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A Search for 'Schizophrenia Spectrum Disorders'

An Application of a Multiple Threshold Model to Blind Family Study Data

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Summary: Family data from schizophrenic and control probands were analyzed using a descriptive analysis and multiple threshold models to determine whether a given group of diagnoses made in accordance with ICD–9 was aetiologically related to schizophrenia. The proportion of relatives receiving any psychiatric diagnosis, other than schizophrenia and affective disorder, was essentially the same between the two study groups. Furthermore, the data did not fit the multiple threshold model tested. Thus, the hypothesis that schizophrenia and a spectrum of disorders defined according to ICD–9 have a common familial aetiology was not accepted.

The present study compared morbidity risks for psychiatric illnesses in first degree relatives of schizophrenics and controls. Both descriptive analysis and a multiple threshold model (Reich *et al*, 1975; Reich *et al*, 1979) were applied to our family data (Tsuang *et al*, 1980a) to detect a cluster or group of conditions which might share an underlying familial aetiology with schizophrenia.

Methods

The relatives for this analysis are part of a long-term follow-up and family study of 200 schizophrenics, 100 manics, and 225 depressives selected from 3,800 consecutive admissions to University of Iowa Psychiatric Hospital from 1934 to 1944 according to specified diagnostic criteria (Feighner *et al*, 1972; Morrison *et al*, 1972). To achieve blindness, a stratified random sample of 160 surgical patients (herniorrhaphy and appendectomy), admitted during the same time period, were selected as a control group. The controls were proportionally matched to the psychiatric patients for sex, pay status (private and public), and age at admission.

We traced the schizophrenia, mania, depression, and control probands concurrently with their first degree relatives. Details of this tracing procedure, which occurred between 1972 and 1976, are presented elsewhere (Tsuang *et al*, 1980a). A special interview form was developed for the purpose of interviewing all consenting study subjects. Extensive tests were performed with this interview form to insure its reliability and validity (Tsuang *et al*, 1980b).

Diagnostic assessment was performed by three psychiatrists after reviewing the completed interview forms. Both relatives and probands were diagnosed at the same time to assure that the psychiatrist was blind regarding the research diagnosis of the proband, or whether the individual assessed was a proband or a relative. Two psychiatrists independently reviewed each interview form and completed a diagnostic assessment sheet. Thereafter, a third psychiatrist examined the two assessment forms to make a final diagnosis by consensus (ICD–9). Details of the diagnostic assessment procedure have been presented in a previous report (Tsuang *et al*, 1980a). The final diagnoses, under ICD–9 terminology, included the following general categories: schizophrenia, mania, depression, neurosis, personality disorder, alcoholism and drug abuse, organic brain syndrome, mental retardation, undiagnosed and other mental disorders, and no diagnosable mental disorder. Of interest in this paper is the distribution of these disorders among the relatives of schizophrenics compared to those among the relatives of controls. The purpose is to determine whether a given group of psychiatric diagnoses is related to the same underlying aetiology as schizophrenia.

To further test the hypothesis that schizophrenia and a defined spectrum of psychiatric illnesses are due to the same underlying aetiology, multiple threshold models were used (Reich *et al*, 1975; Reich *et al*, 1979). The primary assumption for the general model states that the disorder develops by the accumulation of a large number of genetic and environmental risk factors

acting additively—each small in magnitude (Falconer, 1965). This model supposes that all risk factors are combined into an unobservable, normally distributed variable called liability. It is assumed that there is a point on this liability distribution where all individuals who have a liability greater than this point (threshold) are affected, and those with a liability less than the threshold are unaffected. For our analysis we used an extension of the above model to include two thresholds (Reich *et al,* 1972; Reich *et al,* 1975; Reich *et al,* 1979). An illustration of a two threshold model is shown in Fig 1. This model results in three classes of individuals in the general population: unaffected, mildly affected, and severely affected. For our purposes, the severely affected individuals are schizophrenic, and the mildly affected individuals have the spectrum of disorders defined below. The prevalence of schizophrenic individuals is defined by the area under the curve beyond the severely affected threshold; the prevalence of spectrum disorders is defined by the area under the curve between the severely affected and mildly affected thresholds. If the vulnerability of a disorder is transmissible, relatives of affected probands will have a higher mean liability than the general population; thus the liability distribution will shift to the right, and a higher disease prevalence will emerge in the relatives than in the general population. This is illustrated in the Fig where the means of the relatives' distributions shift to the right of the mean of the general population distribution; the shaded areas under the relatives' curves correspond to a higher disease prevalence.

If the assumption of a single liability distribution underlying schizophrenia and the spectrum of disorders is true, then expected frequencies of the two conditions among relatives of schizophrenic probands and controls can be calculated as in Reich *et al* (1979). The goodness of fit of the observed to expected numbers can be assessed using a chi-square test with one degree of freedom. If schizophrenia and the spectrum of disorders are due in large part to different aetiologies (i.e. if they have separate liability distributions), then the chi-square statistic will be large.

A class of threshold models termed the isocorrelational, environmental, and independent has been described in the literature (Reich *et al,* 1972; Reich *et al,* 1979). In all models parameters to be estimated include population prevalences of severe and mild disorders, and correlations in liability between probands and relatives of different types. If one has sufficient data the goodness of fit of all three models can be tested. Since we have no mild probands, and since the numbers of affected are too small to analyze sibs and offspring separately, we have sufficient information (i.e. degrees of freedom) only to fit and test the goodness of fit of the isocorrelational

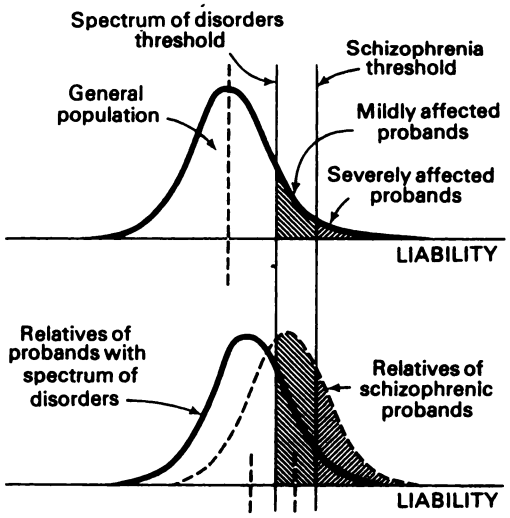

FIG.—Two-threshold multifactorial model with schizophrenic probands as severely affected and probands with spectrum of disorders mildly affected. Adopted from Reich *et al,* 1972.

model. When examining this model the chi-square goodness of fit test has one degree of freedom since we have four independent pieces of data (prevalences of severe and mild disease in relatives of control and schizophrenic probands), and we are estimating three parameters (prevalence of severe and mild disease, and the liability correlation between proband and relative). Therefore the degrees of freedom equal the number of independent pieces of data minus the number of parameters estimated, which in this case is one. The minimum chi-square estimates of the parameters for the isocorrelational model were obtained using an iterative minimization routine (Kaplan and Elston, 1972).

Results

From our tracing and follow-up data, we determined that the number of first degree relatives, who were 18 years old or greater, was 980 for schizophrenic probands and 1,140 for the control probands. We personally interviewed 73 per cent (354/484) of the living relatives in the schizophrenia group and 81 per cent (541/668) of the living relatives in the control group. Because of the design of the study not all consenting relatives were interviewed since if no proband was available for personal interview within a 300 mile radius of a relative, the relative was not interviewed. The mean age at interview for relatives of schizophrenics was 60.6±12.8 years while the mean

TABLE I

Frequencies and morbidity risks of psychiatric illness in interviewed relatives of schizophrenic (n = 354) and control (n = 541) probands

		Proband group					
		Schizophrenia			Control		
Diagnosis	Risk period	N(%)	BZ	MR(%)	N(%)	BZ	MR(%)
Schizophrenia	15–39	11 (3.1)	346.0	3.2	3 (0.6)	472.5	0.6
Mania	15–59	5 (1.4)	272.5	1.8	1 (0.2)	344.0	0.3
Depression	15–59	14 (4.0)	272.5	5.1	25 (4.6)	344.0	7.3
Neurosis	15–39	28 (7.9)	346.0	8.1	45 (8.3)	472.5	9.5
Personality disorder	15–	2 (0.6)	177.0	1.1	13 (2.4)	270.5	4.8
Alcoholism and drug abuse	20–39	11 (3.1)	346.0	3.2	26 (4.8)	463.0	5.6
Organic brain syndrome	40–	5 (1.4)	169.0	3.0	4 (0.7)	202.0	2.0
Mental retardation	15–	1 (0.3)	177.0	0.6	1 (0.2)	270.5	0.4
Undiagnosed and other mental disorders	15–59	31 (8.8)	272.5	11.4	60 (11.1)	344.0	17.4
No diagnosable mental disorder		246 (69.5)			363 (67.1)		

age in the control relatives was 49.8±16.6 years. Even though the mean ages at admission for the schizophrenic probands (29) and control probands (32) are similar, the mean age at interview for the relatives of schizophrenics is substantially higher than the mean age at interview for the relatives of controls. This is because schizophrenics tend to remain single; thus the majority of interviewed relatives are parents and sibs. The majority of interviewed relatives of controls are sibs and children because non-psychotic controls tend to marry and have children. The results of the diagnostic assessment of the interviewed relatives are presented in Table I. Because of the difference in age at interview for the relatives of schizophrenics and controls, the age-adjusted morbidity risks for psychiatric illnesses in the relatives were used for comparison.

We have previously shown that the morbidity risk (3.2 per cent) of schizophrenia in the relatives of schizophrenics is significantly higher than the risk (0.6 per cent) in the relatives of controls (Tsuang *et al,* 1980a). In addition, the differences in morbidity risks of mania and depression in relatives of schizophrenic and control probands did not reach statistical significance at the .05 level. In general, the morbidity risks of schizophrenia, mania, organic brain syndrome, and mental retardation are higher in relatives of schizophrenics when compared to relatives of controls. On the other hand, the age adjusted risks of depression, neurosis, personality disorder, alcoholism and drug abuse, and undiagnosed and other mental disorders are lower in the relatives of schizophrenics when contrasted to the relatives of control probands. The risk of personality disorder among the relatives of controls (4.8 per cent) was significantly higher ($P < .05$) than among the relatives of schizophrenics (1.1 per cent). The total percentage of cases with no diagnosable mental disorder is very similar for relatives of schizophrenia (69.5 per cent) and control (67.1 per cent) probands.

To perform the multiple threshold analysis, we subdivided all disorders among relatives (other than schizophrenia and affective disorder), into four categories consisting of other non-organic psychoses, neurotic disorders, personality disorders and other disorders. Since affective disorders were found to be different from schizophrenia based on our family study data (Tsuang *et al,* 1980a), affective illness was not included as part of the spectrum of disorders. Three groups of criteria were devised ranging from a broad definition to a restricted definition of spectrum disorders, with analyses being performed under each definition. These categories and definitions are shown in Table II along with the specific ICD–9 diagnostic codes.

The primary consideration was as follows: if the isocorrelational model provided an adequate fit to the observed data, then this suggested that schizophrenia and the spectrum of disorders in the first degree relatives were due to the same underlying aetiology. The observed and expected frequencies of schizophrenia, spectrum illnesses, and unaffected in the first degree relatives along with the goodness of fit test under each definition (broad, intermediate, restricted) are presented in Table III. The correlations in liability for each definition are also presented at the bottom of Table III. If the model is adequate for these data we would expect that the observed and expected values would be very similar. For each definition of disorder a statistical test can be performed by calculating a goodness of fit chi-square to compare the observed and expected values. The chi-square value for each of the classifications of illnesses is statistically significant

TABLE II

Three groups of conditions used to define spectrum of disorders related to schizophrenia (ICD–9 codes)

Disorder	Definition		
	Broad	Intermediate	Restricted
Other non-organic psychoses	Any other non-organic psychoses 298.0–298.9	Acute paranoid reaction; unspecified reactive psychosis; unspecified psychosis 298.3, 298.8, 298.9	Acute paranoid reaction; unspecified psychosis 298.3, 298.9
Neurotic disorders	Any neurotic disorder 300.0–300.9	Anxiety, hysteria, phobic, obsessive compulsive, neurasthenia, depersonalization, hypochondriasis, other or unspecified 300.0–300.3; 300.5–300.9	Phobic, obsessive compulsive, depersonalization 300.2, 300.3 300.6
Personality disorders	Any personality disorder 301.0–301.9	Paranoid, schizoid, explosive, compulsive, histrionic, dependent, antisocial, passive-aggressive, other and unspecified 301.0, 301.2–301.9	Paranoid, schizoid, anti social, other personality disorders 301.0, 301.2, 301.7, 301.8
Others	Sexual deviations, physiological malfunction, special symptoms or syndromes, adjustment reaction, disturbance of conduct, emotions specific to childhood, hyperkinetic syndrome 302, 306, 307, 309, 312, 313, 314	None	None

TABLE III

Goodness of fit test for the multiple threshold model-comparison of observed (0) and expected (E) frequencies of schizophrenia, spectrum of disorders and unaffected among relatives of schizophrenic probands and controls

Definition-spectrum of disorders	Diagnosis of relative	Relatives of Schizophrenics O	Relatives of Schizophrenics E	Relatives of Controls O	Relatives of Controls E	χ^2 goodness of fit (1df)
Broad	Schizophrenia	11	(5.9)	3	(8.1)	10.17 ($P < .01$)
	Spectrum	43	(51.3)	83	(73.8)	
	Unaffected	300	(296.8)	455	(459.1)	
Intermediate	Schizophrenia	11	(7.3)	3	(6.6)	5.92 ($P < .05$)
	Spectrum	18	(23.1)	29	(24.2)	
	Unaffected	325	(323.6)	509	(510.2)	
Restricted	Schizophrenia	11	(7.1)	3	(6.8)	7.29 ($P < .01$)
	Spectrum	11	(16.1)	22	(17.1)	
	Unaffected	332	(330.8)	516	(517.1)	

Correlations in liability (r): Broad = .017, Intermediate = .084, Restricted = .077

($P < .05$), indicating the observed and expected values differ. The data does not fit this two-threshold multifactorial model, and thus the hypothesis that schizophrenia and the spectrum of disorders, as defined, have a common familial aetiology is not accepted.

Discussion

We have applied descriptive and multiple threshold model analyses to a set of blind family study data to determine whether a given group of diagnoses is aetiologically related to schizophrenia. Specifically, psychiatric diagnoses of the relatives of schizophrenic and control probands were examined. The proportion of relatives receiving any ICD–9 psychiatric diagnosis was essentially the same between the two study groups. The morbidity risk of schizophrenia in relatives of schizophrenic probands was significantly greater than that found in relatives of control probands. The same trend was observed for mania in the relatives, but the difference did not reach statistical significance. Furthermore, we found that the morbidity risk of personality disorders in families of schizophrenics was significantly lower when compared to the risk in control families. With regard to other disorders, although there were some differences, the overall rates were very similar between the two study groups. In general, our data differed from higher incidence of spectrum disorders and personality disorders in relatives of schizophrenics observed by others. For instance Reich, in a review paper (1976), alluded to the 'inadequate personality' frequently observed in relatives of schizophrenics.

By way of multiple threshold model analysis we demonstrated that little, if any, familial aetiological connection exists between schizophrenia and the spectrum of disorders discussed above. Under broad, intermediate, and restricted sets of criteria for disorder in the families, we tested the goodness of fit of the isocorrelational model. A poor fit to the model disclosed that schizophrenia and the spectrum of disorders, as specified, were due to the different underlying aetiologies. These conclusions, of course, are made with the assumption that the underlying model is correct.

Though we did not accept the hypothesis that schizophrenia and spectrum disorders have a common familial aetiology, it may be that blind family studies using ICD–9 diagnoses are not adequate to distinguish a group of disorders that are aetiologically related to schizophrenia. There has been considerable effort (Carey and Gottesman, 1981) in the direction of defining cases and groups of disorders (schizophrenia spectrum) which share a common genetic aetiology with schizophrenia. To determine a cluster of disorders related to schizophrenia, future researchers may have to look for other useful means of identification such as biological indicators and improved methods of classification and statistical analysis.

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