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The Role of Gender in Identifying Subtypes of Schizophrenia: A Latent Class Analytic Approach

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Abstract

Past literature suggests that schizophrenic men and women may be at different risks for developing different subtypes of schizophrenia. This hypothesis was tested using data from the well-known retrospective cohort family studies, the Iowa 500 and the Iowa non-500. The sample consisted of 171 male and 161 female *DSM-III* schizophrenic patients and 713 of their first-degree relatives. First, bivariate tests for gender differences were conducted regarding family morbidity, age of onset, premorbid history, season of birth, and expression of deficit and affective symptoms. Restricted maximum likelihood latent class analysis was then used to test whether there was a subgroup of schizophrenic men who were more likely to have a low familial risk for schizophrenia or schizophrenia spectrum disorders, deficit symptoms, poor premorbid history, and birth in the winter months, suggesting possible early environmental insults, compared to schizophrenic women. Results showed that although men were more likely to meet these criteria, women also met them, thus suggesting gender differences in the *prevalence* of the subtype. Schizophrenic women were more likely to express a form of the illness characterized by dysphoria, persecutory delusions, and a higher family morbidity risk for schizophrenia than schizophrenic men. Results for spectrum disorders among relatives were equivocal with regard to gender.

Gender differences in schizophrenia have been reported as far back as Kraepelin (1919/1971), who described dementia praecox as a disorder of young men. Since then, descriptive evidence has accumulated demonstrating gender differences in age of onset, premorbid history, early environmental insults, family morbidity risk, psychopathology, structural and functional brain abnormalities, and course of schizophrenia. Schizophrenic men have consistently been found to have an earlier age of onset than schizophrenic women (Lewine 1988). Men tend to have their peak period of onset from ages 18 to 25 years and women from 25 to 35 years. In addition, it has been found that approximately 3 to 10 percent of female cases have onset of illness after 45 years in contrast to few, if any, male cases. It has also been consistently demonstrated across time period that schizophrenic men have a significantly poorer premorbid history than schizophrenic women (Gittelman-Klein and Klein 1969; Goldstein 1988). Women have a better premorbid picture since they are older and more often married at the time of illness onset, but they tend to have better early childhood histories as well, as defined by school achievement and sociability.

Further, there is evidence that schizophrenic men and women may express the illness differently as well. Schizophrenic women tend to exhibit affective symptomatology such as dysphoria, irritability, and anger, as well as more paranoia and explosivity. Schizophrenic men tend to express more flat affect and other symptoms that resemble a negative or deficit symptom picture (Lewine 1981; Goldstein and Link 1988).

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It is important to relate gender differences in the expression of schizophrenia to descriptive findings on family history and biological factors differentiating schizophrenic men and women. A few studies have found that schizophrenic men are *less* likely to have a family history of schizophrenia than women (Bellodi et al. 1986; Goldstein et al., in press). This may be related to other findings that have indicated that schizophrenic men have more birth complications and neurological deficits than schizophrenic women (Mednick et al. 1978; Goldberg 1985). Although these organic insults are not specific to schizophrenia, perhaps they contribute to the severity of the illness for a subgroup of schizophrenic men. There is some preliminary evidence demonstrating gender differences in the corpus callosum and in ventricle-brain ratios, suggesting more diffuse or left hemisphere dysfunction among schizophrenic men (Flor-Henry 1978; Nasrallah et al. 1986). Some of the studies reported in this issue of the *Schizophrenia Bulletin* have supported these findings (Kopala and Clark 1990; Lewine et al. 1990); one other has questioned them (Nasrallah et al. 1990). This is consistent with early work published by Gur and colleagues on gender differences in cerebral blood flow in different hemispheres of the brain. These findings are reviewed in this issue (Gur and Gur 1990).

Taken together, the findings on gender discussed above suggest that schizophrenic men and women may be at *different* risks for expressing particular forms of the illness. Past research has largely been limited to examining bivariate associations between gender and the factors mentioned previously. We were interested in understanding the effect of gender by examining the joint effects of age of onset, premorbid history, symptom expression, family history, and early environmental insults. We hypothesized that schizophrenic men would be more likely to express a form of illness characterized by an early age of onset, deficit symptomatology, a poor premorbid history, low family morbidity risk for schizophrenia, and early environmental insults. In contrast, schizophrenic women would be more likely to express a form of illness characterized by the expression of affective symptomatology, paranoia, and a higher family risk for schizophrenia.

Methods

The data for this study were from the double-blind retrospective cohort studies conducted in Iowa in the 1970's, the Iowa 500 and the Iowa non-500. Sample selection and procedures for the original studies have been fully described previously (Morrison et al. 1972; Tsuang and Winokur 1975). Probands were selected from a blind review of index admissions, followup records, and interviews of 510 consecutive admissions who had a chart diagnosis of schizophrenia from the Iowa Psychopathic Hospital during 1934-44. Probands and relatives were then rediagnosed by two expert psychiatrist-diagnosticians using *DSM-III* criteria (American Psychiatric Association 1980), although the criterion limiting age of onset to 45 years was eliminated, as in *DSM-III-R* (American Psychiatric Association 1987) (Kendler et al. 1985). Diagnoses of first-degree relatives of probands were based on a blind, personal, structured psychiatric interview (Tsuang et al. 1980), hospital records obtained from a systematic search of the five Iowa public psychiatric hospitals, or a combination of the personal interview and hospital records. Diagnostic procedures and reliability are reported in detail elsewhere (Kendler et al. 1985).

The sample consisted of 332 probands with a *DSM-III* diagnosis of schizophrenia (51.5% men and 48.5% women). A detailed description of the sociodemographic and onset history of the probands, as well as a description of the relatives, is provided in a previous publication (Goldstein et al. 1989). Briefly, the Iowa family studies consisted of a middle to lower middle class, non-Hispanic white population of consecutive admissions to a tertiary university-affiliated facility over a 10-year period. Patients were primarily in the early stages of disorder on admission (i.e., 82% were first admissions) and were followed for an average of almost 30 years.

Variables of interest in this study were obtained from a structured interview developed by Tsuang et al. (1980), medical records, and relatives. The instrument has demonstrated reliability and validity in numerous published articles (e.g., Tsuang et al. 1976; Kendler et al. 1987). Age of onset was defined as the onset of a psychotic symptom or bizarre behavior, which reflects the *DSM-III* criterion for onset of the prodromal or active phase of illness. It was assessed using all available information from probands, relatives, and medical charts. Reliability of age of onset determination was high (0.94) (Kendler et al. 1987). Poor versus good premorbid history was assessed by two expert psychiatrist-diagnosticians after a review

of all medical chart and structured interview information.

The symptom variables were coded from clinician ratings at the time of admission to the hospital. Because of the hypotheses in this study, we were interested in deficit and affective symptoms and paranoia. Deficit symptomatology was operationalized as flat or blunted affect. Dysphoria indicated affective expression, and persecutory delusions indicated severe paranoia. Symptoms were coded dichotomously, as present or absent. Diagnoses in probands and relatives were described previously.

Given that early environmental insults, such as perinatal complications, were not measured in this study, we used winter season of birth as a crude indicator, one that is commonly used in the literature (Hare 1988). Winter birth was assessed as present if a proband was born during December through March. Although January through March is often used as the winter observation period, winter in Iowa begins in the middle to end of November.

Analytic Strategy

Simple bivariate relationships between gender and premorbid history, symptom expression, and winter birth were examined using χ^2 statistics. Gender differences in age of onset and family morbidity risks were examined using survival analysis and have been presented in previous reports (Goldstein et al. 1989; Goldstein et al., in press).

Latent class analysis (LCA) was used to examine the corelationships between variables (Lazarsfeld and Henry 1968; Goodman 1974*a*, 1974*b*, 1979; Clogg 1977; Young 1983). As with other latent variable models, like factor analysis, LCA is a procedure that attempts to explain covariation among a set of observed variables, by modeling the covariation of observed variables with unobserved (and hence latent) variables, that are fewer in number than the observed ones. Since it is assumed that the observed variables are related to each other *only* through the latent variables, the latter have considerable explanatory interest. Unlike factor analysis, LCA is designed for use with dichotomous (or polychotomous) variables and assumes that the latent variables are also categorical. LCA has therefore been referred to as the discrete analog to factor analysis (McCutcheon 1987).

Briefly, LCA works as follows: The data required for input consist of the frequencies of all possible cross-classifications of the observed variables. LCA then uses maximum likelihood estimation to fit one or a series of hypothesized models to explain covariance patterns among the observed variables. Each cell in the data table provides the number of patients with the joint occurrence of the corresponding variables. The fit of a model is measured by the likelihood or probability of the observed pattern of cross-classified data, conditional on the model and the parameter estimates. The parameter estimates that maximize this likelihood function are thus the maximum likelihood estimates (MLEs). If the variables are unrelated, then, allowing for random variability, the observed pattern in the cross-classification table would be completely determined by the product of the corresponding marginal frequencies (i.e., would fit a model of independence). If the variables are related, one can test whether the observed relationships are consistent with (or "can be explained by") the hypothesized latent variables, or classes.

As with other maximum likelihood procedures, a χ^2 goodness-of-fit is used to test whether the *hypothesized* model "fits" the *observed* covariances of the variables. (For details of this procedure, see Lazarsfeld and Henry 1968; Goodman 1974*a*, 1974*b*; Clogg 1977; Young 1983; Young et al. 1986; McCutcheon 1987). An advantage of LCA is that one can simultaneously fit a latent class model to several independent samples (e.g., schizophrenic men and women) and thus test the fit of one's hypothesized model across groups of interest. For example, in this study we will test the overall fit of the subtype model in men versus women, and examine gender differences in specific parameters of the model (Clogg and Goodman 1984).

There are two types of parameters in the latent class model: latent class probabilities and latent conditional probabilities. The latent class probabilities provide information about the frequency of occurrence of each latent class. For example, when the analysis is stratified by gender, the latent class probabilities indicate the number of latent classes and the size of each latent class for schizophrenic men versus women. The latent conditional probabilities provide information about the degree of association between each of the observed variables and the latent classes, and are analogous to factor loadings in factor analysis (McCutcheon 1987). As conditional probabilities, these parameters give the sensitivity of the observed variables for indicating a particular latent class. In this investigation, we were interested in the differential expression of two

hypothesized subtypes (i.e., latent classes) for men versus women; therefore, the parameters of the latent class model were estimated separately for men and for women within a single model. This enabled us to compare the frequency of occurrence of each subtype for men versus women and to evaluate the sensitivity of particular variables for identifying a specific subtype for men versus women.

The statistical significance of differences in parameter estimates was tested by using χ^2 to compare the fit of unrestricted models to models where parameters were restricted to specific values or were given equality or inequality constraints. In particular, values of specific parameters in each subtype were restricted to be either equal across gender, higher in one sex than the other, or different in magnitude across the subtypes within one sex. The goodness-of-fit χ^2 of the unrestricted model is subtracted from the χ^2 of the restricted model to examine whether there is an improvement in fit. The difference between the two χ^2 measures is also distributed as χ^2, with degrees of freedom equal to the difference in degrees of freedom between the two models. If the increase in χ^2 is small relative to the difference in degrees of freedom, the fit of the restricted model is found to be acceptable and the restrictions valid. Using standard errors to estimate confidence intervals for significance testing is inappropriate, since latent class models do not follow assumptions for normal distributions. The LCA software, called Maximum Likelihood Latent Structure Analysis, was developed by Clogg (1977) and adapted to personal computers by Eliason (see McCutcheon 1987).

Results

Bivariate Findings: Gender and Symptom Expression, Premorbid History, Season of Birth, Age of Onset, and Family Morbidity Risk. The χ^2 tests of gender and premorbid history, winter birth, flat affect, persecutory delusions, and dysphoria showed no significant differences. However, more schizophrenic men than women experienced a poor premorbid history (46% of the men vs. 39% of the women) and flat affect (60% of the men vs. 52% of the women). On the other hand, more schizophrenic women than men experienced dysphoria (54% of the women vs. 45% of the men) and persecutory delusions (59.5% of the women vs. 51% of the men). An equal proportion of men and women were born in the winter.

In addition, schizophrenic men experienced an earlier age at onset than schizophrenic women. Survival analysis of gender differences in age of onset showed significant results and were presented in a previous report (Goldstein et al. 1989). Findings showed that by age 25, 53 percent of the men had become ill compared to only 32 percent of the women. Eight percent of women became ill at or after 40 years of age compared to only 1 percent of the men who had onset of illness at 40 years. Schizophrenic men also experienced a mean age of onset of 24.3 (SD = 6.2) years versus 27.9 (SD = 8.3) years for schizophrenic women ($t = 4.4$, $df = 287.6$, $p = 0.0001$).

Gender differences in the familial transmission of schizophrenia and spectrum disorders are presented in detail elsewhere (Goldstein et al., in press). Briefly, results showed that schizophrenic women had a significantly higher familial risk for schizophrenia, schizophreniform, and schizoaffective disorders than relatives of schizophrenic men. The findings were due neither to selection bias nor fertility effects. However, when the definition of illness in relatives was expanded to include the full spectrum (i.e., schizophrenia, schizophreniform disorder, schizoaffective disorder, paranoid disorder, atypical psychosis, and schizotypal personality disorder), the difference in the risk to relatives of male versus female probands was attenuated. This was due to the result that relatives of male probands had a significantly higher risk of schizotypal personality disorder than did relatives of female probands (Goldstein et al., in press).

Covariance Patterns. Although bivariate findings between gender and symptom expression, season of birth, and premorbid history were not significant, we hypothesized that when examined in the context of each other as well as with age of onset and familial risk, significant patterns would emerge. As mentioned, the hypothesis was that there would be a subgroup of schizophrenic men whose form of the illness necessitated early environmental insults, measured as winter birth, and that these men would express the earliest age of onset, poor premorbid history, flat affect, and a lack of ill family members with schizophrenia. In contrast, schizophrenic women were expected to express a form of illness characterized by dysphoria, persecutory delusions, and a higher risk of schizophrenia among their relatives.

First, a test of independence among the observed variables was conducted to test whether the observed variables were related to

each other. Results showed that the χ^2 test of a model of independence was marginally insignificant (χ^2 = 274.91, df = 247, p = 0.11); thus, even though insignificant, it most likely did not fit the data well. In fact, the test of whether our hypothesized model fit the covariances between the observed variables demonstrated that it was a very good fit, as indicated by a highly insignificant χ^2 (χ^2 = 181.04, df = 226, p = 0.99). Table 1 presents the results of the latent class analysis which showed that schizophrenic men and women differentially expressed the subtypes.

Seventy percent of the men experienced the class 1 subtype. Among the men in this subtype, 60 percent were born in the winter months, 56 percent had a poor premorbid history, 78 percent expressed flat affect, and 53 percent had an early age of onset. In addition, only 5 percent of their first-degree relatives had suffered from schizophrenia. Only 30 percent of the men experienced the class 2 subtype. Seventy-three percent of these men expressed persecutory delusions, 84 percent dysphoria, 55 percent early onset, and none of their relatives had schizophrenia.

In contrast, 63 percent of the schizophrenic women experienced the class 2 subtype characterized by dysphoria and persecutory delusions. Sixty-six percent of this group of women expressed persecutory delusions, 59 percent dysphoria, and 17 percent of their relatives had schizophrenia. Thirty-seven percent of the women experienced the class 1 subtype which, for women, was characterized primarily by poor premorbid history alone (97% experienced this).

To test the significance of the parameters for differentiating subtypes within gender and for testing differences between the sexes, a series of parameter restrictions were imposed on the model and the fits were compared to the unrestricted model (see detailed discussion under **Methods**; Clogg and Goodman 1984).

Table 2 presents a series of restriction tests applied to specific hypotheses about gender differences in the expression of the two subtypes. A model combining all important restrictions was then compared to the unrestricted model (Clogg and Goodman 1984). For men, the best discriminators between classes 1 and 2 were winter birth, poor premorbid history, and flat affect for class 1, and persecutory delusions and dysphoria for class 2. When equality restriction tests were applied (see Tests 1 and 2, table 2), these parameters were significantly different between classes within men. Test 1 refers to constraining season of birth, premorbid history, and flat affect to be equal between the two classes within men, suggesting that these variables do not differentiate the two classes for men. The χ^2 increase is calculated by subtracting the χ^2 of the unrestricted model, which represents a hypothesis that these variables are not equally present in the two classes among men, from the χ^2 of the Test 1 model restrictions, which suggest that these variables are equally present in the two classes among men. For Test 1, the χ^2 increased 36.55 (df = 3, $p < 0.0001$), indicating that the parameters were not equal. For test 2, equality restrictions were placed on dysphoria and persecutory delusions within men across classes. Again, the restricted model was a poor fit as indicated by an increase in χ^2 of 24.95 (df = 3, $p = 1.6 \times 10^{-5}$), suggesting that dysphoria and persecutory delusions were not equally expressed in the two classes among men. Family history of schizophrenia and early onset did not differentiate the two classes within men (i.e., the parameter estimates were not significantly different). This suggests that men had early onset and had few relatives with schizophrenia, *regardless* of the subtype they expressed.

For women, the best discriminators between classes 1 and 2 were family history of schizophrenia, persecutory delusions, and dysphoria for class 2, and only poor premorbid history for class 1. Test 3 placed equality restrictions on family history, persecutory delusions, and dysphoria across classes within women. A χ^2 increase of 10.9 (df = 3, p = 0.004) indicated that parameters were not equal, suggesting that these variables were good discriminators of the two classes among women. Test 4 placed an equality restriction on premorbid history, which also was not equal within women (χ^2 increase = 6.27, df = 1, p = 0.01). In addition, most women had onset of illness later than 25 years, regardless of subtype, and they equally experienced winter birth and flat affect.

To test whether parameter estimates for early onset, winter birth, poor premorbid history, and flat affect for men were significantly different from these parameter estimates for women in both classes, values for women in class 1 were set equal to the specific values of these variables for men in class 1, and class 2 values for women and men were also set equal. Test 5 in table 2 shows that the restrictions were an unacceptable fit (χ^2 increased 53.58, df = 14, $p = 1.5 \times 10^{-6}$), suggesting that these parameters significantly differed for men and women.

Table 1. Gender differences in expression of observed and latent variables defining subtypes of schizophrenia

Observed variables		Men			Women		
		Latent class probabilities					
		70% Class 1		30% Class 2	37% Class 1		63% Class 2
Family history of schizophrenia	No	0.95		1.00	1.00		0.83
	Yes	0.05	=	0.00	0.00		[0.17]
Early onset (<25 years)	No	0.47		0.45	0.74		0.66
	Yes	0.53	=	0.55	0.26	=	0.34
Season of birth	Non-winter	0.40		0.90	0.55		0.52
	Winter	[0.60]		0.10	0.45	=	0.48
Premorbid history	Good	0.44		0.77	0.03		0.94
	Poor	[0.56]		0.23	[0.97]		0.06
Persecutory delusions	No	0.57		0.27	0.55		0.34
	Yes	0.43		[0.73]	0.45		[0.66]
Flat affect	No	0.22		0.77	0.44		0.49
	Yes	[0.78]		0.23	0.56	=	0.51
Dysphoria	No	0.68		0.16	0.57		0.41
	Yes	0.32		[0.84]	0.43		[0.59]

Likelihood ratio $\chi^2 = 181.04$, $df = 226$, $p = 0.99$.

□ : Boxes denote significant differences between conditional probabilities within a gender group as tested by models represented in table 2.

= : Equality signs between conditional probabilities denote nonsignificant differences within a gender group as tested by models in table 2.

Table 2. Confirmatory restriction tests for the hypothesized model, with schizophrenia only in relatives

Model	Likelihood ratio χ^2	*df*	Increase in χ^2 and *df*	*p* value
Unrestricted hypothesized model	**181.04**	**226**		**0.99**
Test 1	217.59	229	36.55, $df = 3$	5.7×10^{-8}
Test 2	205.99	229	24.95, $df = 3$	1.6×10^{-5}
Test 3	191.94	228	10.90, $df = 2$	0.004
Test 4	187.31	227	6.27, $df = 1$	0.01
Test 5	234.62	240	53.58, $df = 14$	1.5×10^{-6}
Test 6	191.35	234	10.31, $df = 8$	0.24
Test 7	212.22	236	31.18, $df = 10$	0.0005
Test 8	192.60	238	11.56, $df = 12$	0.48

Test 1. Equality restrictions on season of birth, premorbid history, and flat affect across the 2 classes within men.

Test 2. Equality restrictions on dysphoria and persecutory delusions across the 2 classes within men.

Test 3. Equality restrictions on family history, dysphoria, and persecutory delusions across classes within women.

Test 4. Equality restrictions on premorbid history across classes within women.

Test 5. Specific value restrictions on onset, season of birth, premorbid history, and flat affect for females whose values were set to equal males' for class 1 and class 2.

Test 6. Specific value restrictions on dysphoria and persecutory delusions for males whose values were set to equal females' for class 1 and class 2.

Test 7. Specific value restrictions in test 6, plus family history for males whose values were set equal to females'.

Test 8. Combination restrictions from tests 1-7: Specific value restrictions on persecutory delusions and dysphoria; across-sex equality restrictions on family history for class 1 women and class 2 men; within-sex equality for females on season of birth and flat affect; within-sex equality restrictions on onset (within both sexes); and values for premorbid history allowed to vary, as were class 1 male and class 2 female values for family history.

In Test 6 (table 2), parameter estimates for men regarding persecutory delusions and dysphoria were set exactly equal to the values for women in both classes. These restrictions were an acceptable fit (χ^2 increased 10.3, $df = 8$, $p = 0.24$), suggesting that the expression of these symptoms co-occurred similarly for men and women. However, the majority of women (63%) experienced this subtype as compared to the minority (30%) of men.

Restricting the estimates for family history of schizophrenia in men to equal women's was an unacceptable fit (Test 7: χ^2 increased 31.18, $df = 10$, $p = 0.0005$). This suggests that relatives of schizophrenic women who expressed dysphoria and persecutory delusions were significantly more likely to have schizophrenia than relatives of schizophrenic men who expressed these symptoms. Finally, a combined test of all significant restrictions, which represent all of the hypothesized differences between men and women within and across the classes, compared to an unrestricted model that would suggest these differences do not hold, produced a model that fit well (test 8: χ^2 increased 11.56, $df = 12$, $p = 0.48$), thus providing support for our hypotheses about gender differences.

In a second analysis, the definition of illness in relatives was expanded to include the full spectrum (i.e., schizophrenia, schizophreniform disorder, schizoaffective disorder, atypical psychosis, paranoid disorder, and schizotypal personality disorder). It was hypothesized that the expression of spectrum disorders in relatives of schizophrenic men would co-occur with poor premorbid history, winter birth, and flat affect in the probands, even though schizophrenia alone was not expressed by relatives of men with these characteristics. This suggests a vulnerability model, in which the pathogenic gene for schizophrenia among men would be expressed only if an environmental insult occurred. Thus, the expectation was that the parameter estimate for family history of spectrum disorders in relatives of men in class 1 would be significantly higher than its estimate in class 2 for men, and equal to the estimate of this parameter for women in class 1 and class 2.

A test of independence indicated that the observed variables in this model were significantly related to one another ($\chi^2 = 305.80$, $df = 247$, $p = 0.006$). Table 3 presents the latent class analysis with the expanded definition of illness in relatives. Findings showed that the hypothesized model was a good fit, as indicated by a nonsignificant χ^2: $\chi^2 = 222.84$ ($df = 224$) $p = 0.51$. The

majority of males (69%) still expressed class 1, while the majority of females (74%) continued to express class 2. Thirty-one percent of the males expressed the subtype characterized by dysphoria and persecutory delusions, and 26 percent of the females now expressed the same subtype as the majority of males (i.e., the subtype characterized by winter birth, poor premorbid history, and flat affect). Tests of the family history variable did not support the hypothesis.

Table 4 presents the major restriction tests examining the significance of the parameter estimates. Within men, family history of spectrum disorders did not significantly differentiate the two classes (Test 1: χ^2 increased 1.89, $df = 1$, $p = 0.17$), although only 9 percent of men who experienced winter birth, flat affect, and poor premorbid history had relatives with spectrum disorders compared to 19 percent of the men with persecutory delusions and dysphoria.

In contrast, 21 percent of the women who experienced winter birth, poor premorbid history, and flat affect had relatives with spectrum disorders. This was different from the 9 percent of men in class 1, although borderline in significance (Test 2: χ^2 increased 3.45, $df = 1$, $p = 0.06$). Both schizophrenic men and women experienced this subtype, and when across-sex equality constraints were placed on season of birth, premorbid history, and flat affect, the χ^2 did not significantly increase, suggesting that the values were equal (Test 3: χ^2 increased 5.62, $df = 6$, $p = 0.47$). Although both men and women experienced the subtype, they differed in its prevalence: 69 percent of the men versus 26 percent of the women.

In addition, 74 percent of the women expressed the subtype characterized by dysphoria and persecutory delusions, and 15 percent of their relatives expressed spectrum disorders. This was not significantly different from the estimate of 21 percent for family history of spectrum disorder in class 1 for women (Test 4: χ^2 increased 0.33, $df = 1$, $p = 0.57$). Thus, relatives of women had spectrum disorders, regardless of the subtype they expressed. Parameter estimates for this subtype were equal for men and women as indicated by Test 5 (χ^2 increased 5.72, $df = 6$, $p = 0.46$).

Finally, age of onset did not significantly differentiate the subtypes for men or women. That is, most men had onset of illness at 25 years or younger, and most women had onset after 25 years, regardless of what subtype they expressed.

When we subjected the model to all of the hypothesized restrictions, the model remained a good fit, suggesting that the observed differences between men and women (described above) were significant (Test 6: χ^2 increased 8.82, $df = 10$, $p = 0.61$). The fact that family history is not a clear discriminator between the subtypes is illustrated by the fit of the model in Test 7 (including within-sex equality restrictions on family history) which is equally as good as the fit of the model in Test 6. Test 8 merely confirms that the proportions of men and women expressing the class 1 and class 2 subtypes are significantly different.

To test the robustness of the estimates in the two latent class models (in tables 1 and 3), 10 percent random samples (half men/half women) were eliminated in three separate analyses. Parameter estimates in both models were almost identical to the full sample in all three trials, suggesting that the estimates were robust and valid. In addition, when different starting values were used, estimates were essentially unchanged, again suggesting the robustness of the parameter estimates.

Discussion

Findings in this study underscore the importance of gender in understanding the heterogeneity of schizophrenia. Our previous work showed that schizophrenic men have significantly earlier onset of illness and have a lower risk of schizophrenia, schizophreniform, and schizoaffective disorders among their first-degree relatives than do women. In this study, simple bivariate findings showed that men expressed more flat affect and a poorer premorbid history, and women, more dysphoria, although the findings were not significant. It is interesting that although bivariate relationships between gender and some of the factors examined showed no significant effects, *in the context of each other,* patterns emerged that significantly differentiated characteristic subtypes for which men and women were at different risks. This may in part explain why there are some inconsistencies in the literature about gender differences in schizophrenia. Our results underscore the importance of not only examining main effects for factors, such as gender, that may be important for the understanding of schizophrenia, but of also examining their conditional effects, which may be more revealing. That is, in this study, not all schizophrenic men and women differed, and therefore the bivariate relationships between

Table 3. Gender differences in expression of observed and latent variables defining subtypes, with schizophrenia spectrum in relatives

		Men			Women		
		Latent class probabilities					
Observed variables		**69% Class 1**		**31% Class 2**	**26% Class 1**		**74% Class 2**
Family history of schizophrenia spectrum	No	0.91		0.81	0.79		0.85
	Yes	0.09	=	0.19	0.21	=	0.15
Early onset (<25 years)	No	0.48		0.44	0.75		0.67
	Yes	0.52	=	0.56	0.25	=	0.33
Season of birth	Non-Winter	0.41		0.85	0.21		0.64
	Winter	□ 0.59		0.15	□ 0.79		0.36
Premorbid history	Good	0.44		0.76	0.50		0.64
	Poor	□ 0.56		0.24	□ 0.50		0.36
Persecutory delusions	No	0.57		0.27	0.52		0.38
	Yes	0.43		□ 0.73	0.48		□ 0.62
Flat affect	No	0.21		0.77	0.00		0.64
	Yes	□ 0.79		0.23	□ 1.00		0.36
Dysphoria	No	0.71		0.13	0.70		0.39
	Yes	0.29		□ 0.87	0.30		□ 0.61

Likelihood ratio $\chi^2 = 222.84$, $df = 224$, $p = 0.51$.

□ : Boxes denote significant differences between conditional probabilities within a gender group as tested by models represented in table 4.

= : Equality signs between conditional probabilities denote nonsignificant differences within a gender group as tested by models in table 4.

Table 4. Confirmatory restriction tests for the hypothesized model, with schizophrenia spectrum in relatives

Model	Likelihood ratio χ^2	*df*	Increase in χ^2 and *df*	*p* value
Unrestricted hypothesized model	**222.84**	**224**		**0.51**
Test 1	224.73	225	1.89, *df* = 1	0.17
Test 2	226.29	225	3.45, *df* = 1	0.06
Test 3	228.46	230	5.62, *df* = 6	0.47
Test 4	223.17	225	0.33, *df* = 1	0.57
Test 5	228.56	230	5.72, *df* = 6	0.46
Test 6	231.06	234	8.22, *df* = 10	0.61
Test 7	230.56	234	7.72, *df* = 10	0.66
Test 8	256.63	236	33.79, *df* = 12	0.0007

Test 1. Equality restriction on family history within men

Test 2. Equality restriction on family history for class 1 across sex.

Test 3. Equality restrictions on season of birth, premorbid history, and flat affect for classes 1 and 2 across sex

Test 4 Equality restrictions on family history within women.

Test 5 Equality restrictions on family history, dysphoria, and persecutory delusions for classes 1 and 2 across sex.

Test 6. Combination restrictions from tests 1-5· Equality restrictions on family history, season of birth, premorbid history, and flat affect for class 1 across sex; equality restrictions on family history, dysphoria, and persecutory delusions for class 2 across sex; within-sex equality restrictions on age of onset; and restrictions on the latent class probabilities equating class 1 males with class 2 females and class 2 males with class 1 females.

Test 7. Same as test 6 except that equality restrictions on family history are within sex instead of across sex.

Test 8. Identical to test 6 except in the latent class probability equality restrictions. Here class 1 males were set equal to class 1 females and class 2 males and females were equated.

gender and certain characteristics were not always significantly different. Rather, our results suggest that schizophrenic men and women may have similar subtypes; however, the *prevalence* of the subtypes among men and women significantly differ.

The results in this study demonstrated that schizophrenic men were at higher risk for expressing a subtype characterized by poor premorbid history, winter birth, and flat affect. These men also had few relatives with schizophrenia or spectrum disorders. In contrast, schizophrenic women were at higher risk for a form of the illness characterized by dysphoria and persecutory delusions. Women also expressed the first subtype, although the prevalence among women was low (26%). In addition, first-degree relatives of women were at risk for spectrum disorders regardless of the subtype they experienced. Relatives of women were at risk for schizophrenia alone, for the subtype characterized by dysphoria and persecutory delusions.

Our findings raise the question of whether schizophrenic women have a higher genetic loading and higher threshold for the illness. However, this would result in a lower prevalence of less severe forms of the illness among men, which is in contrast to previous literature on gender differences in the expression and course of schizophrenia (Salokangas 1983; Goldstein 1988; Lewine 1988). On the other hand, our results demonstrate that there may be a subtype of the illness for which nonfamilial factors play an important role. Winter birth is a crude indicator, but it has been associated with perinatal complications, vulnerability to viruses, and nutritional deficiencies (Hare 1988). These environmental insults may in part lead to early brain damage, resulting in a poor premorbid history and flat affect. Our findings are also consistent with the idea that the pathogenic gene is not expressed in this subgroup without an environmental insult, or there may be a sporadic form of the illness. Further, men are at higher risk for a subtype of schizophrenia in which nonfamilial factors are significant.

Our results are consistent with the hypothesis of a neurodevelopmental form of the illness (Seidman 1983; Weinberger 1987; Lewis 1989; Murray et al. 1989), and extend this hypothesis by demonstrating that men may be at higher risk for its expression. This is reminiscent of Kraepelin's (1919/1971) description of dementia praecox as an illness afflicting young men.

In addition, schizophrenic women are at higher risk for a form of the illness in which affective symptoms

and familial factors are prominent. Our previous work has shown that relatives of schizophrenic women are at higher risk for unipolar disorder than those of schizophrenic men, although the findings did not quite reach significance (Goldstein et al., in press). Future research must examine how familial factors, affective expression, and gender are related to each other by examining the modes of transmission and their relationship to gender and phenomenology. Our results suggest that the role of affective symptomatology in schizophrenia may provide insights into understanding the heterogeneity of the illness, and that gender may provide clues as to where to begin to search for possible pathological mechanisms.

Finally, findings showed that age of onset did not differentiate the two subtypes. That is, most men became ill at or before 25 years and most women became ill after 25 years, regardless of subtype. Results of the subtype model suggest that age of onset is not differentially related to family morbidity risk, winter birth, poor premorbid history, or symptom expression. Thus, age-of-onset differences between men and women are most likely explained by some other factors. As suggested in other work (see Seeman and Lang 1990), likely etiological candidates are hormonal differences between men and women.

There are some limitations to the model presented in this study. Some of the observed indicators are crude, such as winter birth to measure environmental insults. Since cruder measures are less reliable indicators, the expectation is that they would be less likely to correlate with other factors. In this study, this was not a problem given that winter birth was a significant discriminator between subtypes. Our current work assesses perinatal complications and severe illness or injury before age 1, instead of relying on winter birth, which should facilitate replication in the future.

In addition, the latent class model is not fully specified, since there are limitations on the number of observed variables it can handle. Current software allows up to eight dichotomous variables, although six are thought to be more reasonable given the nature of the statistical procedure (C.C. Clogg 1988, personal communication). Although there are limits to the allowable indicators, this would not invalidate the ability of the chosen indicators to differentiate meaningful classes. Further, latent variable models are highly dependent on the variability of the observed indicators. In this study, however, the robustness of the estimates was established, given that they remained stable after three trials of eliminating random subsamples. Finally, it may be argued that results in this study are wholly attributable to the perceptual bias of clinical raters regarding women and men. Although this argument may be plausible in considering differential symptom expression, it is not plausible for the assessment of winter birth, family morbidity risk, or premorbid history.

Thus, findings in this study provide convincing evidence of the value of gender in providing clues to delineate subtypes of schizophrenia. Given the limitations on the specification of the model, it is important to relate results in this study to findings in previous research suggesting gender differences in structural and functional brain abnormalities (Gur et al. 1985; Nasrallah et al. 1986; Gur and Gur 1990), differential neuroleptic response (Seeman 1985), and neurocognitive functioning (Goldberg 1985; Haas 1987). For example, it is possible that early environmental insults may cause structural brain damage. In view of gender differences in brain development—for example, testosterone has a retarding effect on the left hemisphere of the brain (Geschwind and Galaburda 1985; DeLisi et al. 1989)—men may be at higher risk for consequences from perinatal complications than women. It may be that the explanation of significant gender effects in schizophrenia involves factors inherent to being a man or a woman, such as the effects of estrogen and differences in brain development. It may also be that explanatory factors consist of secondary consequences of being a man or woman, such as differential exposure to head injury. In either case, findings in this study suggest that gender can provide important clues to understanding the etiological heterogeneity of schizophrenia, and should be specifically considered in the selection of samples and evaluation of data in studies of schizophrenia.

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