate of schizophrenia spectrum disorders in the biological relatives of these adoptees was similar to that found in relatives of controls and significantly lower than that found in relatives of the schizophrenia spectrum adoptees. This result suggests that these generally acute and good-prognosis psychotic disorders have little genetic relationship with the schizophrenia spectrum. This finding is not consistent with those of several recent large-sample family studies that suggest a familial relationship between schizophrenia and these nonschizophrenic, nonaffective psychoses.[26,31,32,45,46]

Depression

In the Provincial sample, a nonsignificant excess rate of major depression was found in the first-degree biological relatives of schizophrenic vs control adoptees. However, this trend was not found in the biological relatives of the schizophrenia spectrum adoptees. When results of the Provincial and Copenhagen samples were combined into the National sample, the rates of depression were very similar in the biological relatives of the control, schizophrenic, and schizophrenia spectrum adoptees. Overall, applying *DSM-III* criteria to this adoption sample, our results suggest, consistent with most,[33,36,37,39,45,47] but not all,[31,48,49] recent controlled studies using operationalized criteria, that schizophrenia and major depression have little or no familial/genetic relationship. Too few cases of bipolar disorder were found in the biological relatives in the National sample to provide useful information regarding the genetic relationship between schizophrenia and bipolar disorder.

Anxiety Disorder and Alcoholism

Applying *DSM-III* criteria to the Provincial sample, as in the Copenhagen sample, no significant difference was found in the prevalence of anxiety disorder in the biological relatives of the schizophrenic, schizophrenia spectrum, or control adoptees. Consistent with the results of all five recent controlled family studies,[31,33,36,37,45] these results indicate that schizophrenia and anxiety disorders have no substantial familial/genetic relationship.

In the Provincial adoption study, we found modest evidence of an increased risk for alcoholism in the biological relatives of schizophrenic vs control adoptees. This result just reached traditional levels of statistical significance when considering all cases. Examining either relatives of the schizophrenia spectrum adoptees or only cases in the nonschizophrenia spectrum relative, the result was no longer statistically significant.

An examination by Rimmer and Jacobsen[50] of interviewed relatives in the Copenhagen sample revealed nonsignificantly *lower* rates of alcoholism in the biological relatives of index vs control adoptees. Of the six recent controlled family or family history studies of schizophrenia reporting data on alcoholism in relatives, five found no significant difference in risk in the relatives of

schizophrenics vs controls,[31,33,35-37] whereas one found a significantly *lower* risk for alcoholism in the relatives of the schizophrenic vs control probands.[45] Clearly, further work is required to clarify the familial relationship between schizophrenia and alcoholism.

Adoptive Relatives

Consistent with results from the Copenhagen sample, the Provincial sample provided no evidence for the familial/environmental transmission of schizophrenia or schizophrenia spectrum disorders as defined by *DSM-III*. In the National sample, the rates of schizophrenia spectrum disorders were low and equal in the adoptive relatives of the schizophrenic and control adoptees. These results, which are consistent with those of previous adoption studies,[1,51] must be interpreted from the perspective of two potential limitations, both of which stem from the fact that more than 70% of the interviewed adoptive relatives were parents. First, adoptive parents are unlikely to suffer from early onset of severe forms of psychopathology because of the screening they undergo by adoptive agencies before child placement. While this bias should equally affect adoptive families of schizophrenic and control adoptees, it could lower the base rates of schizophrenia spectrum disorders sufficiently to give any test of differences in rates very low power.

SECOND, EXAMINING rates of schizophrenia spectrum disorders in adoptive parents only tests *direct* cultural transmission, which assumes that it is schizophrenia spectrum disorders in adoptive parents that would be schizophrenogenic. Another family of environmental models for *indirect* cultural transmission would postulate that the schizophrenogenic aspects of the familial environment are not captured by diagnoses in individual adoptive relatives of schizophrenia spectrum disorders.[52] However, models for *direct* and *indirect* cultural transmission of schizophrenia spectrum disorders would predict elevated rates of spectrum illness in adoptive siblings of schizophrenic or schizophrenia spectrum adoptees,[52] which were not seen in the modest number of such individuals contained in the National sample. Although our results provide no evidence for nongenetic familial transmission of schizophrenia, the power of these analyses, particularly for models of indirect cultural transmission, may be low.

DIFFERENCES BETWEEN THE COPENHAGEN AND PROVINCIAL SAMPLES

The risk for schizophrenia spectrum disorders by *DSM-III* was significantly lower in the biological relatives of the spectrum adoptees in the Provincial vs the Copenhagen sample. While this might be a true difference, for example resulting from the greater urbanization of the Copenhagen sample, three other explanations deserve consideration. First, criteria for SPD were developed in part from interviews of the Copenhagen sample.[34] It is possible that reapplying these criteria to the data set from which they were derived produced an artifactually elevated rate of illness in the biological relatives of the spectrum adoptees. Second, the diagnosticians (K.S.K. and A.M.G.) may have become more conservative in their application of criteria in the more than 10 years between reviews of the two samples. Third, the results could be due to sampling fluctuation. Most of the differences between the risk for spectrum disorders is found in the second-degree relatives of spectrum adoptees in the Provincial vs Copenhagen sample. This pattern is difficult to explain from any systematic effect.

COMPARISON OF OUR RESULTS WITH THOSE OF THE ORIGINAL INVESTIGATORS

An adverse effect of our independent approach to the diagnostic review and analysis of the Danish adoption studies is that it prevents any simple comparison between our findings and those of the original investigators.[7] Aside from differences in diagnosticians and diagnostic criteria, our studies differed in two other potentially important ways. First, the samples studied by the two teams were not exactly the same. The two groups did not agree on which relatives with partial information to include and we excluded a small number of relatives with uncertain paternity included by Kety et al.[7] We examined relatives of all control adoptees, while Kety et al[7] examined only those of screened control adoptees. Our sample was restricted to personally interviewed relatives, while Kety et al[7] included noninterviewed relatives.

Second, when examining the same subjects, the two teams did not always use the same sources of information. As in our review of the Copenhagen sample, results presented herein were based only on personal interviews in relatives. However, in their review, Kety et al[7] based diagnoses on personal interviews and, if available, hospital abstracts.

A complete examination of the sources of differences in the findings of our two groups is being prepared and is beyond the scope of this article. Preliminary analyses suggest that, controlling for differences in diagnostic information, our *DSM-III* criteria for schizophrenia and SPD defined a smaller group of adoptees and relatives than the categories of chronic and latent schizophrenia of Kety et al. Furthermore, consistent with previous findings,[45,53] the narrower syndromes defined by *DSM-III* may not have been optimal at identifying the biological relatives of schizophrenic adoptees.

LIMITATIONS OF THE SAMPLE

Two methodologic limitations of our diagnostic review of the Danish adoption studies warrant brief comment. First, because of format differences, we were not blind to the institutional record summaries and knew that these were prepared for index adoptees. Therefore, in assigning diagnoses to these cases, we always knew that they were index adoptees. However, as in the Copenhagen sample, we assigned a wide variety of diagnoses to these index probands and we always remained blind to the key independent variable: the relationship between relatives and adoptees.

Second, as in all family studies, in the Danish adoption studies, the interviewed relatives were almost certainly not a random sample of all relatives. It is probable that relatives who, either through refusal, out-migration, or premature death were unable to be interviewed, had higher rates of schizophrenia spectrum pathology than did interviewed relatives. Given the high completion rate of interviews in both the Provincial and Copenhagen samples, this bias is probably a modest one and, more likely than not, would diminish rather than enhance the observed aggregation of schizophrenia spectrum disorders in the biological relatives of spectrum adoptees.

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