

# The Relative Importance of Family History, Gender, Mode of Onset, and Age at Onset in Predicting Clinical Features of First-Episode Psychotic Disorders

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## Abstract

**Objective:** Family history of psychosis, gender, mode of onset, and age at onset are considered prognostic factors important to clinicians evaluating first-episode psychosis; yet, clinicians have little guidance as to how these four factors differentially predict early-course substance abuse, symptomatology, and functioning. We conducted a “head-to-head comparison” of these four factors regarding their associations with key clinical features at initial hospitalization. We also assessed potential interactions between gender and family history with regard to age at onset of psychosis and symptom severity. **Methods:** Consecutively admitted first-episode patients (n=334) were evaluated in two studies that rigorously assessed a number of early-course variables. Associations among variables of interest were examined using Pearson correlations,  $\chi^2$  tests, Student’s t-tests, and 2x2 factorial analyses of variance. **Results:** Substance (nicotine, alcohol, and cannabis) abuse and positive symptom severity were predicted only by male gender. Negative symptom severity and global functioning impairments were predicted by earlier age at onset of psychosis. General psychopathology symptom severity was predicted by both mode of onset and age at onset. Interaction effects were not observed with regard to gender and family history in predicting age at onset or symptom severity. **Conclusions:** The four prognostic features have differential associations with substance abuse, domains of symptom severity, and global functioning. Gender and age at onset of psychosis appear to be more predictive of clinical features at the time of initial evaluation (and thus presumably longer term outcomes) than the presence of a family history of psychosis and a more gradual mode of onset.

**Key Words:** Age at Onset, Family History, First-Episode Psychosis, Mode of Onset, Psychosis, Schizophrenia

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## Introduction

Considerable clinical heterogeneity exists within the primary psychotic disorders in terms of onset, progression of symptoms, functional outcomes, and long-term course and prognosis. The diagnosis of a specific subtype of a psychotic disorder itself does not account for this heterogeneity. Furthermore, clinicians are unable to choose appropriate medical and psychosocial therapies based solely on the psychiatric diagnosis without considering symptom severity, functional impairments, and past and expected course.

Traditional diagnoses of psychotic illnesses do not provide reliable prognostic information, and clinicians often use other variables for prognostication. Family history of psychosis, gender, mode of onset of psychosis, and age at onset

### Clinical Implications

Several findings of clinical interest emerged from this study involving a large, well-characterized sample of patients with first-episode psychosis. First, gender was predictive of substance abuse at the time of initial evaluation whereas the other three prognostic factors were not. Second, mode of onset of psychosis was unassociated with substance use, symptomatology, and global functioning, except that a gradual mode of onset was associated with a *lesser* (rather than greater) severity of general psychopathology symptoms. Third, among the four predictors, age at onset of psychosis was most robustly associated with negative symptoms, general psychopathology symptoms, and global functioning at the time of initial evaluation. Fourth, in this sample, neither gender nor family history was significantly predictive of age at onset.

In terms of clinical implications, it would appear that among the four commonly promulgated prognostic indicators, the presence of a family history of psychosis and a more gradual mode of onset might be less predictive of clinical features at the time of initial evaluation (and thus longer term outcomes) compared to gender and age at onset. Furthermore, the latter two are predictive of different domains (substance abuse and positive symptoms for male gender, and negative symptom severity, general psychopathology symptom severity, and global functioning for earlier age at onset).

of psychosis are four factors that commonly have been used for this purpose. Specifically, better prognoses are associated with the absence of a family history of psychosis (1, 2), female gender (3), a more acute mode of onset of psychosis (4-7), and an older age at onset of psychosis (8-10). Some of these factors may interact to affect outcomes, making the usefulness of any one factor alone unclear. For example, both male gender and positive family history of psychosis have been associated with younger age at onset (1, 11-13), but the gender difference in age at onset is attenuated in patients with a family history of psychosis (14).

Given that all four factors—family history of psychosis, gender, mode of onset, and age at onset—are considered prognostic indicators of importance by clinicians evaluating and initiating treatment for first-episode psychosis, we compared these four factors in terms of their associations with several clinical domains at the time of the initial evaluation. Although all four factors are commonly assessed as part of the initial evaluation, clinicians have little guidance as to which are more potent prognostic indicators, and how they might differentially predict the clinical domains of substance abuse, symptomatology, and functioning at the time of the initial evaluation. Our main objective was to provide a “head-to-head comparison” of these four factors in a large sample of first-episode patients in terms of their associations with key clinical features at the initial evaluation, which might have relevance for longer term prognostication. For these comparisons, we had no *a priori* hypotheses given the lack of prior studies comparing the four factors within the same sample (i.e., our analyses were exploratory, and secondary to the studies’ overall goals, as described below). Our second objective was to assess two specific associations involving potential interactions between two of the factors: the relation of gender with age at onset, and gender with symptom severity, as a function of family history.

### Methods

#### Setting and Sample

Enrollment of consecutively admitted first-episode psychosis patients took place at five inpatient psychiatric units: three in Atlanta, Georgia and two in Washington, D.C. (the latter site joining the project toward the end of the study period). Participants were predominantly African American, low-income, and socially disadvantaged, consistent with the populations served by the recruitment sites. Patients were excluded if they: 1) were not English speaking; 2) did not have a diagnosis of a primary non-affective psychotic disorder; 3) were outside the age range of 18–40 years; 4) had known or suspected mental retardation; 5) had a Mini-Mental State Examination (15, 16) score of <24; 6) had received >3 months of prior antipsychotic treatment; 7) had been hospitalized for psychosis for any length of time >3 months prior to index admission; 8) had a significant medical condition compromising ability to participate; or, 9) were unable to provide informed consent (regarding the latter, while enrolling the 334 participants, only 19 of 453 patients who were screened but excluded [4.2%] met all eligibility criteria but were deemed to not have capacity to give informed consent). Eligible but not enrolled patients (i.e., 126 who met inclusion criteria but opted not to participate) did not differ from the participating patients in terms of age, gender, race, or ethnicity (the only variables available from the eligible but not consented/enrolled patients).

#### Procedures and Measures

Data from the 334 first-episode patients were collected during two consecutive research projects; the first explored predictors of duration of untreated psychosis (n=109) and the second examined the impact of premorbid cannabis use on the early course of psychotic disorders (n=225). Both stud-

**Table 1 Sociodemographic Characteristics of the Study Sample (n=334)**

	Mean±SD or n (%)
Age, years	23.7±4.7
Educational attainment, years	11.8±2.2
Gender, male	249 (74.6%)
Race, African American	291 (87.1%)
Relationship status, single and never married	295 (88.3%)
Employment status, unemployed in the month prior to hospitalization	220 (65.9%)

ies used the same eligibility criteria, recruitment procedures, and data collection processes. The studies were powered for the main hypotheses pertaining to duration of untreated psychosis and premorbid cannabis use (not presented herein), rather than for the present exploratory/secondary analyses; yet, we deemed a sample size of 334 as sufficient to detect clinically meaningful differences in associations across the four predictor variables.

Patients were invited to participate in the respective studies once their psychotic symptoms were sufficiently stabilized for informed consent and participation. After receiving written informed consent from participants, trained assessors conducted detailed clinical research assessments divided over two or three days. When possible, collateral information was obtained from family members/informants on select variables (e.g., family history, mode of onset, age at onset); all available data were then used, as described below, to arrive at consensus-based best estimates for select variables. Study procedures were approved by all relevant Institutional Review Boards, and all patients gave written informed consent prior to study participation.

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; 17) was used to diagnose psychotic disorders and substance use disorders. We also assessed past cigarette smoking, and dichotomized patients as having used nicotine in the past three months or not. An adapted version of the Family Interview for Genetic Studies (FIGS)—an interview guide for obtaining diagnostic information on family members (18)—was used to determine whether participants had first-degree relatives with a psychotic disorder. A consensus-based best estimate of family history of psychosis was determined from interviews with patients and one or two family members/informants when available (194 of 334 participants [58.1%] had accompanying family member/informant participants).

Mode of onset of psychosis was categorized as one of five types as defined by the World Health Organization International Pilot Study of Schizophrenia (19). Using all available information, a consensus-based best estimate of mode

**Table 2 Intercorrelations among the Four Symptomatology and Functioning Variables\***

	Negative Symptoms	General Psychopathology	Global Functioning
Positive Symptoms	.19	.50	-.29
Negative Symptoms		.57	-.42
General Psychopathology			-.41

\*all  $p < .01$

of onset was rated only when it could be accurately judged (20). Among 267 participants for whom mode of onset of psychosis could be classified, 37 (13.9%) were deemed to have an acute mode without the presence of a prodrome, 63 (23.6%) had an acute mode with a prodrome, 61 (22.8%) had a subacute mode, 99 (37.1%) had a gradual mode, and seven (2.6%) had an insidious mode of onset. We dichotomized this variable by combining the first three levels and the latter two levels, to create a dichotomized acute vs. gradual mode of onset variable. Age at onset of psychosis was determined using the Symptom Onset in Schizophrenia (SOS) inventory (21). Our standardized approach to deriving age at onset using consensus-based best-estimate methods has been previously described (22, 23). To be consistent with the other three prognostic indicators, we created a binary variable for age at onset of psychosis using a median split (<21.4 years as early age at onset, and  $\geq 21.4$  years as later age at onset).

Current- and past-month symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS) (24), which was rated by masters- or doctoral-level research staff using data gathered from a chart review and an in-depth, semi-structured interview. To assess inter-rater reliability of the PANSS subscale scores, intraclass correlation (ICC) coefficients were calculated using a two-way mixed (judges fixed) effects analysis of variance (ANOVA) model in which three assessors were the fixed effect while twelve target ratings were the random effect (25). ICC coefficients were: .92 (95% confidence interval [CI]: .85, .96) for the positive symptom subscale, .92 (95% CI: .86, .96) for the negative symptom subscale, and .67 (95% CI: .42, .82) for the general psychopathology symptom subscale. Overall psychosocial functioning was measured with the Global Assessment of Functioning (GAF) scale (26-28), which has a 100-point range, with each 10-point interval accompanied by an anchoring description. The GAF was rated by the research assessor upon completion of the entire clinical research assessment (e.g., SCID, SOS, PANSS).

**Table 3 Associations Between the Four Prognostic Factors and Substance Use at Initial Evaluation**

	Positive Family History (v. Negative)	Male Gender (v. Female)	Gradual Mode of Onset (v. Acute)	Early Age at Onset (v. Later)
Nicotine Use, Past 3 Months	61.2% (62.0%)	68.1% (44.6%) <sup>†</sup>	61.0% (62.8%)	61.6% (62.9%)
Alcohol Use Disorder	30.8% (30.2%)	34.6% (17.3%) <sup>*</sup>	35.9% (25.3%)	29.5% (28.7%)
Cannabis Use Disorder	55.8% (62.9%)	68.8% (42.4%) <sup>†</sup>	56.3% (60.5%)	56.4% (66.2%)

\*p<.01; †p<.001

**Data Analyses**

Distributional properties of all variables were examined. Bivariate tests (Pearson correlations,  $\chi^2$  tests, and Student’s t-tests) were used to assess associations among variables. When two binary predictor variables were associated with a continuous dependent variable (and for analyses pertaining to our second objective), 2x2 factorial ANOVAs were computed to assess independent associations and interactions. The significance level was set at  $\alpha=.05$ , and all tests were two-tailed. IBM SPSS Statistics 18.0 was used for all analyses.

**Results**

**Sample Characteristics**

Sociodemographic characteristics of the study sample of 334 first-episode patients are given in Table 1. The mean age at initial hospitalization was 23.7±4.7 years, and the mean years of educational attainment was 11.8±2.2. The majority of participants were male, African American, single and never married, and unemployed in the month prior to hospitalization.

SCID-based diagnoses of psychotic disorders were as follows: schizophrenia, paranoid type (142, 42.5%); schizophreniform disorder (46, 13.8%); psychotic disorder not otherwise specified (44, 13.2%); schizophrenia, undifferentiated type (34, 10.2%); schizoaffective disorder, depressive type (23, 6.9%); schizophrenia, disorganized type (20, 6.0%); schizoaffective disorder, bipolar type (10, 3.0%); brief psychotic disorder (6, 1.8%); delusional disorder (5, 1.5%); schizophrenia, catatonic type (2, .6%); and, schizophrenia, residual type (2, .6%).

**Associations among the Independent Variables, and among the Dependent Variables**

Regarding our four independent variables, 53 participants were deemed to have a positive family history of psychosis in a first-degree family member (among 333 participants for whom family history could be classified, 15.9%),

249 were male (74.6%), 106 had a gradual mode of onset (among 267 for whom mode of onset could be classified, 39.7%), and 153 had an early age at onset (among 308 participants for whom age at onset could be determined, 49.7%).

The four prognostic indicators were unrelated to one another, except that family history of psychosis was associated with a greater likelihood of having a more gradual mode of onset of psychosis. Specifically, the likelihood of having a family history was 11.8% among those with an acute mode of onset, compared to 20.8% among patients with a gradual mode of onset ( $\chi^2=3.94$ ,  $df=1$ ,  $p=.05$ ).

Surprisingly, in this sample, age at onset of psychosis was not significantly related to gender (21.8±5.0 among males and 22.5±5.3 among females;  $t=1.01$ ,  $df=307$ ,  $p=.31$ ) or family history (21.3±6.7 among those with a family history and 21.5±4.6 among those without a family history;  $t=.17$ ,  $df=309$ ,  $p=.82$ ). Furthermore, in a 2x2 factorial ANOVA including both gender and family history as factors, and continuous age at onset as the dependent variable, neither main effects nor the interaction were significant.

Regarding the dependent variables, as expected, the three substance use variables were significantly associated with one another in three  $\chi^2$  tests (all  $p<.001$ ). Intercorrelations among the four symptomatology and functioning variables are given in Table 2. Although all correlations were significant at  $p<.01$ , only one correlation was  $>.50$  (the correlation between negative symptom severity and general psychopathology symptom severity;  $r=.57$ ).

**Associations between the Four Prognostic Factors and Substance Use**

As shown in Table 3, family history of psychosis, mode of onset of psychosis, and age at onset of psychosis were not associated with nicotine use in the past three months, the presence of an alcohol use disorder, or the presence of a cannabis use disorder. However, gender was a significant predictor of each; for example, 163 male first-episode patients (68.8%) had a cannabis use disorder, compared to 35 female patients (42.4%;  $\chi^2=18.54$ ,  $df=1$ ,  $p<.001$ ).



**Table 4** Associations Between the Four Prognostic Factors and Symptomatology and Global Functioning at Initial Evaluation

	Positive Family History (v. Negative)	Male Gender (v. Female)	Gradual Mode of Onset (v. Acute)	Early Age at Onset (v. Later)
Positive Symptoms	23.5±5.6 (24.3±5.3)	24.5±5.3 (23.0±5.2)*	24.1±5.6 (23.9±5.0)	23.9±5.1 (24.4±5.3)
Negative Symptoms	23.4±7.1 (22.0±6.5)	22.2±6.5 (22.3±6.9)	20.9±6.1 (22.1±6.3)	23.6±6.3 (20.6±6.7) <sup>‡</sup>
General Psychopathology	45.3±8.6 (44.7±9.2)	44.8±9.0 (44.9±9.5)	42.7±8.8 (45.6±8.6) <sup>‡</sup>	46.3±8.8 (43.5±9.1) <sup>‡</sup>
Global Functioning	33.0±12.6 (35.5±11.4)	34.7±11.4 (36.3±12.2)	35.4±12.7 (34.9±10.9)	33.8±11.2 (36.4±12.0)*

\*p<.05; <sup>‡</sup>p<.01; <sup>†</sup>p<.001

### Associations between the Four Prognostic Factors and Symptomatology and Functioning

As given in Table 4, family history of psychosis was not significantly associated with positive symptom severity, negative symptom severity, general psychopathology symptom severity, or global functioning. Gender was associated only with positive symptom severity, with male patients having a mean PANSS positive symptom score of 24.5±5.3 compared to 23.0±5.2 among female patients ( $t=2.26$ ,  $df=332$ ,  $p=.02$ ). Four 2x2 factorial ANOVAs including both family history and gender revealed no significant main effects or interactions with regard to any of the four symptomatology/functioning variables.

Mode of onset of psychosis was only associated with general psychopathology symptom severity, with patients who had experienced a more gradual mode of onset having a mean PANSS general psychopathology symptom score of 42.7±8.8, which was less than the mean of 45.6±8.6 among patients with an acute mode of onset ( $t=2.65$ ,  $df=265$ ,  $p=.009$ ). Early age at onset was associated with greater negative symptom severity ( $t=3.89$ ,  $df=306$ ,  $p<.001$ ), greater general psychopathology symptom severity ( $t=2.79$ ,  $df=306$ ,  $p=.006$ ), as well as poorer global functioning ( $t=1.98$ ,  $df=298$ ,  $p=.05$ ). Given that both mode of onset of psychosis and age at onset of psychosis were predictive of severity of general psychopathology symptoms, we conducted a 2x2 factorial ANOVA including both independent variables. A significant main effect was observed for both mode of onset ( $F[1, 257]=8.75$ ,  $p=.003$ ) and age at onset ( $F[1, 257]=5.02$ ,  $p=.026$ ), though the interaction was not significant ( $F[1, 257]=.36$ ,  $p=.55$ ). Estimated marginal means are shown in Figure 1.

### Discussion

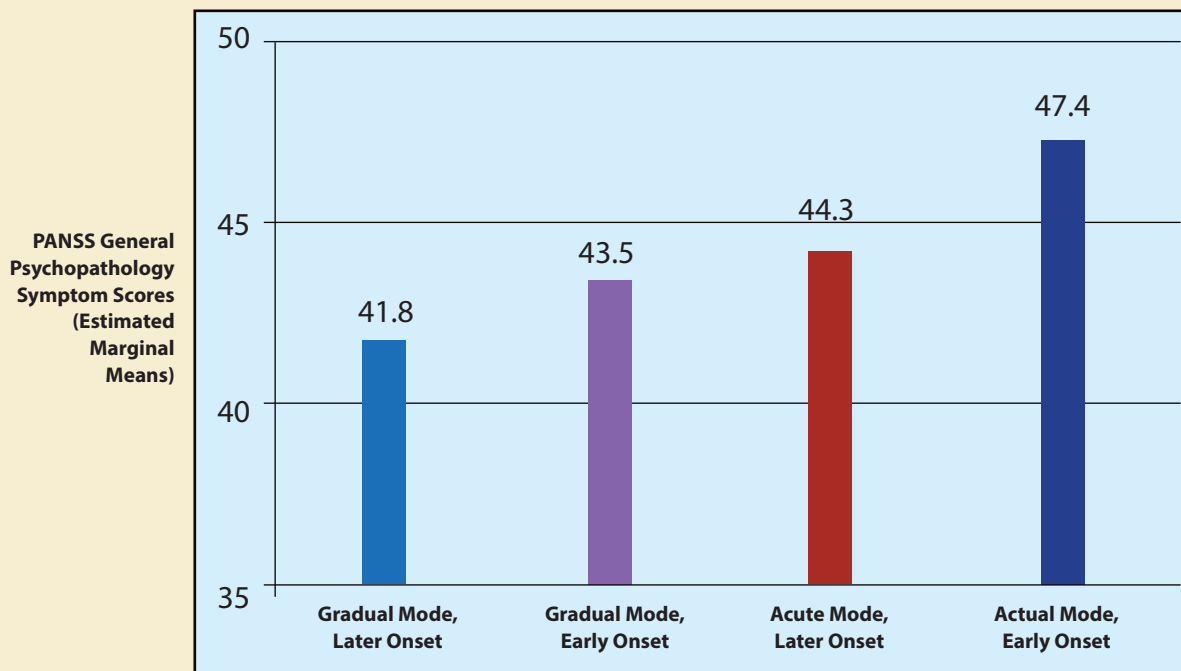
Several findings of clinical interest emerged from this study involving a large, well-characterized sample of patients

with first-episode psychosis. First, gender was predictive of substance abuse at the time of initial evaluation whereas the other three prognostic factors were not. Second, mode of onset of psychosis was unassociated with substance use, symptomatology, and global functioning, except that a gradual mode of onset was associated with a *lesser* (rather than greater) severity of general psychopathology symptoms. Third, among the four predictors, age at onset of psychosis was most robustly associated with negative symptoms, general psychopathology symptoms, and global functioning at the time of initial evaluation. Fourth, in this sample, neither gender nor family history was significantly predictive of age at onset.

We found a positive association between male gender and nicotine, alcohol, and cannabis use. The high prevalence of substance use in first-episode psychosis patients, especially male patients, has been previously described (29-32), and the association with male gender holds in the general population (33-35). Our findings support a higher index of suspicion for substance abuse among male patients. Knowledge of this gender association is helpful for clinicians, given the fact that first-episode patients are often reluctant to disclose their history of substance use. Clinicians may want to obtain collateral information from family members and friends, when possible, regarding substance abuse, particularly because substance abuse is known to be clearly associated with poorer outcomes. Male gender was also positively associated with the severity of positive symptoms during the first episode. The higher prevalence of substance use and greater positive symptom severity among male patients likely contributes to an overall worse prognosis among males.

Although a more gradual mode of onset of psychosis has been clearly linked to a longer duration of untreated psychosis (20, 23, 36), which, in turn, is known to be associated with poorer outcomes, mode of onset was not associated in the present analysis with substance use, symptomatology, or global functioning, except that a gradual mode of onset

**Figure 1** Estimated Marginal Means from a 2x2 Factorial ANOVA Comparing PANSS General Psychopathology Symptom Scores by Mode of Onset and Age at Onset of Psychosis at the Time of Initial Evaluation\*



\*A significant main effect was observed for both mode of onset ( $p=.003$ ) and age at onset ( $p=.026$ ), though the interaction was not significant ( $p=.55$ ).

was associated with a lesser (rather than greater) severity of general psychopathology symptoms. Thus, although a more gradual mode of onset might be important to consider in efforts to reduce the duration of untreated psychosis, it is not clearly linked with these particular clinical features at the time of the initial evaluation. Although the present analysis focused on four factors determinable before the onset of psychosis (family history and gender) or at the time of the onset of psychosis (mode of onset and age at onset), other characteristics occurring later, like duration of untreated psychosis, are also important predictors of initial clinical presentation. With regard to duration of untreated psychosis, many studies show its association with outcomes (37-41), and it is possible that it interacts with the variables that we studied.

While age at onset of psychosis was not associated with substance use or positive symptom severity (whereas gender was), it was clearly associated with negative symptoms, general psychopathology symptoms, and global functioning at the time of initial evaluation. These effects appear to be independent of gender, mode of onset, and family history. Thus, of the four factors assessed, age at onset proved to be the most robust predictor of these key clinical features of first-episode psychosis.

Regarding our secondary objective, surprisingly, neither gender nor family history were significantly predictive of

age at onset, independently or in an interaction. This differs from prior results (42) showing that gender, family history, and the interaction between the two are predictive of age at onset (such that female patients with no family history had a significantly later age at first diagnosis than females with a family history, males with a family history, and males without a family history). However, the sample of that prior study differed substantially from ours, with roughly equal numbers of males and females, a later mean age at onset (28.7 and 32.6 among males and females, respectively), and a greater proportion of participants with a family history of psychosis (25%). We also found that neither gender nor family history was significantly predictive of symptom severity or global functioning, independently or in an interaction.

Several methodological limitations should be acknowledged. First, our outcome variables (assessed at initial evaluation) represent intermediate outcomes that, though likely predictive of later outcomes, are in this case proxies or intermediaries for longer term course and outcomes. That is, there was no long-term follow-up of the patients, and because prognostic factors are generally important for long-term outcomes in response to treatment—as opposed to predicting acute clinical presentations of the illness—our findings are relevant to clinicians only as a general guide (e.g., male gender is associated with substance abuse and positive symp-

tom severity, age at onset is associated with negative symptom severity and global functioning). Second, though not a limitation of the study per se, it should be noted that none of the prognostic factors are modifiable, making their utility as prognostic factors less powerful in terms of the potential for altering illness course. Third, we acknowledge the challenges of accurately identifying a positive or negative family history, even though we were able to conduct family member/informant interviews for more than half of participants. Fourth, although we had a reasonably thorough method of assessing family history of psychosis, we did not attempt to collect data on family history of substance abuse (which would be difficult due to the more hidden nature of many substance abuse-related behaviors). Yet, family history of substance abuse would perhaps have been more relevant than family history of psychosis for predicting substance abuse at initial presentation for first-episode psychosis. Fifth, we also did not have data on family history of other psychiatric illnesses, such as depression and bipolar disorder, as these data were not collected in the parent projects; however, such data might well have been relevant. As such, it might be premature to assume that family psychiatric history is not associated with age at onset or the other variables since our family history data were limited to psychotic disorders. Sixth, including only subjects with a first hospitalization at the age of 18 or older might have excluded some with a strong family history and/or a worse prognosis. However, although our age inclusion criterion was 18–40 years, many of our participants had an age at onset of <18; that is, despite an age restriction to  $\geq 18$  for enrollment (at the time of first hospitalization), many patients had their first onset at <18 years and had an extended duration of untreated psychosis. Seventh, the sociodemographic and clinical characteristics of our sample limit generalizability of our findings to dissimilar samples. Specifically, our participants were predominantly urban, socially disadvantaged, low-income African Americans, and they were being evaluated in acute inpatient settings; the latter likely truncated the lower end of the distributions of symptom severity. Furthermore, it is possible that the effects of family history in this sample were obscured by a generally higher rate of exposure to environmental risk factors, perhaps beginning early in life, even prenatally. In future research, it would be informative to conduct the same analyses with a more diverse sample, including both disadvantaged and non-disadvantaged groups, and minority and non-minority groups. Despite the limitations, prominent strengths include the large sample of first-episode patients and the rigorous methods for rating key factors that have rarely been assessed together in the same sample, including family history, mode of onset of psychosis, and age at onset of psychosis.

In terms of clinical implications, it would appear that among the four commonly promulgated prognostic indicators, the presence of a family history of psychosis and a more gradual mode of onset might be less predictive of clinical features at the time of initial evaluation (and thus longer term outcomes) compared to gender and age at onset. Furthermore, the latter two are predictive of different domains (substance abuse and positive symptoms for male gender, and negative symptom severity, general psychopathology symptom severity, and global functioning for earlier age at onset).

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