Morbidity Risk of Psychiatric Disorders Among the First Degree Relatives of Schizophrenia Patients in Taiwan

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Abstract

This study aimed to assess the boundaries of the schizophrenia spectrum and whether inclusion of such phenotypes increases power for linkage analysis of schizophrenia. Participants were 234 first degree relatives (FDRs) of 94 schizophrenia probands in Northern Taiwan who completed a direct interview using the Diagnostic Interview for Genetic Studies (DIGS). Based on best estimate diagnosis, the morbidity risk in the relatives for schizophrenia was 2.5 percent (Weinberg's shorter method) or 3.9 percent (Kaplan-Meier estimate). Depending on the stringency of diagnosis, lifetime prevalence was 2.6 percent to 4.7 percent for schizotypal personality disorder, 3.4 percent to 8.6 percent for paranoid personality disorder, and 1.3 percent to 3.4 percent for schizoid personality disorder. These figures are significantly higher than the corresponding figures in the general population. However, none of the recurrence risk ratio for any spectrum that included both schizophrenia and a personality disorder (3.0 to 5.9) was greater than that of schizophrenia alone (9.3 to 14.4). Thus, including schizophrenia-related personality disorders in the spectrum did not increase power for linkage analysis of schizophrenia.

Keywords: Family study, personality disorder, psychiatric interview, recurrence risk ratio, spectrum, schizophrenia.

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Family studies have been instrumental in establishing the diagnostic validity and familial aggregation of schizophrenia (Tsuang et al. 1980). Furthermore, the concept of a spectrum—that illnesses other than schizophrenia may appear in increased rates in relatives of schizophrenia patients—and the possible genetic heterogeneity of clinical schizophrenia can be assessed through family studies (Kendler 2000). A definition of schizophrenia-related phenotype that reflects the underlying genetic basis is crucial for a successful linkage search for schizophrenia (Kendler and Diehl 1993; Tsuang and Faraone 2000). However, the interpretation of which disorders are included in the schizophrenia spectrum is complicated by the wide variations in methodologies used in the collection of such information (Kendler et al. 1993*a*, 1993*b*; Webb and Levinson 1993; Varma et al. 1997; Kendler 2000). Important methodological issues included discrepancies in the sources of diagnostic information about the relatives of the probands (family study method vs. family history method), the varied diagnostic procedures (best estimate diagnosis or not), and the different instruments of phenotype assessment (structured or not) (Faraone and Tsuang 1995; Kendler and Gardner 1997).

The family history method involves interviewing probands or other family informants to gather data pertaining to relatives' psychiatric status. The advantages of this approach are saved time and cost, but lack of sensitivity (i.e., underestimating true rates) for many psychiatric disorders is its major drawback (Roy et al. 1996; Davies et al. 1997; Li et al. 1997). In contrast, the family study method, in which all available relatives are directly interviewed, provides more accurate information than does the family history method for diagnosing psychiatric disorders in relatives, particularly in the assessment of schizophrenia-related personality disorders (Faraone and Tsuang 1995). However, the family study method may be prone to selection and participation biases if there are systematic differences between relatives interviewed and those who are inaccessible (Kendler et al. 1993*a*). Therefore, the best way to collect information regarding family psychopathology is to interview directly as many relatives as possible and to collect supplementary family history data on unavailable relatives (Davies et al. 1997).

In terms of diagnosing psychiatric disorders in relatives, combining all sources of information about a subject

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(e.g., direct interview with the subject, history from family informants, and relevant medical records) to derive a best estimate diagnosis is considered the most valid method (Leckman et al. 1982; Maziade et al. 1992; Roy et al. 1997). Specific diagnostic criteria, multiple independent diagnosticians, blindness of interviewer, and uniformity of methods for any subjects are other characteristics of diagnostic procedures required in current psychiatric genetic epidemiology (Maziade et al. 1992; Roy et al. 1997).

Because the spectrum of schizophrenia covers not only Axis I disorders but also Axis II disorders, an instrument used in family studies of schizophrenia should cover both. The Diagnostic Interview for Genetic Studies (DIGS), developed by collaborators from the National Institute of Mental Health (NIMH) Genetic Initiative, is a semistructured clinical interview instrument designed specifically for this purpose (Nurnberger et al. 1994). It covers major mood and psychotic disorders and their spectrum conditions and focuses in detail on schizophrenia, affective disorders, and substance use disorders. The Modified Structured Interview for Schizotypy (SIS; Kendler et al. 1989) is also included in the DIGS for the diagnosis of Axis II schizophrenia-related personality disorders. Additional features of the DIGS include a detailed assessment of the onset and course of the illness. These are important for estimating the morbidity risk of various psychiatric disorders because they have a variable age at onset (Faraone et al. 1994). DIGS has been translated into Chinese (Chen et al. 1998*b*) and Hindi (Deshpande et al. 1998) with satisfactory interrater reliabilities. A companion to the DIGS for collecting family history on relatives is the Family Interview for Genetic Studies (FIGS, NIMH Genetic Initiative 1992).

Reviews of recent well-designed family studies of schizophrenia have found that schizophrenia strongly aggregated in families with a relative risk of about 11 as compared with matched controls, and there is no evidence that such familial aggregation differs across samples (Kendler 2000). Regarding the boundaries of the schizophrenia spectrum, the evidence is substantial for the inclusion of schizotypal personality disorder and less so for the inclusion of schizoaffective, schizophreniform, and psychotic affective disorders. Other disorders—including anxiety disorder, alcoholism, delusional disorder, and probably most forms of affective illness—appeared to have little relationship with schizophrenia (Prescott and Gottesman 1993; Kendler 2000). However, including these spectrum disorders in the phenotype definition may not necessarily lead to an increase in power for genetic analysis for schizophrenia. Risch (1990) demonstrated that the statistical power of a linkage study increases with the magnitude of recurrence risk ratio, the so-called λ, defined as the prevalence of a disorder among relatives of diseased probands versus that of the general population. By computing the values of this index for various schizophrenia spectrum phenotypes from data of previous family studies, Faraone et al. (1995) found that adding a spectrum phenotype to the definition of affection might not lead to an increase in power for linkage analysis of schizophrenia unless the prevalence of the spectrum in relatives is 11 or more times that of the general population. Thus, the next-generation family studies of schizophrenia should investigate the boundaries of the schizophrenia spectrum and whether inclusion of such boundaries will lead to increased power in the search for genes that increase susceptibility to schizophrenia (Parnas 2000; Tsuang and Faraone 2000).

It is worthwhile to note that the majority of previous family studies were conducted in Western populations, except for studies in Malaysians (Varma and Sharma 1993; Varma et al. 1997) and the second-generation African-Caribbean population in Britain (Hutchinson et al. 1996). The DIGS has been used primarily as an ascertainment tool for molecular genetic studies for schizophrenia (Cloninger et al. 1998), bipolar disorders (Blehar et al. 1998; Foroud et al. 2000), and alcoholism (Gorwood et al. 2000). However, there has been no report of a family study of schizophrenia using the DIGS yet. In this study we aimed to estimate the morbidity risk of schizophrenia spectrum disorders among the FDRs of schizophrenia patients in Taiwan using the family study method. We conducted direct interviews with available subjects using the DIGS and obtained family histories of other family members using the FIGS. Consensus best estimate diagnosis was reached by combining information from the DIGS, the FIGS, and relevant medical records. By comparing the morbidity risk among the FDRs of schizophrenia probands with the corresponding prevalence from two epidemiological studies, we also evaluated the boundaries of the schizophrenia spectrum and its potential for an increase in power for linkage analysis.

Methods

Subjects. Schizophrenia probands were selected from a prospective study of schizophrenia in Northern Taiwan, the Multidimensional Psychopathology Group Research Project (MPGRP). This project aimed to test the diagnostic validity of dichotomized negative versus nonnegative subtypes of schizophrenia by multidisciplinary approaches, including phenomenological assessments and prospective followup, family and molecular genetic studies, and studies about the family burden and need of care. The sampling design was to recruit schizophrenia patients admitted to three participating hospitals, in which the

ratio of patients admitted for the first time to those for relapse was set to 1:2. The purpose was to include patients in different phases of the illness. These patients and their family members were interviewed and assessed during hospitalization, and patients were periodically followed up for 2 years after discharge. The recruitment procedures have been described in detail in earlier reports of this project (Liu et al. 1997; Chen et al. 1998*b*). Briefly, from August 1, 1993, to June 30, 1998, the patients admitted to the acute wards of three hospitals, National Taiwan University Hospital, Taipei City Psychiatric Center, and Taoyuan Psychiatric Center, were recruited in the MPGRP if they met the *DSM–III–R* (APA 1987) criteria for schizophrenia disorders and the sampling designs. During the study period, the diagnostic criteria were shifted to *DSM–IV* (APA 1994) after it became available. Earlier subjects were rediagnosed and met the updated criteria. The diagnoses were reevaluated at discharge by consensus among three senior psychiatrists using all information available from clinical observations, medical records, and key informants. All patients with a discharge diagnosis other than schizophrenia and patients with a history of physical illness or substance abuse that cast the diagnosis in doubt were excluded.

Eligible schizophrenia patients were included as the probands of the present-family genetic study when they fulfilled the following inclusion criteria: (1) the proband agreed to let researchers approach his or her relatives; (2) at least one of the proband's FDRs agreed to participate; and (3) more than half of the proband's FDRs were logistically accessible (living within Northern Taiwan, from Hsinchu County to Yilan County). All the FDRs 16 years old or older were included in the present study. Written informed consent was obtained from all subjects after complete description of the study.

Although there were normal control probands recruited through a separate project, the number of probands (n = 20) and their directly interviewed FDRs (n = 40) was very limited (Chen et al. 1998*b*) because of budget constraints. Instead, we used two other sources of subjects as comparison groups. The first group is taken from a community-based survey using the Chinese version of the Diagnostic Interview Schedule among residents in metropolitan Taipei, small towns, and rural villages (n = 11,004) (Hwu et al. 1989). Combined lifetime prevalences of major psychiatric disorders for the three strata were reported later (Compton et al. 1991). The second comparison group is from a two-phase survey for schizophrenia-like personality disorders in Chinshan Township, Taipei County. The sampling of the phase 1 study subjects has been described in detail elsewhere (Chen et al. 1998*a*, submitted). Briefly, on the basis of random samples from a voter list, 365 (65%) subjects completed a composite questionnaire used in the phase 1 interview, which included the Perceptual Aberration Scale (PAS; Chapman et al. 1978) and the Schizotypal Personality Questionnaire (SPQ; Raine 1991). The two-stage translation and test-retest reliability of the two scales have been reported previously (Chen et al. 1998*a*). A 90th percentile of each scale was chosen as the cutoff point, and the whole sample was divided into four subgroups as follows: 3.55 percent for PAS (+) SPQ (+), 6.56 percent for SPQ (+) PAS (–), 6.56 percent for SPQ (–) PAS (+), and 83.33 percent for SPQ (–) PAS (–). The Chinese version of the DIGS (DIGS-C) was then employed for the phase 2 interview for all subjects in the first three subgroups and 10 percent of the subgroup of SPQ (–) PAS (–). Estimates of the weighted prevalence and its standard error were calculated according to the methods described in Shrout and Newman (1989). Because the DIGS-C was used in the second phase of this survey, prevalence of common disorders such as major depression, dysthymia, alcohol abuse, and alcohol dependence could also be estimated according to the same weighting system used in the estimation of the prevalence of schizophrenia-related personality disorders.

Interview Instruments and Diagnostic Procedures. Probands and their FDRs were interviewed in person using the DIGS-C. The interviews were carried out mainly in Mandarin. For some older subjects who could not understand Mandarin, the interview was done in Taiwanese dialect. The development of the DIGS-C and the assessment of its interrater reliability have been reported elsewhere (Chen et al. 1998*b*). Briefly, the kappas for the diagnoses of schizophrenia, bipolar disorder, and major depression by three physicians (C.J.C., W.J.C., and S.K.L.) and two research assistants ranged from 0.86 to 0.93, whereas those for the diagnoses of three personality disorders were 0.72 for schizotypal personality disorder, 0.68 for paranoid personality disorder, and 0.90 for schizoid personality disorder. According to the DIGS training manual, the major modifications in the SIS section of the DIGS were a newly added section on anger to perceived slights to meet *DSM–III–R* criterion A.6 for paranoid personality disorder. The DIGS-C interviews were carried out by six well-trained research assistants majoring in either psychology or psychiatric nursing. They had received standardized psychiatric interview training for 4 weeks and completed six sessions of videotape reliability testing before participating in the data collection. Interviewers used the Chinese version of the FIGS (FIGS-C) to collect relevant information from other family members about relatives who were not interviewed for the study.

Two psychiatrists (C.J.C. and S.K.L.) and one psychiatric epidemiologist (W.J.C.) independently reviewed all

available information (DIGS-C, FIGS-C, other side information, and copies of medical records) pertaining to the probands and their relatives. Best estimate lifetime psychiatric diagnoses according to the *DSM–IV* criteria were determined independently and then finalized in a consensus meeting. Three levels of diagnoses according to the *DSM–IV* were possible: none, probable (met the required number of criteria but one criteria was near threshold), and definite. The interviewers were not blind to the proband's status, because providing relevant knowledge about schizophrenia probands was essential in motivating relatives to participate.

Statistical Analysis. We applied both Weinberg's shorter method (Slater and Cowie 1971) and the Kaplan-Meier method (Kaplan and Meier 1958) to estimate age-corrected rates of illness (i.e., morbidity risk) among relatives. Although Weinberg's shorter method, in which BZ (*Bezugsziffern*, i.e., sample size corrected for age) is computed as an adjusted denominator, is commonly used in the literature, it may bias the estimation of morbidity risk substantially (Chase and Kramer 1986; Chen et al. 1993*b*). Besides, Weinberg's shorter method requires knowledge of the earliest and latest possible onset age. To be comparable with previous studies, the at-risk period in this study was set to be 15–39 years for schizophrenia, alcohol abuse, and alcohol dependence and 15–59 years for affective disorders. In contrast, the Kaplan-Meier estimate adjusts for censoring nonparametrically and does not group ages into arbitrary intervals (Chen et al. 1992). In the Kaplan-Meier analysis, the survival time is counted until the age of onset for ill relatives, and until the age of interview for well relatives. The standard error of the Kaplan-Meier estimate was computed with Greenwood's formula. In this study, the age at onset was defined as the earliest age at which the subject met the criteria for the disorder. However, like Kendler et al. (1993*b*), we did not think it practical to have an age at onset for personality disorders and hence did not compute their morbidity risk. Only lifetime prevalences were computed for personality disorders. Group comparisons of morbidity risks were made with z tests. The 95 percent confidence interval for a risk ratio was calculated by Wald limit (Rothman and Greenland 1998).

The recurrence risk ratio for a spectrum that included both schizophrenia and a personality disorder was calculated according to Faraone et al. (1995) as follows. The numerator was derived as (risk of schizophrenia in relatives) + (1 − risk of schizophrenia in relatives) × (risk of the personality disorder in relatives), while the denominator was derived as (risk of schizophrenia in the population) + (1 − risk of schizophrenia in the population) × (risk of the personality disorder in the population). Because the morbidity risk of schizophrenia in relatives estimated by Kaplan-Meier was higher than that estimated by Weinberg's shorter method, the former was used in the calculation of recurrence risk ratio for a spectrum. All analyses were performed with the SAS computer package (SAS Institute 1997). A p value of less than 0.05 was considered significant.

Results

Among 234 schizophrenia patients recruited for the MPGRP, 94 (40.2%) met the inclusion criteria for this family study. The reasons for nonparticipation in the family study could roughly be classified into four categories: probands' refusal to let researchers approach their relatives (about 15%), no living first degree relatives available for interviewing (about 20%), caregivers' refusal to let researchers approach their relatives (about 35%), and logistical problems in interviewing relatives (about 30%). There was no difference in ethnicity between the participating probands and the nonparticipating ones, but the nonparticipating probands were older (32.2 ± 7.1 years vs. 28.9 ± 7.3 years) and had a lower education level (10.5 ± 2.8 years vs. 11.4 ± 3.0 years) than the participating ones.

Among a total of 450 FDRs, 441 were 16 years old or older. Of these, 45 were excluded from interviewing (30 were dead, 13 were abroad, and 2 were profoundly mentally retarded) and 234 (59.1%) of the remaining 396 were directly interviewed. The completion rate was higher in parents (80%) than in siblings or children (42%). Most of the FDRs who could not be directly interviewed were living outside the research area. The majority of the families (77.8%) in this study were "Taiwanese" or "Formosans," the descendants of Chinese immigrants originating from Fukien (i.e., South Fukienese, 68.9%) and, to a lesser extent, Kwangtung (i.e., Hakka, 8.9%) provinces between the 17th and 19th centuries. There were only four families (4.4%) with both parents emigrating from Mainland China after 1949. The remaining ones were intermarriages among the three ethnic groups. None of the studied families were aborigines. Hence, the possibility of a "genetic bottleneck" caused by immigrants with psychopathology can be ignored. The demographic features of probands with schizophrenia and their FDRs 16 years old or older are shown in table 1. Among the directly interviewed relatives, 56 percent were parents and 43 percent were siblings of the probands.

Table 2 displays the distribution of Axis I psychiatric diagnoses in the FDRs of schizophrenia probands. Because there was little change in the prevalences of Axis I disorders when the stringency of diagnosis moved from definite diagnoses only to both definite and probable diag-

Table 1. Demographic characteristics of schizophrenia probands and their first degree relatives

			Relatives ($n = 441$)			
	Probands ($n = 94$)		Direct interview ($n = 234$)		Family history only ($n = 207$)	
Variable	*n*	(%)	*n*	(%)	*n*	(%)
Sex						
Male	51	(54)	109	(47)	117	(56)[1]
Female	43	(46)	125	(53)	90	(44)
Relationship with proband						
Parent			131	(56)	55	(27)[1]
Sibling			100	(43)	151	(73)
Offspring			3	(1)	1	(0)
Age (yrs.)						
16–29	55	(59)	46	(20)	68	(33)[1]
30–39	32	(34)	33	(14)	55	(26)
40–49	7	(7)	49	(21)	26	(13)
50–59	0	(0)	49	(21)	25	(12)
> 60	0	(0)	57	(24)	21	(10)
Missing					12	(6)
Education level (yrs.)						
≤ 6	9	(10)	86	(37)	13	(6)
7–10	20	(21)	36	(15)	8	(4)
11–12	39	(41)	55	(24)	12	(6)
≥ 13	26	(28)	57	(24)	20	(10)
Missing					154	(74)

[1] Significant difference in the distribution of the variable between relatives with direct interview and those with family history only, χ^2 or Fisher's exact test (2-tailed), $p < 0.05$ (those with missing values were not included in the comparison).

Table 2. Psychiatric disorders among first degree relatives of schizophrenia probands

	Direct interview ($n = 234$)		Direct interview or family history ($n = 441$)	
Diagnosis	*n*	(%)	*n*	(%)
Schizophrenia	5	(2.1)	12	(2.7)
Schizophreniform disorder	1	(0.4)	1	(0.2)
Major depression	6	(2.6)	7	(1.6)
Dysthymia	15	(6.4)	17	(3.8)
Alcohol abuse	10	(4.3)	10	(2.3)
Alcohol dependence	4	(1.7)	6	(1.4)
Drug abuse	1	(0.4)	1	(0.2)
Drug dependence	1	(0.4)	1	(0.2)
Panic disorder	1	(0.4)	1	(0.2)
Adjustment disorders	6	(2.6)	6	(1.4)
Mental retardation	1	(0.4)	3	(0.7)
Pathological gambling	1	(0.4)	2	(0.4)

noses, we presented here only the figures including both definite and probable diagnoses. Dysthymia was the most common mental illness in the directly interviewed relatives (6.3%), followed by alcohol abuse (4.3%), major depression (2.6%), and adjustment disorders (2.6%). Five cases with schizophrenia (2.1%) and no cases with bipolar or schizoaffective disorders were diagnosed in the relatives. When family history information was incorporated, another seven relatives with schizophrenia were identified but only a few cases in the other diagnostic categories were identified. The total prevalence of schizophrenia in the first degree relatives of schizophrenia probands by either direct interview or family history was 2.7 percent, which was higher than that of all other diagnoses except dysthymia (3.8%).

Morbidity risks of six major Axis I psychiatric diagnoses in directly interviewed relatives are presented in table 3. The morbidity risk of schizophrenia was 2.5 percent (Weinberg's shorter method) or 3.9 percent (Kaplan-Meier estimate). To estimate the recurrence risk ratio among FDRs of schizophrenia probands versus the general population, lifetime prevalences from a nationwide epidemiological study in Taiwan (Hwu et al. 1989; Compton et al. 1991) and a recent community survey in Chinshan Township were taken as denominators, respectively. The risk ratios were similar for both Weinberg's shorter method and the Kaplan-Meier estimate in most diagnostic categories except schizophrenia. Risk ratio in schizophrenia was higher by Kaplan-Meier estimate (14.4) than by Weinberg's shorter method (9.3). The risk ratio in schizophrenia obviously exceeded the risk ratios in the other diagnoses.

The lifetime prevalences of the three schizophrenia-related personality disorders among the directly interviewed FDRs of schizophrenia probands are shown in table 4. For both definite and broad diagnoses, paranoid personality disorder (3.4% to 8.6%) was the most prevalent Axis II diagnosis in the relatives of schizophrenia probands, followed by schizotypal (2.6% to 4.7%) and schizoid (1.3% to 3.4%) personality disorders. Change in diagnostic stringency by just one criterion had substantial impact on the prevalences and hence risk ratios of these disorders, in which the prevalence of schizoid personality disorder increased nearly 3-fold when the diagnostic threshold was broadened. Compared with the lifetime prevalences of schizophrenia-related personality disorders in the community residents of Chinshan Township, the risk ratio ranged from 2.6 (paranoid personality disorder) to 1.3 (schizoid personality disorder) for definite diagnosis, and ranged from 4.8 (paranoid personality disorder) to 1.9 (schizotypal personality disorder) for broad diagnosis. Because the diagnostic criteria of these three personality disorders are partially overlapping, the prevalence of two

Table 3. Morbidity risk of psychiatric diagnosis in the interviewed first degree relatives of schizophrenia probands compared with the lifetime prevalence in two epidemiological studies in Taiwan

	Weinberg's Shorter Method			Kaplan-Meier Estimate			Lifetime prevalence in Taiwan
Diagnosis	MR (%)	SE	Risk ratio	MR (%)	SE	Risk ratio (95% CI)	
Schizophrenia	2.5[1]	1.1	9.3	3.9[2]	1.6	14.4 (6.8–29.4)	0.27 (0.05)[3]
Major depression	4.1[1]	1.6	3.6	3.8[1]	1.6	3.3 (1.7–6.6)	1.14 (0.10)[3]
	4.1	1.6	1.1	3.8	1.6	1.0 (0.4–2.3)	3.74 (3.12)[4]
Dysthymia	10.3[2]	2.5	6.2	9.8[2]	2.6	5.9 (3.9–9.0)	1.66 (0.12)[3]
	10.3[1]	2.5	3.3	9.8[1]	2.6	3.2 (1.6–6.6)	3.09 (3.09)[4]
Alcohol abuse/dependence	6.2	1.7	1.1	7.4	2.2	1.1 (0.6–1.6)	7.18 (0.25)[3]
Alcohol abuse	4.6	1.5	0.6	5.3	1.8	0.6 (0.3–1.2)	8.32 (4.36)[4]
Alcohol dependence	2.1	1.0	0.6	2.5	1.3	0.7 (0.3–2.0)	3.41 (3.10)[4]

Note.—CI = confidence interval; MR = morbidity risk; SE = standard error.
[1] $p < 0.05$ comparing relatives' morbidity risk with population's lifetime prevalence (*z* test, 2-tailed).
[2] $p < 0.01$ comparing relatives' morbidity risk with population's lifetime prevalence (*z* test, 2-tailed).
[3] Based on data from a nationwide one-phase survey among 11,004 subjects (Compton et al. 1991).
[4] Based on data from a two-phase survey among 365 community subjects in Chinshan Township.

Table 4. Prevalence of personality disorders among the interviewed first degree relatives of schizophrenia probands

	Relatives of Schizophrenia Probands ($n = 234$)				Community Subjects[1] ($n = 365$)		Recurrence Risk Ratio for Spectrum
Diagnosis	*n*	%	(SE)	Risk ratio (95% CI)	%	(SE)	
Definite diagnosis							
Schizotypal PD	6	2.6	(1.0)	2.0 (0.6–6.1)	1.3	(0.6)	4.1
Paranoid PD	8	3.4[3]	(1.2)	2.6 (0.8–7.5)	1.3	(0.6)	4.6
Schizoid PD	3	1.3	(0.7)	1.3 (0.3–7.7)	1.0	(0.6)	4.1
Either 1 or 2	14	6.0[4]	(1.6)	2.6 (1.2–6.4)	2.3	(0.8)	3.8
Either 1, 2, or 3	17	7.3[4]	(1.7)	2.8 (1.3–6.5)	2.6	(0.9)	3.8
Broad diagnosis[2]							
Schizotypal PD	11	4.7	(1.4)	1.9 (0.8–4.5)	2.5	(0.9)	3.0
Paranoid PD	20	8.6[4]	(1.8)	4.8 (2.1–12.8)	1.8	(0.8)	5.9
Schizoid PD	8	3.4[4]	(1.2)	3.4 (1.1–15.5)	1.0	(0.6)	5.7
Either 1 or 2	28	12.0[4]	(2.1)	3.6 (1.9–7.0)	3.3	(1.0)	4.3
Either 1, 2, or 3	35	15.0[4]	(2.3)	4.2 (2.3–7.7)	3.6	(1.1)	4.7

Note.—CI = confidence interval; PD = personality disorder; SE = standard error.
[1] Based on data from a two-phase survey among 365 community subjects in Chinshan Township (Chen et al., submitted).
[2] Includes both definite and possible diagnosis.
[3] $p < 0.05$ comparing relatives' morbidity risk with population's lifetime prevalence (z test, 2-tailed).
[4] $p < 0.01$ comparing relatives' morbidity risk with population's lifetime prevalence (z test, 2-tailed).

combined categories was also reported, one satisfying either schizotypal or paranoid personality disorders and the other one satisfying any of the three personality disorders. Although the combination of two or three personality disorders led to considerable increase in prevalence, it did not result in increased risk ratios, which remained close to that of paranoid personality disorder alone. In addition to schizophrenia, if these personality disorders were included in the definition of affection status, the risk ratios for the spectrum (ranging from 3.0 to 5.9) in fact became less than that of schizophrenia alone.

Discussion

In this study we have collected information pertaining to Axis I and II psychiatric disorders among FDRs of schizophrenia probands via direct interview using instruments designed specifically for family study (the DIGS-C) and complementary family history (the FIGS-C) for schizophrenia. However, we did not have enough FDRs of control families assessed in similar ways. This indeed limits our ability to make inferences regarding the familiality of schizophrenia or its spectrum disorders (Faraone and Tsuang 1995). Nevertheless, we did have the prevalence of both Axis I and II disorders in the general population from two epidemiological studies to calculate corresponding recurrence risk ratios. These results enable us to assess the boundaries of the schizophrenia spectrum and its potential for increase in power for linkage analysis. Another limitation of this study is that the nonparticipating patients were older and of lower education level than the participating ones. The morbidity risks reported in this study might be underestimated if the features of the nonparticipating patients were associated with higher risks for schizophrenia spectrum disorders among their FDRs.

Morbidity Risk of Schizophrenia. The morbidity risk of schizophrenia in the FDRs of schizophrenia probands in this study (2.5% to 3.9%) was low compared with those obtained in the other major family studies using similar methodology, as thoroughly reviewed by Kendler (2000). All these studies used a normal control group, a personal interview with relatives using structured psychiatric assessments, operationalized diagnostic criteria (*DSM–III*, *DSM–III–R*, or Research Diagnotis Criteria [RDC]), and blind diagnosis. The morbidity risk estimated in these studies varied widely, from 1.4 percent to 6.5 percent (excluding two high-risk studies with higher morbidity risk in the offspring only).

There are several possible explanations for the low morbidity risk of schizophrenia in the relatives. First, the proportion of directly interviewed relatives (59.1%) in this study was lower than that of previous major family studies. For example, the figure was 85 percent for a

study in the United States (Baron et al. 1985) and a study in Ireland (Kendler et al. 1993*a*) and was 75.6 percent for a study in Germany (Maier et al. 1994). Furthermore, uninterviewed relatives in this study tended to be the siblings of the probands, who have higher risk for schizophrenia than parents of schizophrenia patients because of the reduced fertility effect of schizophrenia (Kendler and MacLean 1989). Nevertheless, supplementary family history data on noninterviewed relatives were collected in this study. Family history aproach might also help reduce possible selection and participation biases of the family study method (Davies et al. 1997). Indeed, there were seven more cases of FDRs with schizophrenia identified by family history than by direct interview alone in the present study. However, the prevalence of schizophrenia in the FDRs of schizophrenia probands remained at a similar level (2.7%) when FDRs with family history only were included for the estimation. Thus, we do not think that the lower rate of direct interview alone accounted for the low morbidity risk of schizophrenia in our study population.

Second, the low morbidity risk of schizophrenia in the relatives may be simply a reflection of the mental health status of Taiwanese adults. When the same diagnostic instrument (Diagnostic Interview Schedule) was used in cross-national studies, the lifetime prevalences of psychiatric disorders in Taiwan were much lower than those of the United States (Compton et al. 1991) or eight other countries (Weissman et al. 1997). The Taiwanese tendency toward low prevalences of mental disorders was also found in residents of Hong Kong (Chen et al. 1993*a*) and China (Lee and Kleinman 1997). However, a recent survey of behavioral and emotional problems among adolescents indicates that the magnitude of mental health problems in Taiwanese adolescents is not much lower than that in American adolescents (Yang et al. 2000). Whether the low prevalences of mental disorders among Chinese adults are due to developmental changes, cohort effect, or underreporting warrants further investigation.

Third, the reason for the low morbidity risk of schizophrenia in the relatives may be that the schizophrenia susceptibility gene(s) can be expressed in different ways in different cultures (Kendler et al. 1993*a*). Based on the results of the Roscommon Family Study, Kendler et al. (1995*b*) have suggested that five schizophrenia spectrum disorders (schizophrenia, schizoaffective disorders, schizotypal/paranoid personality disorders, other nonaffective psychosis, and psychotic affective disorders) are manifestations, of varying severity, of the same underlying vulnerability. This vulnerability is strongly transmitted within families. Owing to potential differences in genetic and environmental risk factors across populations, the expression of schizophrenia spectrum disorders in the FDRs of Taiwanese schizophrenia probands might be different from those of other populations.

Despite the relatively low morbidity risk of schizophrenia in our study population, the recurrence risk ratio of schizophrenia among FDRs of schizophrenia probands as compared with that of the general population ranged from 9.3 to 14.4. FDRs of schizophrenia probands are often assumed to be at 5- to 10-fold increased risk of schizophrenia (Kendler and Diehl 1993). However, in a recent meta-analysis of three independent family studies, Kendler and Gardner (1997) showed that this figure might be an underestimate, with the true relative risk being closer to 15. Thus, our results provide further support for their finding.

Morbidity Risk of Other Axis I Disorders. Similar to previous researchers, we did not find that the FDRs of schizophrenia probands were at increased risk for alcohol use disorders. Although previous studies suggested that nonschizophrenia nonaffective psychosis and psychotic affective disorders may be also part of the schizophrenia spectrum (Kendler et al. 1993*a*), only one FDR was found to have schizophreniform disorder in this study. In contrast, the morbidity risk of major depression and dysthymia was found to be significantly higher than that of the general population in this study. When a nationwide epidemiological study in Taiwan (Hwu et al. 1989; Compton et al. 1991) was taken as comparison, the risk ratio in the Kaplan-Meier estimate was significantly higher than one for major depression (3.3) and dysthymia (5.9), although lower than that of schizophrenia (14.4). However, when the figure from a recent community survey in Chinshan Township was taken as comparison, the risk ratio of major depression was no longer higher than 1, but that of dysthymia was still as high as 3.2.

The differences in prevalence of depressive disorders in these two epidemiological studies might be due to their differences in cohorts and methodology. The nationwide survey by Hwu et al. (1989), which was carried out in the early 1980s, employed a one-phase design and used the Diagnostic Interview Schedule as the instrument for psychiatric assessment. The survey in Chinshan Township was performed in the late 1990s and adopted a two-phase survey with the DIGS-C as the diagnostic interview at phase 2. Recent cohorts of the population may have increased prevalence of depressive disorders (Cross-National Collaborative Group 1992). Besides, more detailed coverage on depressive disorders and semistructured interviewing of the DIGS-C performed by interviewers with a longer training period might in part account for the higher prevalence of depressive disorders in the Chinshan study. Because the present study and the Chinshan study used the same diagnostic instrument, their estimates

were more comparable. Thus, the higher risk of dysthymia in FDRs of schizophrenia probands could not be accounted for by different instruments.

Previous studies have shown conflicting results regarding the relationship between affective illness and the schizophrenia spectrum. As reviewed by Kendler and Diehl (1993), one study (Frangos et al. 1985) found that FDRs of schizophrenia probands had lower risk for affective illness than FDRs of control probands, two studies (Gershon et al. 1988; Maier et al. 1990) found that FDRs of schizophrenia probands had a higher risk for affective illness than FDRs of control probands, and the remaining studies found that the risk for affective illness in both groups of relatives was similar. It is interesting to note that both Gershon et al. (1988) and Maier et al. (1990) found that only unipolar and not bipolar illness was significantly more common in relatives of schizophrenia probands than in relatives of control probands. This is similar to our finding. Furthermore, the present study showed that the increase in unipolar illness was in dysthymia and not in major depression. Whether this was due to the chronic stress of living with a relative with schizophrenia or a correlation between susceptibility for schizophrenia and dysthymia warrants further investigation. There were no patients diagnosed as having schizoaffective disorder in the present study. Two factors may account for this. First, the use of this diagnostic category tends to be conservative in Taiwanese psychiatry. Second, in view of the poor interrater reliability of schizoaffective disorder reported in the reliability study of the DIGS (Nurnberger et al. 1994), we might have adopted more stringent criteria for this category at meetings for diagnostic consensus.

It is interesting to note that the sensitivity of FIGS in detecting Axis I disorders other than schizophrenia is much lower than that of the DIGS. Very few relatives were found to meet diagnostic criteria when assessment was based solely on family history. This is consistent with previous findings of the low sensitivity (usually < 50%) of the family history method in diagnosing nonpsychotic disorders (Rice et al. 1995; Roy et al. 1996; Davies et al. 1997; Li et al. 1997).

Lifetime Prevalence of Personality Disorders. The lifetime prevalence of schizophrenia-related personality disorders in the directly interviewed FDRs of schizophrenia probands in this study varied substantially pending on the stringency used in the diagnosis (table 4). Our results indicated that the change might be as large as 2-fold. Many other researchers have also encountered the same situation; they reported either separate figures for different stringency (e.g., Baron et al. 1985) or figures for combined stringency (e.g., Kendler et al. 1993*b*).

Before comparing these prevalences of schizophrenia-related personality disorders across studies, two caveats should be pointed out. First, different diagnostic criteria might have much impact on the estimation of these prevalences. For example, in contrast to *DSM–III*, *DSM–III–R* and *DSM–IV* added an additional criterion (odd/eccentric behavior) to the diagnosis of schizotypal personality disorder and narrowed the diagnostic construct by requiring five of nine instead of four of eight criteria. This might account in part for the findings in an earlier report that employed *DSM–III* criteria, in which the prevalence of schizotypal personality disorder was extremely high (14.6%), followed by 7.3 percent of paranoid personality disorder and 1.6 percent of schizoid personality disorder in the FDRs of schizophrenia probands (Baron et al. 1985).

Second, different instruments might also contribute to differences in estimated prevalences. Among major family studies using personal interviews to estimate for such disorders (Kendler 2000), Maier et al. (1994) reported the lowest prevalences of schizophrenia-related personality disorders in FDRs of schizophrenia probands using Structured Clinical Interview for *DSM–III–R* Personality Disorders (SCID-II): 2.1 percent for schizotypal, 1.7 percent for paranoid, and 0.7 percent for schizoid personality disorders. The authors attributed their findings to poorer sensitivity for general-purpose instruments like SCID-II as compared with instruments specifically designed for schizophrenia-related personality disorders (such as SIS). However, there might still be considerable differences in estimated prevalences of schizophrenia-related personality disorders between two studies even if they employed the same diagnostic instruments. For example, in another study using SCID-II as the diagnostic instrument (Torgersen et al. 1993), the prevalence was much higher (7.5% for schizotypal, 5.2% for paranoid, and 1.5% for schizoid personality disorders) than that of Maier et al. (1994). Similarly, the Roscommon Family Study adopted the same personality assessment tool (i.e., SIS) as the present study. However, the Roscommon study showed a pattern of prevalences different from ours: 6.9 percent for schizotypal, 1.4 percent for paranoid, and 1 percent for schizoid personality disorders (Kendler et al. 1993*b*). It is worthwhile to note that there was a minor modification in the SIS section used in the DIGS, in which a new section on anger to slights was added to meet the *DSM–III–R* diagnostic criterion of paranoid personality disorder. This might lead to the higher prevalence obtained in the present study, although it is doubtful that such a minor modification could account for the large difference in prevalence of paranoid personality disorder between the two studies.

Regardless of the varying prevalences of schizotypal personality disorders in FDRs of schizophrenia probands

in various major family studies, all of them were significantly higher than that of control groups (Kendler and Diehl 1993; Webb and Levinson 1993). In this aspect, our results provide further evidence to support the familial relationship between schizotypal personality disorder and schizophrenia.

Unlike schizotypal personality disorder, only a few studies have examined paranoid personality disorders in the relatives of schizophrenia probands (Stephens et al. 1975; Kendler and Gruenberg 1982; Webb and Levinson 1993). A unique finding of the present study was that the prevalence of paranoid personality disorder (3.4% to 8.6%) in the FDRs of schizophrenia probands was higher than that of schizotypal personality disorder (2.6% to 4.7%). In contrast, schizotypal personality disorder predominates in the FDRs of schizophrenia probands in Western populations. For example, in a study that used the same diagnostic instrument as the present study, paranoid personality disorders had a modest prevalence (1.4%) in the FDRs of schizophrenia probands but was significantly higher than that of control relatives (Kendler et al. 1993*b*). Although this phenomenon might be due to inbred difference in disease expression in different populations, the possibility of cultural difference in matching the definition of schizotypal and paranoid personality disorders could not be excluded (Maier et al. 1994). The latter possibility is supported by our experience that if we deemphasized some items in diagnosis of personality disorders (e.g., broadening the diagnostic threshold by allowing one criterion to be met in borderline fashion), we would have a remarkable increase in prevalence. This result implies the significance of the culture-equivalence issue in the diagnosis of schizophrenia-related personality disorders.

Another possibility is that overlapping features between schizotypal personality disorder and paranoid personality disorder make independent diagnosis of each disorder more difficult (Livesley and Schroeder 1990; Levinson and Mowry 1991; Fulton and Winokur 1993). One way to surpass this difficulty is to combine both disorders in diagnosis. When definite diagnosis of either schizotypal or paranoid personality disorders was considered, 14 FDRs (6%) of schizophrenia probands had either diagnosis in the present study, but the figure increased to 28 (12%) when broad diagnosis was considered. The corresponding figure in the Roscommon Family Study (8.3%, Kendler et al. 1993*b*) was in between these two estimates.

Even fewer studies have examined the genetic relationship between schizoid personality disorder and schizophrenia. Generally speaking, the prevalence of schizoid personality disorder in FDRs of schizophrenia probands is consistently low (around 1%) across studies. In this study, only when broad diagnosis was considered did the prevalence of schizoid personality disorder become higher than that of the general population. A moderate but significant relationship between schizoid personality disorder and schizophrenia was also reported in the Roscommon Family Study (Kendler et al. 1993*b*). However, some studies did not support this relationship and did not include schizoid personality disorder as one of the schizophrenia spectrum disorders (Levinson and Mowry 1991; Fulton and Winokur 1993). Because the number of the subjects with schizoid personality disorder in most studies is small, it is still difficult to make conclusions regarding the genetic relationship between schizoid personality disorder and schizophrenia.

Clinical Implications. Clear delineation of the boundaries of the schizophrenia spectrum not only contributes to the selection of informative phenotypes for linkage studies but also provides the opportunity to use genetic data to validate clinical diagnoses (Prescott and Gottesman 1993). However, as discussed earlier and reviewed by Kendler (2000), the reported risk ratios and hence the boundaries of the schizophrenia spectrum differ considerably across studies, including family studies, twin and adoption studies, and high-risk designs. There are important implications of these findings. The first is the suitability of using operational criteria in diagnosing personality disorders. Most of the personality disorder criteria are dimensional in nature and construct dependent. Alteration in the construct, arbitrary demarcation, and varied ways to stipulate on the operational criteria may all influence the validity of these diagnoses. This effect is more exaggerated in diagnosing less severe or less clearly defined syndromes (Farmer et al. 1992; Parnas 2000). As pointed out earlier in this article, minor modifications in the assessment tools (SIS) and cultural difference in matching the diagnostic criteria of personality disorders might have led to the increased prevalence of paranoid personality disorders in this study. Thus, as Parnas (2000) suggested, more integrated phenomenological approaches for the revision of diagnostic criteria of personality disorders are indicated.

The second implication is whether schizophrenia-related personality disorders are lifelong traits or have a risk period as schizophrenia disorders do. In the present study, we adopted Kendler et al.'s (1993*b*) argument that estimation of the age of onset of personality disorders was impractical and thus did not perform age correction in calculating the risks for these disorders. Nevertheless, it remains to be determined whether onset age can be reliably identified in the life history of schizotypal or paranoid subjects and to make the correction for age necessary in estimating morbidity risk for these personality disorders (Lenzenweger 1994).

The final implication, maybe the most frustrating for genetic studies of schizophrenia, is that the morbidity risk may be underestimated because of unexpression of geno-

types (Gottesman and Bertelsen 1989). As shown in this study, the three schizophrenia-related personality disorders can be included in the spectrum of schizophrenia on the basis of their increased relative risk among FDRs of schizophrenia probands. However, this expansion of phenotype definition should be balanced by the potential pitfall of including "phenocopies" (i.e., those who have the phenotypes but do not carry the susceptible genotypes). This can be judged by the recurrence risk ratio. In this regard, including schizophrenia-related personality disorders in the spectrum did not increase the recurrence risk ratio (3.0 to 5.9) as compared with that of schizophrenia alone (9.3 to 14.4). One way to surpass this difficulty is to incorporate measurements on the so-called endophenotypes of schizophrenia (Lenzenweger 1994; Tsuang and Faraone 2000). For example, the recurrence risk ratios of sustained attention deficit as measured by the Continuous Performance Test alone was as high as 30 (Chen et al. 1998*b*; Chen and Faraone 2000). Thus, in assessing subjects at increased risk for schizophrenia, clinicians or researchers may need to measure some neurobehavioral characteristics rather than solely relying on traditional symptoms and signs.

In summary, the present study indicates that schizotypal and paranoid personality disorders are part of the schizophrenia spectrum, while schizoid personality may be as well. The role of dysthymia is still questionable. However, on the basis of the recurrence risk ratios, including these personality disorders in the spectrum does not increase power for linkage analysis of schizophrenia.

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