ORIGINAL ARTICLE

The Structure of Psychosis

Latent Class Analysis of Probands From the Roscommon Family Study

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Background: The nosologic structure of psychotic illness, still influenced as much by historical as empirical perspectives, remains controversial.

Methods: Latent class analysis was applied to detailed symptomatic and outcome assessments of probands (n=343) with broadly defined schizophrenia and affective illness ascertained from a population-based psychiatric registry in Roscommon County, Ireland. First-degree relatives (n=942) were assessed by personal interview and/or review of hospital record.

Results: Six classes were found, all of which bore substantial resemblance to current or historical nosologic constructs. In order of decreasing frequency, they were (1) classic schizophrenia, (2) major depression, (3) schizophreniform disorder, (4) bipolar-schizomania, (5) schizodepression, and (6) hebephrenia. These classes differed on many historical and clinical variables not used in the latent class analysis. Compared with relatives of controls, significantly increased rates of major depression were seen in relatives of depressed and schizodepressed probands. Significantly increased rates of bipolar illness were restricted to relatives of bipolar-schizomanic probands. The risks for schizophrenia and schizophrenia spectrum disorders were significantly increased in relatives of all proband classes except major depression. This increase was moderate for bipolar-schizomanic probands, substantial for schizophrenic, schizophreniform, and schizodepressed probands, and marked for hebephrenic probands.

Conclusions: These results suggest a relatively complex typology of psychotic syndromes consistent neither with a unitary model nor with a Kraepelinian dichotomy. The familial vulnerability to psychosis extends across several syndromes, being most pronounced in those with schizophrenialike symptoms. The familial vulnerability to depressive and manic affective illness is somewhat more specific.

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THE NOSOLOGIC structure of psychotic illness has been debated since the beginnings of psychiatry.[1-4] While many diagnostic systems have been proposed, most attention has focused recently on 3: (1) the unitary model, (2) Kraepelin's dichotomous model, and (3) the *DSM-III* model. The unitary model of psychosis, dating back into the 19th century[5] and recently championed by Menninger et al[6] and Crow,[1,4] hypothesizes a single continuum of psychotic illness. The clinical diversity of psychosis is explained as resulting either from quantitative variation along this single dimension or from different stages in the longitudinal course of one illness entity.

Kraepelin[7] has been widely credited with dividing psychotic illnesses into 2 categories: dementia praecox and manic-depressive insanity. While an oversimplification (Kraepelin always recognized a category of paranoia[8] and late in life delineated another group of delusional psychoses, the paraphrenias[9,10]), this remains the most historically influential typology in psychiatry.

Beginning with the Kraepelinian dichotomy, the developers of *DSM-III*,[11] *DSM-III-R*,[12] and *DSM-IV* [13] added other historical traditions, including schizoaffective disorder,[14,15] paranoid or delusional disorders,[16] schizophreniform disorder,[17,18] and atypical psychosis.

See also pages 502 and 508

Many studies, using a range of statistical methods, have examined the typology of psychosis.[2,19-27] In this study, we apply latent class analysis (LCA) to probands from the Roscommon Family Study and attempt to validate the resulting typology.

This article is also available on our Web site: www.ama-assn.org/psych.

SUBJECTS AND METHODS

SAMPLE

The Roscommon Family Study is an epidemiologically based family study of major psychiatric illness conducted in the west of Ireland.[28] Two groups of index probands were ascertained from the population-based Roscommon County Case Register[29]: (1) "schizophrenic"—all subjects with any diagnosis of schizophrenia in the registry born in or after 1930 (n=303); and (2) "affective"—a randomly chosen subsample of 75% of the subjects from the case register with any diagnosis of major affective disorder born in or after 1925 (n=99).[28] In addition, an unscreened matched sample of control probands (n=150) was also included in the study. Of the schizophrenic probands, 18 were ascertained through 2 private hospitals and we could not access these individuals, reducing the number of schizophrenic probands to 285. On average 15 years after onset, we followed up all 384 index probands of whom 37 were dead, 23 were untraceable, 50 refused interview, and 274 were personally interviewed by 1 of 2 Irish psychiatrists (M. McGuire, MB, and M. NiNuallain, MB). Medical records were obtained on 359 probands.

We attempted to personally interview, without knowledge of the status of the proband, all first-degree relatives of the index and control probands, aged 16 years and older and residing in Ireland, Northern Ireland, and central or eastern England. We also obtained, wherever possible, and abstracted psychiatric hospital records for all hospitalized relatives. As several individuals and families were ascertained more than once, to obtain the correct risk in relatives we used the general proband method, in which all individuals are counted once for each time they are independently ascertained. Of the living and traceable relatives of all proband groups, 86% (n=1753) were personally interviewed.

The personal interview with probands and relatives was based on the Structured Clinical Interview for *DSM-III-R* Diagnoses[30] for Axis I disorders and the Structured Interview for Schizotypy[31] for schizophrenia-related personality disorders.

Blind, best-estimate diagnoses using all available information were also made for all relatives and probands with personal interviews and/or hospital records using *DSM-III-R* criteria[12] by one of us (K.S.K.) or Alan M. Gruenberg, MD, with high interrater reliability.[28] In addition to coding diagnoses, 2 of us (K.S.K. and A.M.G.) completed the Major Symptoms of Schizophrenia Scale (MSSS),[32] an instrument designed for use in a best-estimate procedure to code symptom and course features as assessed over the *entire* duration of illness. The MSSS contains 9 symptomatic dimensions, as well as ratings of the chronicity of course and global outcome, course being rated on a 5-point scale and outcome on a 4-point scale. The reliability of the MSSS was tested on 47 subjects with psychotic illness rated blindly by one of us (K.S.K.) and Alan M. Gruenberg, MD. Intraclass correlations for these 11 variables ranged from 0.60 to 0.91 with a mean ± SD of 0.77±0.11. In addition, for all individuals demonstrating psychotic or major affective syndromes, one of us (K.S.K.) completed the 74-item version of the OPCRIT checklist.[33] This checklist covers a wide range of historical, psychotic, and affective symptoms, with a manual of definitions. High interrater reliability has been demonstrated on this instrument by its developers.[33]

Eligible for inclusion in the LCA were all probands originally ascertained from the Roscommon case registry with a diagnosis of schizophrenia or affective illness who had adequate clinical information for a final project diagnosis (n=374). Thirty individuals were excluded as lacking a final project diagnosis of psychotic or major affective illness or clinical information detailed enough for extensive coding of historical and symptomatic features. Individuals with a clinical diagnosis of simple schizophrenia were included in these analyses.[32]

We used the term *all nonaffective psychoses* to refer to *DSM-III-R* schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, and atypical psychosis. Total schizophrenia spectrum refers to these disorders plus schizotypal and paranoid personality disorder.

Continued on next page

RESULTS

LATENT CLASS ANALYSIS

In applying LCA to the individual symptoms from the 343 probands, we found continued improvement in fit up through a 6-class solution (results available on request). The results of this solution are given in **Table 1**. In order of declining frequency, the first class—which consisted of 26.2% of the sample—was characterized by prominent delusions, hallucinations, and negative symptoms, low levels of affective symptoms, and a chronic course and poor outcome. This clinical picture was very similar to the descriptions of schizophrenia by Kraepelin[7] and Bleuler[39] and is hence termed *classic schizophrenia*.

The second class, which comprised 20.8% of the sample, rarely demonstrated psychotic and negative symptoms and had a benign course of illness and good outcome. Manic symptoms were nearly absent, but depressive symptoms were common and prominent. Affective symptoms were seen to dominate the clinical picture in nearly all cases. This syndrome is easily recognizable as *major depression*.

The third class, made up of 18.0% of the probands, had levels of delusions and hallucinations similar to those seen in classic schizophrenia, but had less prominent negative symptoms, a more benign course of illness, and a much better outcome. In particular, this class was characterized by short episodes of illness—as those ill for 6 months or more (only 16%)—was the lowest seen for any proband class. Affective symptoms were sometimes present—more frequently manic than depressive—but these symptoms rarely dominated the clinical picture. This class is termed *schizophreniform disorder* because of its close resemblance to the syndrome first described by Langfeldt.[17]

The fourth class—which consisted of 17.6% of the sample—displayed the broadest array of symptoms. Individuals so classified were characterized by prominent psychotic, manic, and depressive symptoms. Intermedi-

CHOICE OF VARIABLES FOR THE LCA

Twenty-one items, chosen to represent a broad range of symptoms and signs, were used in the LCA. Of these, 19 came from the OPCRIT checklist, 12 of which were original OPCRIT items. The remaining 7 were compound items developed to increase symptom coverage while keeping the number of items—and the resulting computational burden—in the LCA within limits. These 7 items (with our new name in italics) and the OPCRIT items from which they were formed were "speech difficult to understand," "incoherent,"and "positive formal thought disorder" into *positive thought disorder*; "restricted affect" or "blunted affect" into *reduced affect*; "thought insertion," "thought withdrawal," and "thought broadcast" into *Schneiderian delusions*; "third-person auditory hallucinations" and "running commentary voices" into *Schneiderian hallucinations*; "abuse/accusatory/persecutory voices" and "other (nonaffective) auditory hallucination" into *other auditory hallucinations*; "agitated activity" and "slowed activity" into *psychomotor change*; and "poor appetite" and "weight loss" into *reduction in appetite/weight*. These compound items were counted positive if 1 or more of the constituent OPCRIT items were positive.

While most OPCRIT items were scored as present or absent, several had 3 or 4 response options. To reduce these to dichotomies for LCA, those with a 0, 1, or 2 scoring were counted positive if a 1 or 2 was present. Those with a 0, 1, 2, or 3 scoring were counted positive if a 2 or 3 was given. The 16 symptomatic items derived from the OPCRIT were distributed as follows: positive psychotic symptoms, 5 items; negative symptoms, 2 items; manic symptoms, 4 items; and depressive symptoms, 5 items. The remaining 3 OPCRIT items reflected length of illness, the presence of deterioration, and predominant affective symptoms.

As the OPCRIT checklist contained no items that directly assessed the key nosologic constructs of course or outcome, we added 2 items from the MSSS that assessed global course (from single acute episode to chronic course with no recovery) and outcome.

STATISTICAL METHODS

Latent class analysis, a statistical tool best characterized as a "categorical analog" of factor analysis,[34] assumes that there exist, in the population under study, a certain number of mutually exclusive and exhaustive classes of subjects. The distribution of responses to each item is entirely determined by class membership. Within each class, responses to individual items are independent.

Using a FORTRAN program,[35] we applied LCA to a 344×21 (individual probands × symptom items) data matrix. Individual probands were assigned class membership on the basis of the likelihood of their particular item profile.

To validate the LCA solution, we first examined historical and symptomatic data not used in the LCA. For categorical variables, we used 2×6 χ^2 analyses that, if significant, were followed by a series of 2×2 χ^2 analyses. For continuous measures (eg, age at onset), a 1-way analysis of variance was used followed by multiple comparisons using the Tukey-Kramer Studentized Range test.[36]

Second, we examined the pattern of risk of *DSM-III-R*–defined psychiatric disorders in relatives of the LCA-defined proband classes. Morbid risk was calculated by the lifetable method (LIFETEST in SAS[36]) using relatives with personal interviews. We tested the difference in risk against relatives of unselected controls and relatives of the "classic schizophrenia" class. These analyses were performed using the Cox proportional hazard model (PHREG[36]), including relatives with only hospital records, controlling for relationship to proband, and presence/absence of a personal interview.

In comparing the risk of psychotic and affective illness in relatives of LCA-defined proband groups vs relatives of controls, we are testing directional hypotheses—that the risk for homotypical disorders will be higher in the relatives of the LCA probands. This expectation is in accord with prior studies of the familial aggregation of psychotic[37] and affective disorders.[38] Therefore, for these analyses we used 1-tailed *P* values. All other results reported here use a 2-tailed test.

ate levels of negative symptoms were seen. The course was generally benign and outcome nearly always favorable. In approximately three quarters of these cases, the affective symptoms were predominant. We found no single term that succinctly described this class, settling on the compound name of *bipolar-schizomania*.

The fifth class comprised 14.5% of probands. Compared with those with classic schizophrenia, these individuals had more prominent psychotic symptoms and a similar level of negative symptoms. Yet, members of this fifth class had depressive symptoms nearly as prominent as those seen in major depression. Of all the classes, only this one had an intermediate course and outcome, much worse than that seen with major depression, but somewhat better than that seen with classic schizophrenia. Affective symptoms were seen as clinically predominant in only around one seventh of these cases. We called this class *schizodepression*, although clinically this class appeared to resemble schizophrenia a good deal more than typical major depression.

The sixth, and by far the rarest class, constituted only 3.6% of the sample. The symptom profile closely resembled that seen with classic schizophrenia with 2 noteworthy differences. Individuals in this class were much more likely than those with classic schizophrenia to be thought disordered and to demonstrate symptoms that might be considered excited, manic, or disinhibited. Both groups had prominent negative symptoms, a chronic course, and very poor outcome. This clinical picture most closely resembled the classic descriptions of *hebephrenia*.[40]

COMPARISON WITH *DSM-III-R* DIAGNOSES

Table 2 depicts the relationship between LCA class membership and hierarchical *DSM-III-R* diagnoses assigned to these probands. The association between these 2 classifications was highly significant (χ^2_{30}=614.6, $P \ll .001$). Of those classified as classic schizophrenia, 84% were diagnosed as schizophrenia by *DSM-III-R*. Of the pro-

Table 1. Observed Class Membership and Endorsement Frequencies of 21 Clinical Items in the Best-Fitting 6-Class Latent Class Analysis Model

Clinical Items	Class 1: Classic Schizophrenia	Class 2: Major Depression	Class 3: Schizophreniform Disorder	Class 4: Bipolar-Schizomania	Class 5: Schizodepression	Class 6: Hebephrenia
Frequency, % of symptoms	26.2	20.8	18.0	17.6	14.5	3.0
Ill 6 mo	0.75	0.28	0.16	0.39	0.73	0.79
Positive thought disorder	0.37	0.01	0.36	0.33	0.27	0.69
Negative thought disorder	0.53	0.02	0.05	0.02	0.34	0.41
Affective symptoms predominate	0.00	0.93	0.18	0.76	0.14	0.20
Reduced affect	1.00	0.13	0.64	0.46	0.95	0.91
Persecutory delusions	0.63	0.09	0.64	0.59	0.92	0.40
Schneiderian delusions	0.18	0.05	0.16	0.17	0.42	0.40
Schneiderian hallucinations	0.19	0.01	0.12	0.12	0.52	0.58
Other auditory hallucinations	0.64	0.04	0.51	0.45	0.89	0.79
Deterioration from premorbid condition	1.00	0.02	0.23	0.31	0.91	1.00
Elevated mood	0.01	0.02	0.35	0.91	0.00	0.79
Excessive activity	0.00	0.00	0.31	0.88	0.00	1.00
Reckless acts	0.01	0.00	0.22	0.60	0.00	0.70
Pressured speech	0.04	0.00	0.31	0.93	0.04	1.00
Dysphoria	0.07	1.00	0.19	1.00	1.00	0.21
Psychomotor change	0.02	0.70	0.09	0.78	0.76	0.20
Tired	0.06	0.84	0.03	0.84	0.65	0.10
Excessive self-reproach	0.03	0.40	0.00	0.39	0.30	0.10
Reduction in appetite/weight	0.03	0.68	0.02	0.56	0.60	0.00
Chronic course	0.58	0.00	0.00	0.01	0.30	0.60
Poor outcome	0.81	0.00	0.00	0.11	0.35	0.79

bands placed in the major depression class, more than 95% were diagnosed as major depression. Individuals placed in the schizophreniform disorder class were more heterogeneous, most commonly receiving *DSM-III-R* diagnoses of other nonaffective psychosis (54%), schizophrenia (21%), and bipolar illness (15%).

Probands classified as bipolar-schizomania were most frequently diagnosed as bipolar illness (57%) or schizoaffective disorder (32%). Those assigned the class of schizodepression were commonly diagnosed as schizophrenia (58%) or schizoaffective disorder (26%). Hebephrenia was assigned to individuals diagnosed either as schizophrenia (60%) or schizoaffective disorder (30%). Of the 10 individuals given a clinical diagnosis of simple schizophrenia,[32] 9 were assigned to the classic schizophrenia and 1 to the hebephrenia class.

OTHER CLINICAL FEATURES IN THE CLASSES

Table 3 depicts the clinical features of the 6 LCA classes using age at onset and OPCRIT checklist variables not included in the LCA analysis. Significant differences across the classes were seen for all these items. Although the results varied across individual variables, in general major depression, sometimes accompanied by bipolar-schizomania was most frequently differentiated from the other classes, especially classic schizophrenia, schizodepression, and hebephrenia.

It is of particular interest to examine items from variable domains not included in the LCA. Compared with all other classes, major depression had a significantly later age at onset, higher levels of insight, and lower levels of bizarre behavior and inappropriate affect. Individuals with major depression and schizomania, sometimes accompanied by schizophreniform disorder, had better premorbid and current social functioning.

RISK OF ILLNESS IN RELATIVES—*DSM-III-R* DIAGNOSES

As seen in **Table 4**, compared with relatives of controls, the risk for schizophrenia was significantly increased in relatives of all proband classes except major depression. The increased risk was moderate in relatives of probands with bipolar-schizomania; substantial in relatives of probands with classic schizophrenia, schizophreniform disorder, and schizodepression; and especially marked in relatives of hebephrenic probands. The same pattern of findings was seen for all nonaffective psychoses and for the schizophrenia spectrum.

Compared with relatives of probands with classic schizophrenia, the risk for schizophrenia, all nonaffective psychoses, and schizophrenia spectrum was significantly higher in relatives of hebephrenic probands. Relatives of probands with major depression had, compared with relatives of classic schizophrenic probands, significantly lower risks for all nonaffective psychoses and schizophrenia spectrum.

The risk for total affective illness significantly exceeded that seen in relatives of controls only in relatives of probands with major depression and schizodepression. The risk was also elevated in relatives of bipolar-schizomanic probands, but this fell just short of statistical significance (P=.08). The risk for total affective illness was significantly greater in relatives of major depressive vs classic schizophrenia probands.

Relatives of 3 proband groups demonstrated substantial elevations in risk for bipolar illness—major de-

Table 2. Relationship Among Probands, Between LCA-Assigned Class and Best-Estimate *DSM-III-R* Diagnosis*

DSM-III-R Diagnoses	Class 1: Classic Schizophrenia	Class 2: Major Depression	Class 3: Schizophreniform Disorder	Class 4: Bipolar-Schizomania	Class 5: Schizodepression	Class 6: Hebephrenia
Schizophrenia	76 (84.4)	0	13 (21.3)	2 (3.3)	29 (58.0)	6 (60.0)
Schizoaffective disorder	1 (1.1)	0	3 (4.9)	19 (31.7)	13 (26.0)	3 (30.0)
Other nonaffective psychoses	4 (4.4)	3 (4.2)	33 (54.1)	3 (5.0)	3 (6.0)	0
Bipolar disorder	0	0	9 (14.8)	34 (56.7)	0	0
Unipolar disorder	0	69 (95.8)	3 (4.9)	2 (3.3)	5 (10.0)	0
Simple schizophrenia†	9 (10.0)	0	0	0	0	1 (10.0)
Total No.	**90 (100)**	**72 (100)**	**61 (100)**	**60 (100)**	**50 (100)**	**10 (100)**

**Values are given as number (percentage). LCA indicates latent class analysis.*
†For criteria used, see Kendler et al.[32]

Table 3. Frequency of Endorsement of Validating Items by Class

	Class 1: Classic Schizophrenia	Class 2: Major Depression	Class 3: Schizophreniform Disorder	Class 4: Bipolar-Schizomania	Class 5: Schizodepression	Class 6: Hebephrenia	Classes That Are Significantly Different*
Mean age at onset, y	25.20	32.80	28.00	27.70	26.20	25.70	1345;26
Single	0.90	0.36	0.74	0.57	0.76	1.00	1356;46;24
Unemployed	0.56	0.06	0.19	0.19	0.37	0.50	156;345;234
Poor premorbid social adjustment	0.51	0.20	0.16	0.09	0.40	0.33	156;2356;2346
Poor premorbid work adjustment	0.38	0.00	0.12	0.00	0.16	0.50	156;356;24
Premorbid personality disorder	0.37	0.10	0.18	0.08	0.26	0.33	156;23456
Bizarre behavior	0.70	0.04	0.48	0.47	0.54	0.80	13456;2
Catatonia	0.22	0.01	0.07	0.02	0.12	0.10	1356;2346
Inappropriate affect	0.60	0.01	0.28	0.23	0.43	0.70	156;3456;2
Difficulty establishing rapport	0.77	0.00	0.18	0.17	0.53	0.70	156;34;2
Well-organized delusions	0.37	0.03	0.33	0.15	0.59	0.50	1356;1346;1234
Grandiose delusions	0.26	0.01	0.28	0.32	0.20	0.20	13456;2
Bizarre delusions	0.47	0.03	0.31	0.23	0.58	0.40	1356;346;2
Delusions of passivity	0.38	0.07	0.30	0.28	0.64	0.50	56;1346;2
Delusions and hallucinations ≥1 wk	0.44	0.04	0.41	0.32	0.80	0.60	56;1346;2
Lack of insight	0.99	0.04	0.80	0.63	0.82	1.00	16;3456;2
Any nonaffective delusions	0.69	0.03	0.57	0.45	0.86	0.90	156;346;2
Increased self-esteem	0.01	0.00	0.15	0.37	0.00	0.10	346;1256
Distractibility	0.01	0.00	0.20	0.55	0.04	0.40	46;36;35;125
Excessive self-reproach	0.02	0.39	0.00	0.38	0.30	0.10	2456;136
Suicidal ideation	0.07	0.50	0.08	0.47	0.48	0.10	2456;346;136
Initial insomnia	0.03	0.83	0.07	0.72	0.64	0.10	245;136
Early-morning waking	0.02	0.58	0.05	0.57	0.40	0.00	245;56;136

**That is, classes listed together do not differ significantly by post hoc tests. So, for the proportion of subjects who are "single," classes 2 and 4 do not differ significantly, nor do classes 4 and 6, nor do classes 1, 3, 5, and 6. If classes are not listed together, then they do differ significantly by post hoc tests. So, for "single," class 2 differs significantly from classes 1, 3, 4, 5, and 6 but not from class 4. However, class 4 differs significantly only from classes 1, 3, 5, and 6.*

pression, schizophreniform disorder, and bipolar-schizomania. However, only in relatives of bipolar-schizomanic probands did the risk for mania significantly exceed that found in relatives of controls. The risk for unipolar illness significantly exceeded that found in relatives of control probands only in relatives of probands with major depression and schizodepression.

COMMENT

We applied LCA to the epidemiological proband sample from the Roscommon Family Study, and then attempted to validate the resulting typology using historical and symptom data and the pattern of disorders in relatives. We review, in turn, the resulting 6 classes.

CLASSIC SCHIZOPHRENIA

Latent class analysis defined a class of probands—characterized by positive psychotic symptoms, prominent negative symptoms, chronicity, and a poor outcome with deterioration—which closely resembles the classic descriptions of Kraepelin[7] and Bleuler.[39] However, while Bleuler noted that affective symptoms were common in schizophrenia,[39] individuals in this class had almost no depressive or manic symptoms.

This group was also characterized by low rates of marriage, employment, and insight and poor premorbid social and occupational adjustment. Compared with relatives of controls, relatives of probands with classic schizophrenia had increased risks for schizophrenia and schizo-

Table 4. Morbid Risk of Psychotic and Affective Illness, as Defined by *DSM-III-R*, in Relatives of Probands in LCA-Assigned Classes*

Class	Relatives, No.	Schizophrenia	All Nonaffective Psychoses	Schizophrenia Spectrum	Total Affective Illness	Bipolar Illness	Unipolar Illness
Classic schizophrenia	232	5.1 ± 1.6†	7.9 ± 2.0†	13.6 ± 2.4†	25.3 ± 4.8	1.4 ± 0.8	24.1 ± 4.8
Major depression	240	1.9 ± 0.9	3.3 ± 1.3‡	6.4 ± 1.7§	37.8 ± 7.2†‡	4.7 ± 3.2	33.7 ± 6.9‖
Schizophreniform disorder	161	5.7 ± 2.0†	13.8 ± 3.7†	16.6 ± 3.9†	22.8 ± 5.8	5.3 ± 3.9	17.3 ± 4.7
Bipolar-schizomania	194	3.8 ± 1.8‖	9.0 ± 2.7†	13.0 ± 2.9†	36.9 ± 12.3	4.4 ± 2.3‖	33.1 ± 12.8
Schizodepression	178	6.5 ± 2.5†	12.4 ± 3.7†	19.0 ± 4.2†	28.5 ± 5.2†	2.8 ± 1.4	25.9 ± 5.2‖
Hebephrenia	31	16.1 ± 6.6†‡	25 ± 8.6†‡	45.5 ± 10.1†§	10.3 ± 5.6	0 ± 0	10.3 ± 5.6
Control	584	0.5 ± 0.3§	1.9 ± 0.7§	3.7 ± 0.9§	23.2 ± 3.9	0.8 ± 0.5	21.8 ± 3.9

*Values are given as morbid risk ± SE. Statistical significance was determined by Cox proportional hazard analysis,[36] controlling for the relationship to proband and the presence of a personal interview. LCA indicates latent class analysis.

†Risk of illness in relatives compared with relatives of controls: $P<.01$.

‡Risk of illness in relatives compared with relatives of classic schizophrenia probands: $P<.05$.

§Risk of illness in relatives compared with relatives of classic schizophrenia probands: $P<.01$.

‖Risk of illness in relatives compared with relatives of controls: $P<.05$.

phrenia spectrum disorders, but no increased risk for affective illness. Probands with a diagnosis of "simple schizophrenia" were nearly all assigned to this class, supporting the suggestion that simple schizophrenia is closely related syndromally to classic schizophrenia.[32]

Overall, these results support the validity of the narrowly defined "schizophrenia" construct as conceptualized by Kraepelin and operationalized by *DSM-III*,[11] *DSM-III-R*,[12] and *DSM-IV*.[13]

MAJOR DEPRESSION

Our LCA identified a syndrome that closely resembles both historical and current concept of major depression,[41,42] characterized by prominent depressive symptoms. Both negative symptoms and chronicity were rare. No individual in this class had a poor outcome. Around 10% demonstrated psychotic symptoms—most commonly persecutory delusions.

Compared with all other proband classes, individuals classified as having major depression had the highest rates of marriage and employment, the lowest rate of abnormal premorbid personality, and, in their relatives, the lowest risk for schizophrenia and schizophrenia spectrum illness and the highest risk for total affective and unipolar illness. These results provide substantial support for a Kraepelinian concept of good-outcome depressive illness that is distinct from other clinical syndromes in terms of symptoms, course, and family background.

SCHIZOPHRENIFORM DISORDER

As originally proposed by Langfeldt,[17,43] schizophreniform disorder was characterized by schizophrenialike symptoms and a good prognosis. Since its incorporation into *DSM-III*, this diagnostic category has attracted considerable controversy,[18,44] it being argued that this disorder (1) is closely related to affective illness,[45] (2) has a close relationship with schizophrenia,[46,47] (3) is an independent psychotic illness,[48] or (4) is a heterogeneous group of psychotic syndromes.[18]

In our LCA, we identified a class of ill probands similar to that first described by Langfeldt. Compared with probands with classic schizophrenia, probands in this class had (1) comparable levels of positive psychotic symptoms, (2) lower levels of negative symptoms and deterioration and (3) much shorter episodes, (4) more manic symptoms, and (5) dramatically better outcomes, comparable to that seen with depression.

Attempts at validation of this syndrome were mixed. Compared with classic schizophrenia, individuals with schizophreniform had a higher marital and employment rate and better premorbid functioning. The risk for schizophrenia, all nonaffective psychoses, schizophrenia spectrum disorders, total affective illness, and unipolar illness were indistinguishable in relatives of probands with classic schizophrenia and schizophreniform disorder. Bipolar illness was nonsignificantly more common in relatives of schizophreniform vs classic schizophrenic probands. While the clinical differences between classic schizophrenia and schizophreniform disorder were relatively striking, from the perspective of familial risk factors, our results suggest that they are essentially the same disorder.

BIPOLAR-SCHIZOMANIA

Our LCA identified a class characterized by prominent manic, depressive, and positive psychotic symptoms. The intensity of thought disorder, delusions, and hallucinations resembled those seen in classic schizophrenia and schizophreniform disorder, while the prominence of depressive symptoms was similar to that observed in probands with major depression. With respect to negative symptoms, outcome, and course, individuals in this category functioned much better than probands with schizophrenia, but somewhat worse than those with major depression.

Marital and employment rates were much better in this class than those seen with schizophrenia as was premorbid personality. This was the only group in which the risk for bipolar illness in relatives significantly exceeded that seen in relatives of controls. However, the risk for schizophrenia and schizophrenia spectrum disorders was also significantly elevated in probands with bipolar-schizomania.

This class represents a blending of traditional concepts of bipolar illness and manic schizoaffective disor-

der. This syndrome resembles categories previously described as "delusional mania," "delirious mania,"[49] or "stage 3" mania.[50]

SCHIZODEPRESSION

The fifth LCA class had a level of depressive symptoms similar to that seen with major depression accompanied by the most prominent delusions and hallucinations seen in any class. Chronicity, outcome, and negative symptoms were less pronounced than in classic schizophrenia, but substantially more prominent than in the classes of major depression, schizophreniform disorder, and bipolar-schizomania.

Marital and employment rates and premorbid personality functioning in individuals in this class were some what better than found for classic schizophrenia but considerably lower than seen with the affective and schizophreniform classes. The pattern of risk of illness in relatives was unique. While the risks for schizophrenia and schizophrenia spectrum disorder were indistinguishable from those found for classic schizophrenia, the risk for total affective illness and unipolar illness was also increased in relatives. From a familial perspective, individuals in this class, like patients with bipolar-schizomania, have an increased familial liability to both affective illness and schizophrenia and related disorders.

HEBEPHRENIA

The smallest class was defined by pronounced positive and negative symptoms of schizophrenia, chronicity, and deterioration accompanied by substantial "manic/excited" symptomatology. This unexpected juxtaposition yielded a class that resembles the syndrome of hebephrenia as originally described by Hecker[40] and Kraepelin.[51] In particular, compared with probands with classic schizophrenia, patients in the hebephrenic class had more pronounced positive thought disorder, inappropriate affect, euphoria, bizarre behavior, distractibility, and recklessness.

Despite the prominent manic symptomatology, relatives of these hebephrenic probands demonstrated a paucity of affective illness in relatives rather than an excess. Particularly striking was the substantially increased risk for schizophrenia and schizophrenia spectrum disorders in the relatives of the hebephrenic probands. Several early family studies of schizophrenia also showed a particularly high risk for illness in relatives of hebephrenic probands,[52-54] but this finding has not been replicated in later studies of schizophrenic subtypes.[55-57] Recently, Liang and Pulver[58] found that manic symptomatology in schizophrenic patients meeting *DSM-III* criteria was substantially and positively correlated with risk for schizophrenia in relatives.

CONCLUSIONS

What implications do these findings have for our typology of psychotic illness? These results argue strongly against unitary models of psychosis.[1,4-6] We identified and validated a range of distinct psychotic syndromes that appeared to differ qualitatively from one another. In particular, the pattern of illness in the relatives of these proband classes would be very difficult to explain under the assumption—implicit in the unitary model—that they all represented quantitative variation of a single underlying syndrome.

Our results are also inconsistent with Kraepelin's original typology.[51] In particular, his nosologic framework had no place for our classes of schizophreniform disorder and schizodepression. By contrast, our results are broadly congruent with the current *DSM-IV* typology.[13] In addition to classes of poor-outcome psychotic illness (eg, schizophrenia) and relatively good-outcome affective illnesses, our results suggest that complete nosologic systems need contain categories for both good-outcome psychotic illness and schizoaffective disorder (or at least schizodepression).

Complementing our more conventional prior analyses of the Roscommon Family Study,[28,59,60] these results confirm the nonspecificity of a familial loading for schizophrenia spectrum disorders. An increased risk for these syndromes is seen in relatives of probands with a wide range of psychotic disorders and not just in relatives of probands with schizophrenia.

LIMITATIONS

These results should be interpreted in the context of 3 potentially significant methodological limitations. First, while LCA can indicate whether a pattern of observed symptoms in a population is consistent with the existence of discrete latent classes, this method cannot prove that such discrete classes exist.[34] The utility of the derived classification is best assessed through attempts at validation and independent replication.

Second, the generalizability of our results is limited both by the specific items we chose to include in the LCA and by the patient sample used. For example, if our proband sample had contained more individuals with nonpsychotic mania or with good-outcome psychotic depression, new or different classes might have been identified. While the original probands were representative of all treated cases from a defined epidemiological population[29] and we chose a variety of items for the LCA, representative of a broad range of psychotic and affective symptoms, variation in the patient or item "mix" might well have produced different results.

Third, LCA assumes local independence within the resultant classes. We examined this validity of this assumption in our "hybrid" classes of schizodepression and bipolar-schizomania by examining whether risk of illness in relatives could be predicted within class by the original *DSM-III-R* diagnoses. Although no findings were significant at the 5% level, the risk of total affective illness in relatives of the schizodepression class was increased (odds ratio, 1.87; P=.09) when the original diagnosis of the proband was schizoaffective disorder vs schizophrenia. This finding suggests the possibility of further etiologic heterogeneity within some of the defined classes.

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