


Family History of Psychiatric Disorders and Clinical Factors Associated With a Schizophrenia Diagnosis

INQUIRY: The Journal of Health Care Organization, Provision, and Financing
Volume 58: 1–10
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/00469580211060797
journals.sagepub.com/home/inq


Lina Díaz-Castro, MD, PhD¹ , Kurt Hoffman, PhD², Héctor Cabello-Rangel, MD, PhD³, Armando Arredondo, MD, PhD⁴, and Miguel Ángel Herrera-Estrella, MD⁵

Abstract

Background: Schizophrenia (SCH) and bipolar disorder (BD) have both shared and unique genetic risk factors and clinical characteristics. The aim of the present study was to identify potential risk factors significantly associated with SCH, relative to a BD reference group.

Methods: Data were obtained from medical records of patients that entered a major Mexico City hospital during 2009–2010 presenting psychotic symptoms ($n = 1132$; 830 cases of SCH, 302 cases of BD; 714 men and 418 women). SCH and BD diagnoses were compared with respect to a number of family and clinical characteristics. Logistic and linear regression analyses were used to respectively identify factors selectively associated with the SCH diagnosis relative to the BD diagnosis and explore the relationship between PANSS scores and parental age at time of birth to the age of SCH onset.

Results: Patients with SCH showed greater functional impairment than those with BD. Family history of mental illness, premorbid schizoid-like personality, and obstetric trauma were significantly associated with the SCH diagnosis. The association of obstetric trauma with SCH was greatest in male patients with a family history of mental illness. In women, increased paternal and decreased maternal age at time of the patient's birth were associated with an earlier age of SCH onset.

Conclusion: Male gender, showing premorbid schizoid-like personality, familial SCH, and obstetric trauma are risk factors that distinguish SCH from BD. Additionally, our results suggest that risk for SCH relative to BD may be importantly influenced by interactions between familial risk, gender, and obstetric trauma.

Keywords

schizophrenia, family history, social functioning, paternal age effect, premorbid schizoid personality

¹Research in Medical Sciences, Direction of Epidemiological and Psychosocial Research, National Institute of Psychiatry Ramon de la Fuente Muñiz, Mexico City, Mexico

²Carlos Beyer Center for Investigation of Animal Reproduction (CIRA), Autonomous University of Tlaxcala and Center for Investigation and Advanced Studies of the National Polytechnic Institute (UATx - CINVESTAV), Tlaxcala, Mexico

³Research in Health Systems, Diagnostic Auxiliary Division, Psychiatric Hospital Fray Bernardino Álvarez, Mexico City, Mexico

⁴Research in Medical Sciences, Health Systems Research Center, National Institute of Public Health, Cuernavaca, Mexico

⁵Medical Doctor, Hospitalization Services, Psychiatric Hospital Fray Bernardino Álvarez, Mexico City, Mexico

Corresponding Author:

Lina Díaz-Castro, Research in Medical Sciences, National Institute of Psychiatry Ramon de la Fuente Muñiz, Direction of Epidemiological and Psychosocial Research, Calz. México-Xochimilco #101, Col. San Lorenzo Huipulco, Mexico City, MX 14370, USA.
Email: lina.diaz@graduateinstitute.ch



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and

Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

Highlights

1. What do we already know about this topic?

Schizophrenia (SCH) and bipolar disorder (BD) share a number of genetic liability factors and clinical characteristics; yet, each also has distinct genetic liability factors and distinct diagnostic characteristics. Environmental factors such as childhood trauma, obstetric trauma, maternal infections during pregnancy as well as biological or psychological factors influence the presentation of schizophrenia, depression, or BD.

2. How does your research contribute to the field?

The results of the present study corroborate a number of published findings, including the association of family history of mental illness, obstetric trauma, and premorbid personality characteristics with SCH. However, our study further associates these factors with SCH relative to a BD diagnosis, suggesting that these factors may participate more specifically in the pathogenesis of SCH relative to other psychotic disorders (e.g., BD). Our study also suggests important interactions between genetic liability, gender, and obstetric trauma that are associated with the SCH diagnosis.

3. What are your research's implications towards theory, practice, or policy?

With regards to neurodevelopmental theories for the pathogenesis of psychotic disorders, the present results suggest important gene by sex by environment interactions that may be specific to the pathogenesis of SCH, relative to BD. These possible interactions require further investigation within epidemiological and translational/neurobiological contexts. With regards to clinical practice, the present results corroborate a large body of published work that has associated specific factors with increased risk for SCH; such factors should be considered in the clinical treatment of youth, in order to devise and apply strategies aimed at prevention and early detection of SCH.

Introduction

Clinical descriptions of schizophrenia (SCH) have been the subject of several publications since 1899, and the current diagnostic criteria for SCH reflect the main clinical features of the disorder as described historically by diagnostic experts.¹ Traditionally, BD has been considered a clinical entity distinct from SCH; yet, the validity of this distinction has been consistently questioned.² SCH and BD are associated with unique and shared genetic susceptibility factors, and the final diagnostic manifestation of psychotic disease most likely depends on the interaction between specific environmental factors and these shared and unique genetic factors.²⁻⁴ Thus, having a parent with a mental disorder increases the risk that the individual will suffer from mental illness, compared to individuals of healthy parents,⁵ and risk of familial transmission further varies according the particular family member affected (e.g., mother or father), as well as the sex of the individual.⁶

Indeed, interactions between genetic vulnerability and gender can modify pathogenesis of mental illness. Published studies related to the family risk of suffering SCH are contradictory; some find no association between age, gender and family risk,⁷ while others have reported higher risk in siblings of male patients who had early onset of the disease.⁸ It has been suggested that women may require a higher presence of family risk of SCH, compared to men, to develop the disease.⁹

Finally, various environmental factors such as childhood trauma, infectious agents, and obstetric complications have been associated with a range of psychiatric disorders, including SCH and BD.^{10,11} These risk factors can be biological, physical, psychological or social, and may operate at

different times in the life of the affected individual (fetal period, childhood, adolescence, and early adulthood). Moreover, several risk factors associated with childhood and adolescence can predict the age of onset of psychosis in patients, either with or without the component of familial vulnerability (SD).¹² Thus, the ultimate diagnostic manifestation of psychotic illness most likely is determined by a complex interaction of underlying genetic vulnerability, sex of the individual, and a variety of environmental and social factors.

Among the clinical characteristics associated with SCH, age of onset is an important variable in determining the expression and course of disease.¹³ An early age of onset of psychosis is associated with more psychopathology¹⁴ increased cognitive impairment,¹⁵ previous behavioral problems¹⁶ and premorbid personality changes.¹⁷ Moreover, patients with earlier onset often have unfavorable risk factors, such as a long duration of untreated psychosis, premorbid personality, and higher rates of substance use.¹⁸ Identifying predictive factors and elucidating the underlying mechanisms of psychosis onset are fundamental for facilitating the clinical evolution and functional improvement of patients with SCH.

The BD and SCH diagnoses are among the most prevalent in inpatient psychiatric healthcare, and are the most well studied with respect to genetic liability. These disorders share genetic vulnerability, have a similar symptomatology and chronic clinical course, but they differ importantly in the degree of their neuropsychological effects and social repercussions. The aim our study was to identify family and clinical factors that were associated with a SCH diagnosis

relative to a reference group with a BD diagnosis, and explore the possibility that gender might modify the effects of these factors. We also examined the effects of PANSS positive and negative scores and parental age at the time of the patient's birth, on the age of first psychotic episode.

Material and Methods

Setting

The present study was carried out in the largest public psychiatric hospital in Mexico City. The data for the analysis were collected from a database derived from medical records, and includes a large sample ($n = 1040$) of patients treated from 2009 until 2010. The data collected were strictly anonymous and confidential.

Study Assessments

The medical records included data on psychiatric diagnosis according to Structured Clinical Interview for DSM-IV. Other data that were collected during the interview with the patient and his/her caregiver, and that were analyzed in the present study were: (1) functional indicators including relationship status (having or not a long-term stable relationship), maximum education level, and employment; (2) familial indicators including family history of mental illness, family member diagnosed with mental illness, specific mental illness of family member, age of father, and age of mother at the time of the patient's birth; (3) personal and clinical data of the patient, including comorbid conditions (obesity, diabetes, and others), alcoholism, drug abuse, smoking, obstetric trauma associated with the patient's birth (as reported retrospectively by the patient's mother), and if the patient had been breastfed as an infant; and (4) indicators of disease severity including age of first psychotic episode, PANSS positive and PANSS negative symptom scores, and course of illness (a single psychotic episode, multiple psychotic episodes, or continuous psychosis).

Statistical Analysis

Descriptive and Inferential Analyses. Frequencies and proportions were analyzed using the Chi2 and Fisher's Exact test. Means were compared using the Student's t-test.

Binary Logistic regression. We created a series of logistic regression models with the dependent variable "diagnosis" (SCH = 1, with the reference category being BD = 0), in order to identify factors that were significantly and specifically associated with the SCH diagnosis, relative to the BD diagnosis (the latter being assigned as the reference category). The following explanatory variables were entered into the logistic regression analysis in a single step: sex (male, female; female = reference category), family history of mental disorders (yes or no; no = reference category), type of familial history of mental disorders (none, SCH, BD, or

depression), family member with mental disorder (father, mother, sibling, and others), obstetric trauma associated with the patient's birth (yes or no, as reported retrospectively by the mother of the patient; no = reference category), having been breastfed as an infant (yes or no; yes = reference category), premorbid personality characteristics (yes or no; no = reference category; examples of premorbid characteristics, and relationship status (yes or no; yes = reference category). These explanatory variables were chosen based on existing evidence in the published literature.¹⁹⁻²¹

Multiple Linear Regressions. Linear regression was carried out considering age of the first psychotic episode as the outcome variable and PANSS negative scores, PANSS positive scores, and the age of the father and age of the mother at the time of the patient's birth as predictors. All predictor variables were entered as a single step. For all statistical analyses we used the software SPSS Version 25.

Results

Comparisons Between SCH and BD

First, we compared patients diagnosed with SCH and patients diagnosed with BD, with respect to a number of variables of interest (Table 1). Patients with SCH were significantly less often in a long-term stable relationship compared to those with BD, and also differed significantly with respect to educational level and occupation. With regards to maximum education level achieved, patients with SCH more often reported secondary school as their maximal level of education, while those with BD more often reported enrolling in or completing post-secondary professional degree (technical school or university level). Patients with SCH were more likely to be unemployed, while patients with BD more often reported working within the home.

There was no difference between the SCH and BD diagnoses with regards to the proportions of patients that reported having a family history of mental disorder; however, SCH and BD patient groups differed with respect to type of familial disorder and the specific family member affected. Thus, patients with BD more often reported that their mother suffered from a mental disorder compared to patients with SCH, and more often reported a family history of BD. By contrast, patients with SCH more often reported a family history of SCH. SCH and BD patient groups also differed significantly with respect to premorbid (i.e., present before onset of illness) personality characteristics. Specifically, premorbid schizoid characteristics were reported significantly more often in patients with SCH compared to those with BD.

The age of the parents at the time of the patient's birth did not differ between SCH and BD patient groups, nor did these groups differ with respect to the likelihood of being breastfed as infants. However, patients with SCH more often reported that their birth was associated with obstetric trauma.

Table 1. Comparison of the Schizophrenia (SCH) and Bipolar Disorder (BD) Diagnoses.

Variable	SCH	BD	Hypothesis test
Age of patient (years, mean)	36.4 (n = 830)	36.5 (n = 210)	$T = .165, P = .869$
Stable relationship	13.1% (108/825)	40.4% (84/208)	$\chi^2 = 81.78, P < .0001$
Maximum education level			$\chi^2 = 29.24, P = .002$
None	.3% (3/830)	1.4% (3/210)	ns
Primary	18.2% (151/830)	16.2% (34/210)	ns
Secondary	29.3% (243/830)	22.4% (47/210)	$P = .047$
High school	24.3% (202/830)	23.8% (50/210)	ns
Professional	27% (224/830)	36.2% (76/210)	$P = .01$
Employment			$\chi^2 = 46.1, P < .0001$
None	43.7% (242/554)	17.5% (25/143)	$P < .0001$
Home	15.7% (87/554)	30.8% (44/143)	$P < .0001$
Paid employment	37.2% (206/554)	42.7% (61/143)	ns
Student	2.7% (15/554)	7.0% (10/143)	$P = .022$
Family history of mental disorder	45.4% (442/811)	50% (105/210)	$\chi^2 = 1.34, P = .24$
Family member with mental disorder			$\chi^2 = 12.2, P = .033$
Father	5.3% (43/810)	3.8% (8/208)	ns
Mother	5.3% (42/810)	9.1% (19/208)	$P = .048$
Sibling	14.7% (119/810)	15.4% (32/208)	ns
Other	20.1% (163/810)	21.6% (45/208)	ns
Type of familial mental disorder			$\chi^2 = 329.6, P = .000$
Schizophrenia	41.8% (338/808)	5.8% (12/207)	$P < .0001$
Bipolar disorder	1.4% (11/808)	38.6% (80/207)	$P < .0001$
Depression	.2% (2/808)	1.4% (3/207)	ns
Other	1.2% (10/808)	3.9% (8/207)	$P = .017$
Premorbid personality			$\chi^2 = 108.2, P = .000$
Schizoid	49.3% (300/608)	3.2% (4/126)	$P < .0001$
Irritable	2.3% (14/608)	4.0% (5/126)	ns
Hyperactive	2.0% (12/608)	1.6% (2/126)	ns
Age of parent at patient's birth (years, mean)			
Father	31.6 (n = 718)	31.5 (n = 179)	$T = -.105, P = .92$
Mother	27.4 (n = 725)	28.0 (n = 180)	$T = 1.09, P = .28$
Obstetric trauma	31.3% (160/511)	18.6% (16/86)	$\chi^2 = 5.72, P = .017$
Breastfed	82.9% (418/504)	85.7% (72/84)	$\chi^2 = .4, P = .53$

Mean years (age of patient; maternal and paternal age) or percentages are shown, with number of cases in parentheses. Student's T-tests were used to compare ages, all other comparisons were by the Chi2 test (χ^2). Statistical significance was assumed at $P < .05$; ns: non-significant comparisons.

Comparisons Between Male and Female Patient Groups

Male and female patients differed significantly with respect to certain clinical characteristics associated with the SCH and BD diagnoses (Table 2). With regards to the SCH diagnosis, men had a significantly earlier age of first psychotic episode, showed higher PANSS negative and PANSS total scores, and more often suffered from comorbid substance abuse, alcoholism and smoking. Women with SCH were significantly more likely than men to suffer from comorbid obesity (8.5% of women, compared to 1.4% of men; data not shown) or tardive dyskinesia (4.3% of women, compared to .7% of men; data not shown). Considering the BP diagnosis, male patients differed significantly from females in that they more often were smokers, or suffered from substance abuse or alcoholism. Men

and women of either SCH or BD diagnoses did not differ with respect to the chronicity of psychosis (i.e., a single psychotic episode, multiple psychotic episodes, or continuous psychosis).

Binary Logistic Regression

The initial logistic regression model comprised 560 cases (481 cases of SCH, 79 cases of BD; 386 men, 174 women); 480 cases could not be included due to missing data. This model was significant ($\chi^2 = 134.33, P = .000$; Nagelkerke $R^2 = .383$), and correctly predicted 87.1% of the cases of SCH. Statistically significant individual predictors were: a positive family history of a mental disorder (OR = 160.34), the presence of premorbid personality characteristics (OR = 4.98), the familial relationship (father, mother, brother, grandparent, and other) of the affected family member to

Table 2. Comparisons Between Male and Female Patients Diagnosed With Schizophrenia or Bipolar Disorder.

Clinical variables	Schizophrenia			Bipolar disorder		
	Male (n = 583)	Female (n = 247)	Hypothesis test	Male (n = 80)	Female (n = 130)	Hypothesis test
Age (first psychotic episode)	$\bar{x} = 23.2$; SD = 7.5 (n = 577)	$\bar{x} = 26.4$; SD = 9.2 (n = 238)	$T = -4.7^{**}$	$\bar{x} = 24.9$; SD = 9.5 (n = 80)	$\bar{x} = 27.1$; SD = 9.6 (n = 130)	$T = 1.5$
Positive PANSS	$\bar{x} = 2.7$; SD = 1.0 (n = 548)	$\bar{x} = 2.7$; SD = 1.1 (n = 232)	$T = -0.1$	$\bar{x} = 2.3$; SD = .8 (n = 6)	$\bar{x} = 2.4$; SD = 1.1 (n = 5)	$T = -0.1$
Negative PANSS	$\bar{x} = 3.1$; SD = .8 (n = 548)	$\bar{x} = 2.8$; SD = .9 (n = 232)	$T = 4.1^{**}$	$\bar{x} = 3.1$; SD = .7 (n = 6)	$\bar{x} = 2.2$; SD = .9 (n = 5)	$T = 2.0$
General PANSS	$\bar{x} = 3.59$; SD = .8 (n = 546)	$\bar{x} = 3.4$; SD = .9 (n = 232)	$T = 2.1^{**}$	$\bar{x} = 3.6$; SD = 1.2 (n = 6)	$\bar{x} = 2.4$; SD = .9 (n = 5)	$T = 2.1$
Duration of disease	$\bar{x} = 11.9$; SD = 9.4	$\bar{x} = 11.0$; SD = 8.9	$T = 1.58^*$	$\bar{x} = 10.5$; SD = 1.7	$\bar{x} = 10.4$; SD = 0.7	$T = 1.3$
Evolution of psychosis			$\chi^2 = 151^{**}$			$\chi^2 = 181^{**}$
A single episode of psychosis	40/583 (7%)	20/247 (8%)		16/80 (20%)	17/130 (13%)	
Psychosis episodically	452/583 (78%)	188/247 (76%)		64/80 (80%)	113/130 (87%)	
Continuous psychosis	90/583 (15%)	37/247 (15%)		0/80 (0%)	0/130 (0%)	
Comorbidity			$\chi^2 = 12.9^*$			$\chi^2 = 34.2$
Without comorbidity	208/272 (76%)	83/117 (71%)		26/32 (81%)	51/66 (77%)	
Medical	33/272 (12%)	23/117 (20%)		5/32 (16%)	14/66 (21%)	
Psychiatric	31/272 (11%)	11/117 (9%)		1/32 (3%)	1/66 (1.5%)	
Smoking (yes)	249/550 (45%)	38/230 (16%)	$\chi^2 = 57.6^{**}$	33/74 (45%)	29/123 (24%)	$\chi^2 = 9.4^*$
Abuse of substances (yes)	92/426 (22%)	5/186 (3%)	$\chi^2 = 34.7^{**}$	8/61 (13%)	1/106 (.9%)	$\chi^2 = 11.2^*$
Alcoholism (yes)	50/374 (13%)	7/155 (5%)	$\chi^2 = 8.9^{**}$	7/49 (14%)	3/94 (3%)	$\chi^2 = 6.0^*$

Mean, standard deviation (SD), and sample sizes are shown for age of patient, PANSS scores, and duration of disease, and comparisons were done by the Student's T-test. Proportions and corresponding percentages are shown for all other variables; statistical comparisons were done by the Chi2 test (χ^2). Asterisks denote statistical significance at $P < .05$ (*) and $P < .01$ (**).

Table 3. Logistic Regression: Factors Associated With a Schizophrenia Diagnosis.

Variable	B	SE	Wald	df	Sig	Exp(B)	95% C. I. (Lower)	95% C. I. (Upper)
Family history	5.08	1.31	15.02	1	<.0001	160.34	12.30	2090.97
Family member affected	.60	.23	6.57	1	.010	1.82	1.15	2.87
Type of familial mental disorder	1.76	.32	30.28	1	<.0001	5.80	3.10	10.85
Sex	1.01	.30	11.52	1	.001	2.74	1.53	4.92
Obstetric trauma	.38	.37	1.07	1	.300	1.46	.71	3.02
Breastfed	-.11	.40	.02	1	.776	.89	.41	1.96
Premorbid personality	1.59	.38	17.51	1	<.0001	4.89	2.32	10.27
Relationship	-1.35	.36	13.97	1	<.0001	.26	.13	.53
Constant	-7.41	1.42	27.04	1	<.0001	.001		

Logistic regression considering diagnosis as the outcome variable (BD vs SCH; BD as reference category). S.E. = Standard Error. Sig. = Significance (One-tailed P value). C. I. = Confidence Intervals. Family history (yes or no; reference category: no). Family member affected (father, mother, siblings, others, nobody; reference category: nobody)). Type of familial mental disorder (schizophrenia, bipolar disorder, depression, others, none; reference category: none). Obstetric trauma during birth (yes or no; reference category: no). Breastfeeding (yes or no; reference category: no). Premorbid personality (yes or no; reference category: no). With a relationship (yes or no; reference category: no). Sex (female or male; reference category: female).

the patient (OR = 1.82) and the type of familial mental disorder (OR = 5.80). Having a stable long-term relationship was a significant negative predictor (OR = .26). Given the body of published literature that has associated

obstetric trauma with SCH, we tested 3 further models in order to examine the possibility that obstetric trauma might interact with genetic liability (i.e., family history of mental illness) and/or gender (Table 3).

Table 4. Logistic Regression: Factors Associated With a Schizophrenia Diagnosis in Patients Having a Positive Family History of Mental Illness.

Variable	B	SE	Wald	df	Sig	Exp(B)	95% C.I. (Lower)	95% C.I. (Upper)
Family member affected	.68	.25	7.47	1	.006	1.98	1.21	3.22
Type of familial mental disorder	1.87	.35	28.53	1	<.0001	6.53	3.28	13.01
Sex	1.21	.54	5.08	1	.024	3.34	1.17	9.54
Obstetric trauma	1.34	.66	4.060	1	.044	3.81	1.04	13.98
Breastfed	1.95	1.21	2.62	1	.11	7.05	.663	74.94
Premorbid personality	1.03	.59	3.05	1	.08	2.80	.88	8.89
Relationship	-1.77	.80	4.93	1	.03	.17	.04	.81
Constant	-9.89	2.16	21.04	1	<.0001	<.0001		

Logistic regression considering diagnosis as the outcome variable (BD vs SCH; BD as reference category), only cases that had a positive family history of mental disorder were entered into the analysis. S.E. = Standard Error. Sig. = Significance (One-tailed *P* value). C. I. = Confidence Intervals. Family member affected (father, mother, siblings, others, nobody; reference category: nobody). Type of familial mental disorder (schizophrenia, bipolar disorder, depression, others, none; reference category: none). Obstetric trauma during birth (yes or no; reference category: no). Breastfeeding (yes or no; reference category: no). Premorbid personality (yes or no; reference category: no). With a relationship (yes or no; reference category: no). Sex (female or male; reference category: female).

The first model incorporated only those patients *with a family history of mental disorders*. There were 263 such cases included in this analysis (231 cases of SCH, 32 cases of BD); 210 cases were omitted due to missing data. The resulting model was significant ($\chi^2 = 88.3$; $P = .000$; Nagelkerke $R^2 = .55$), and correctly predicted 89.4% of the cases of SCH. Significant positive predictors were being male (OR = 3.34) and obstetric trauma (OR = 3.81), type of familial psychiatric disorder (OR = 6.53), and family member with psychiatric disorder (OR = 1.98). Having a stable long-term relationship (.17) was a significant negative predictor (Table 4).

The second model considered these same predictors, but *male and female cohorts were analyzed separately*. With regards to the male patient group (186 cases: 172 cases of SCH, 14 cases of BD; 109 cases omitted due to missing data) the model was significant ($\chi^2 = 46.00$; $P = .000$; Nagelkerke $R^2 = .53$), and correctly predicted 91% of the cases of SCH. The only significant positive predictor in this model was obstetric trauma (OR = 19.33). Family member with psychiatric illness (OR = .27) and type of familial mental illness (OR = .14), and having a stable long-term relationship (OR = .014) remained significant negative predictors. Having premorbid personality characteristics was not a significant predictor in this model. This same analysis of women patients (18 cases of SCH, 59 cases of BD; 102 cases omitted due to missing data) was also significant ($\chi^2 = 41.20$; Nagelkerke $R^2 = .63$) and correctly predicted 70.1% of cases. However, this model showed only 1 significant negative predictor of a small effect size: family member with psychiatric illness (OR = .056).

A final model considered only cases in which there was *no family history of a mental disorder*. This analysis included 297 cases (250 cases of SCH, 49 cases of BD; 200 men, 97 women); 250 cases were omitted due to missing data. The resulting model was significant ($\chi^2 = 54.3$, $P = .000$; Nagelkerke $R^2 = .28$), and correctly predicted 83.6% of the cases of SCH. Significant positive predictors were being male (OR = 2.42) and the presence of premorbid personality characteristics (OR = 7.32).

Having a stable long-term relationship was negatively associated with the SCH diagnosis (OR = .27). Notably, obstetric trauma did not emerge as a significant predictor in this model.

Multiple Linear Regression

We used linear regression to model predictor variables for 1 indicator of SCH severity: age of first psychotic episode. Predictor variables were: age of father at the birth of the patient, age of mother at the birth of the patient, PANSS positive symptom scores, and PANSS negative symptom scores. Three regression analyses were carried out: the first considered *all patients* with SCH ($n = 669$ cases), the second considered only *male patients* with SCH ($n = 477$), and the third considered *female patients* with SCH ($n = 192$). The first model was significant ($B = 29.0$; $t = 16.71$; $P = .000$), and predicted 5.8% of the variance in age of first psychotic episode (adjusted $R^2 = .058$). Father's age ($B = .128$; $t = 2.29$, $P = .022$) was positively associated with the age of first psychotic episode, while PANSS positive score ($B = -1.369$; $t = -4.43$; $P = .000$) and PANSS negative score ($B = -.903$; $t = -2.57$; $P = .01$) were significant negative predictors. The second model, considering only men with a SCH diagnosis, was also significant ($B = 26.08$; $t = 13.37$; $P = .000$), and explained 4.3% of the variance in the dependent variable (adjusted $R^2 = .043$). PANSS positive symptom score was the only statistically significant negative predictor ($B = -1.50$; $t = -4.33$; $P = .000$). The third model, which considered only women with SCH, explained 9.0% of the variance in the dependent variable (adjusted $R^2 = .09$). All 4 predictor variables were statistically significant (Table 5). Thus, in women patients, having an older father, a younger mother, higher positive PANSS scores, and higher negative PANSS scores were each significant predictors of an earlier age of psychosis onset.

Discussion

The present results corroborate those of previous studies as well as reveal some novel findings. Considering factors that

Table 5. Multiple Linear Regression: Effects of Parental Age and PANSS on Age of First Psychotic Episode in Females With Schizophrenia.

Variables	β (Not standardized)	S. E	β (Standardized)	T stat	P value	Lower 95% C.I.	Upper 95% C.I.
Positive PANSS	−1.29	.61	−.16	−2.10	.037	−2.49	−.08
Negative PANSS	−1.36	.68	−.15	−2.01	.046	−2.69	−.03
Paternal age	.27	.12	.24	2.30	.022	.04	.51
Maternal age	−.32	.13	−.26	−2.56	.011	−.58	−.07
(Constant)	33.70	3.50		9.63	<.0001	26.79	40.60

distinguish the SCH and BD diagnoses, we found that the SCH diagnosis was more often associated with lower academic performance, unemployment, and the lack of a stable long-term relationship. Both diagnoses were strongly associated with familial mental illness: SCH was strongly associated with a SCH diagnosis within the patient's family, while BD was strongly associated with a familial BD diagnosis. Obstetric complications and schizoid-like premorbid personality characteristics were also more frequently observed in patients with SCH compared to those with BD. Logistic regression analyses suggest an interaction between family history of mental illness and obstetric trauma in predicting a SCH diagnosis relative to a BD diagnosis, and that this interaction is observed in male patients only. On the other hand, linear regression analyses indicate that younger maternal age and older paternal age at the patient's birth were associated with an earlier onset of psychosis in the female patient group, while these associations were not observed in the male patient group.

Our results concerning academic and social function of individuals with SCH or BD are consistent with the current literature (for a complete review of such studies, see Parellada and colleagues¹¹.) Thus, patients diagnosed with SCH as adults more often had shown impaired academic performance during childhood and adolescence compared to those that did not develop SCH.²² Subjects with SCH had performed more poorly academically at age 7 (although this difference was not statistically significant),²³ and decline in cognitive function across ages 12–18 was associated with later SCH diagnosis, but not with a BD diagnosis.²⁴ In the present study, significantly more individuals with SCH reported not having an education beyond the secondary level, and significantly more individuals with BD reported having been enrolled in university or other post-secondary degree programs. Patients with SCH were more likely to be unemployed, while those with BD were more likely to report working at the home (e.g., homemaker).

Along with poorer premorbid academic functioning in individuals with SCH compared to those with BD, individuals with SCH are also reported to present schizoid-like personality and negative emotional characteristics during the adolescent years prior to onset of illness. In a prospective study, Jones and colleagues²² reported that preference for solitary play, low social confidence, and increased premorbid social anxiety and schizoid-like social functioning during childhood were significantly associated with a SCH diagnosis between ages 16–43. Another prospective study interviewed

healthy men at age 18; those later diagnosed with SCH were more likely to have reported having few friends, a preference to socialize in very small groups, and not having a stable long-term relationship, compared to those later diagnosed with a non-SCH psychosis.²⁵ Our results are in agreement with these observations: in our sample more patients with SCH described themselves as having had premorbid schizoid-like characteristics, compared to those with BD. Likewise, significantly fewer subjects with SCH reported being in a stable, long-term relationship, compared to those with BD. However, we found that having such premorbid personality characteristics was a significant positive predictor for the SCH diagnosis only in logistic regression models that included subjects with no family history of mental illness (notably, in these models, obstetric trauma did not emerge as a significant predictor). These results suggest interactions between factors of family history of mental illness, obstetric trauma, premorbid personality, and possibly gender that require further investigation.

Around half of the patients in the present study reported familial antecedents of some psychiatric disorder, and a family history of SCH and BD were by far the most commonly reported. This finding is underscores the high genetic liability of psychotic disorders and significant shared genetic risk between SCH and BD that has been consistently observed.² However, the present results also indicate the presence of genetic liability unique to each of these disorders: patients with SCH more often reported a family member that had SCH, while those patients with BD more often reported that a family member suffered from BD. Genetic liability unique to each of these disorders has also been previously reported in the literature.^{2,26} Although the accuracy of our data rely on how informed the patient was with respect to their family history of mental illness (e.g., we do not have records of the actual diagnoses of the family member that suffered from mental illness), the magnitude of the difference between SCH and BD in this regard is striking (Table 1). Interestingly, BD was significantly more often associated with mental illness of the patient's mother, compared to SCH. Although this surprising finding requires replication, some studies have shown that maternal mental illness (specifically, maternal BD) might confer vulnerability to BD in the offspring due to the effects of negative maternal caregiving style on the development of the frontal lobe and executive function.²⁷

Our results underscore a number of gender-associated differences between SCH and BD diagnoses. Published studies have reported that males showed an earlier age of

onset of SCH (3 years earlier), had poorer performance and premorbid adjustment,²⁸ and generally have poorer social functioning as indicated, for example, by the lack of stable long-term relationships.²⁹ In the present study, men were approximately one-third more likely to have a SCH diagnosis compared to women, while women were approximately 2.8 times more likely to have BD diagnosis compared to men. Men with SCH had a significantly younger age of first psychotic episode, and had significantly worse PANSS negative and PANSS total scores, compared to women. Male patients of both SCH and BD diagnostic groups were more likely than women to smoke tobacco, abuse illicit substances, and suffer from alcoholism. The present findings are important, given that male sex and family history of mental illness are factors associated with diagnostic stability in SCH over time.³⁰ These findings are also relevant within the clinical context, in which the specialized interventions must be differentiated by sex. One study reported that males with SCH and comorbid substance abuse were hospitalized more often, and more often subjected to mechanical restraint.³¹

Our results concur with many studies that have demonstrated an association between obstetric trauma and SCH, while this association has been less consistently observed for BD.^{32–34} “Obstetric trauma” encompasses a wide range of birth complications; in the present study patients and/or their caregivers reported hypoxia during birth, premature birth, preeclampsia, and other complications. Nevertheless, hypoxia has been identified as a specific risk factor, and its effects are suggested to be mediated by inflammation and immune mechanisms.³⁴ In the present study, we found that obstetric trauma (as reported retrospectively by the patient or caregiver) was specifically associated with the SCH diagnosis, and that the effect of obstetric trauma was increased in patients with familial antecedents of mental illness, strongly suggesting a gene by environment interaction, and consistent with the conclusions of previously published studies.³⁵ Although the literature in this area is sparse, published studies have reported possible interactions of a number of genetic variants with obstetric trauma: specific polymorphisms of the *AKT1* (RAC-alpha serine/threonine protein kinase 1), *BDNF* (brain derived neurotrophic factor), *DTN3P1* (distrobrevin binding protein 1), *GRM3* (glutamate metabotropic receptor 3), and *NDE1* (NudE neurodevelopment protein 1) genes.^{36–39} Our analyses indicate that the effects of obstetric trauma are further increased by familial psychiatric antecedents only in male patients, thereby indicating a sex by gene by environment interaction.

Finally, we found that 1 index of SCH severity, age of psychosis onset, was significantly associated in both sexes with PANSS scores. When men and women SCH patients were analyzed together, paternal age emerged as a *positive* predictor of age of first psychotic episode: that is, increased paternal age was associated with an older age of first psychotic episode. However, when men and women were

each analyzed independently, an earlier age of onset was associated with higher PANSS negative scores, *older* paternal age, and *younger* maternal age in women only. Older paternal age has been repeatedly associated with the SCH diagnosis, while such an association has been less consistently observed for BD.⁴⁰ Few studies have examined whether this factor might differentially affect men and women, but 1 published study suggests that this effect might be slightly more important in women than in men,⁴¹ and a meta-analysis of such studies reported that very young (less than 25 years old) paternal age was associated with SCH in men, in addition to a clear negative effect of advanced paternal age that was not sex specific.⁴² Paternal age effects are suggested to be due to increased de novo mutations in the germ line, age-associated differences in sperm DNA methylation patterns, psychiatric vulnerability factors (e.g., compromised social skills) that make late fatherhood more likely, and/or certain environmental and social factors that are associated with the age of the father.⁴⁰ To our knowledge, an association between younger maternal age and SCH has not been previously reported, but such an effect could be due to physiological, environmental, or social correlates of young motherhood.

There are important limitations of the present study. Most notably, all data were retrospective, collected by interviewing the patient and his/her caregiver. Therefore, data accuracy may have been influenced by the patient’s or caregiver’s memory biases as well as by possible interviewer biases. This limitation may be particularly relevant for data on obstetric trauma, family history of mental illness, specific familial psychiatric diagnoses, and premorbid personality characteristics. However, in support of the reliability of our data set, results of the present analyses are entirely consistent with the published literature, and our novel findings are not without published precedent.

In conclusion, the present study identified a number of factors that were significantly associated with the SCH diagnosis, as compared to BD. These include generally poorer academic and social functioning, the presence of premorbid schizoid-like personality characteristics, a family history of SCH, and obstetric trauma. We found evidence that interactions between family history of mental illness, obstetric trauma, and male gender may be more associated with the SCH diagnosis as compared to BD. Our results also indicate that interactions between gender and parental age (father and/or mother) at time of the patient’s birth may be associated with an earlier age of onset of SCH psychosis. Putative interactions between genetic vulnerability, gender, and obstetric trauma should be further investigated in a neurobiological and neurodevelopmental context.

Acknowledgments

None

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

The database from which the present study arises is a secondary database. Dr Miguel Angel Herrera Estrella as leader investigator, authorized the use of the present database.

ORCID iD

Lina Díaz-Castro  <https://orcid.org/0000-0002-9123-8641>

References

- Kendler KS. Phenomenology of schizophrenia and the representativeness of modern diagnostic criteria. *JAMA Psychiatr.* 2016;73(10):1082-1092.
- Owen MJ, Craddock N, Jablensky A. The genetic deconstruction of psychosis. *Schizophr Bull.* 2007;33(4):905-911.
- Carpenter WT, Bustillo JR, Thaker GK, van Os J, Krueger RF, Green MJ. The psychoses: Cluster 3 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med.* 2009;39(12):2025-2042.
- Kendler KS, Ohlsson H, Sundquist J, Sundquist K. An extended swedish national adoption study of bipolar disorder illness and cross-generational familial association with schizophrenia and major depression. *JAMA Psychiatr.* 2020;77(8):814-822.
- Goldstein BI, Shamseddeen W, Axelson DA, Kalas C, Monk K, Brent DA, et al. Clinical, demographic, and familial correlates of bipolar spectrum disorders among offspring of parents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2010;49:388-396.
- Maciejewski D, Hillegers M, Penninx B. Offspring of parents with mood disorders: Time for more transgenerational research, screening and preventive intervention for this high-risk population. *Curr Opin Psychiatr.* 2018;31(4):349-357.
- Kendler KS, Walsh D. Gender and schizophrenia. Results of an epidemiologically-based family study. *Br J Psychiatry.* 1995;167(2):184-192.
- Pulver AE, Liang K-Y, Vogler GP Estimating effects of proband characteristics on familial risk: II. The association between age at onset and familial risk in the Maryland schizophrenia sample. *Genet Epidemiol.* 1991;8(5):339-350.
- Ochoa S, Usall J, Cobo J, Labad X, Kulkarni J. Gender differences in schizophrenia and first-episode psychosis: A comprehensive literature review. *Schizophr Res Treatment.* 2012;2012:916198. doi:10.1155/2012/916198.
- Robinson N, Bergen SE. Environmental risk factors for schizophrenia and bipolar disorder and their relationship to genetic risk: Current knowledge and future directions. *Front Genet.* 2021;12:686666. doi:10.3389/fgene.2021.686666.
- Parellada M, Gomez-Vallejo S, Burdeus M, Arango C. Developmental differences between schizophrenia and bipolar disorder. *Schizophr Bull.* 2017;43(6):1176-1189.
- Scherr M, Hamann M, Schwerthöffer D, Froböse T, Vukovich R, Pitschel-Walz G, et al. Environmental risk factors and their impact on the age of onset of schizophrenia: Comparing familial to non-familial schizophrenia. *Nord J Psychiatr.* 2012;66(2):107-114.
- Butjosa A, Gómez-Benito J, Huerta-Ramos E, Del cacho N, Barajas A, Baños I, et al. Incidence of stressful life events and influence of sociodemographic and clinical variables on the onset of first-episode psychosis. *Psychiatr Res.* 2016;245:108-115.
- Langeveld J, Joa I, Friis S, ten Velden Hegelstad W, Melle I, Johannessen JO, et al. A comparison of adolescent- and adult-onset first-episode, non-affective psychosis: 2-year follow-up. *Eur Arch Psychiatr Clin Neurosci.* 2012;262:599-605.
- Rajji TK, Ismail Z, Mulsant BH. Age at onset and cognition in schizophrenia: Meta-analysis. *Br J Psychiatry.* 2009;195(4):286-293.
- Vinokur D, Levine SZ, Roe D, Krivoy A, Fischel T. Age of onset group characteristics in forensic patients with schizophrenia. *Eur Psychiatr.* 2014;29(3):149-152.
- Skokou M, Katrivanou A, Andriopoulos I, Gourzis P. Sintomatología de las fases activa y prodrómica de la esquizofrenia paranoide de inicio en el joven y de inicio tardío [Active and prodromal phase symptomatology of young-onset and late-onset paranoid schizophrenia]. *Rev Psiquiatr Salud Ment.* 2012;5(3):150-159.
- Pencer A, Addington J, Addington D. Outcome of a first episode of psychosis in adolescence: A 2-year follow-up. *Psychiatr Res.* 2005;133(1):35-43.
- Lyne J, Renwick L, O'Donoghue B, Kinsella A, Malone K, Turner N, et al. Negative symptom domain prevalence across diagnostic boundaries: The relevance of diagnostic shifts. *Psychiatr Res.* 2015;228(3):347-354.
- van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabendam L. A systematic review and meta-analysis of the psychosis continuum: Evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med.* 2009;39(2):179-195.
- Wigman JTW, Wardenar KJ, Wanders RBK, Booij SH, Jeronimus BF, van der Krieke L, et al. Dimensional and discrete variations on the psychosis continuum in a Dutch crowd-sourcing population sample. *Eur Psychiatr.* 2017;42:55-62.
- Jones P, Murray R, Rodgers B, Marmot M. Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet.* 1994;344(8934):1398-1402.
- Seidman LJ, Cherkerzian S, Goldstein JM, Agnew-Blais J, Tsuang MT, Buka SL. Neuropsychological performance and family history in children at age 7 who develop adult schizophrenia or bipolar psychosis in the New England Family Studies. *Psychol Med.* 2013;43(1):119-131.

24. Osler M, Lawlor DA, Nordentoft M. Cognitive function in childhood and early adulthood and hospital admission for schizophrenia and bipolar disorders in Danish men born in 1953. *Schizophr Res.* 2007;92(1–3):132-141.
25. Malmberg A, Lewis G, David A, Allebeck P. Premorbid adjustment and personality in people with schizophrenia. *Br J Psychiatry.* 1998;172:308-313.
26. Ruderfer DM, Ripke S, McQuillin A, Boocock J, Stahl EA, Pavlides JMW, et al. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. *Cell.* 2018; 173(7):1705-1715.e16.
27. Meyer SE, Carlson GA, Wiggs EA, Ronsaville DS, Martinez PE, Klimes-Dougan B, et al. A prospective high-risk study of the association among maternal negativity, apparent frontal lobe dysfunction, and the development of bipolar disorder. *Dev Psychopathol.* 2006;18(2):573-589.
28. Hui CL-M, Leung C-M, Chang W-C, Chan SK-W, Lee EH-M, Chen EY-H. Examining gender difference in adult-onset psychosis in Hong Kong. *Early Interv Psychiatry.* 2016;10(4):324-333.
29. Pang S, Subramaniam M, Abdin E, Poon LY, Chong SA, Verma S. Gender differences in patients with first-episode psychosis in the Singapore Early Psychosis Intervention Programme. *Early Interv Psychiatry.* 2016;10(6):528-534.
30. Palomar-Ciria N, Cegla-Schwartzman F, Lopez-Morinigo J-D, Bello HJ, Ovejero S, Baca-García E. Diagnostic stability of schizophrenia: A systematic review. *Psychiatr Res.* 2019;279: 306-314.
31. Lykke J, Hjorthøj C, Thomsen CT, Austin SF. Prevalence, predictors, and patterns of mechanical restraint use for inpatients with dual diagnosis. *Psychiatr Care.* 2020;56(1):20-27.
32. Cannon M, Jones PB, Murray RM. Obstetric complications and CannonObstetric complications and schizophrenia: Historical and meta-analytic reviewschizophrenia: Historical and meta-analytic review. *Am J Psychiatry.* 2002;159(77):1080-1092.
33. Scott J, McNeill Y, Cavanagh J, Cannon M, Murray R. Exposure to obstetric complications and subsequent development of bipolar disorder. *Br J Psychiatry.* 2006;189:3-11.
34. Belbasis L, Köhler CA, Stefanis N, Stubbs B, van Os J, Vieta E, et al. Risk factors and peripheral biomarkers for schizophrenia spectrum disorders: An umbrella review of meta-analyses. *Acta Psychiatr Scand.* 2018;137(2):88-97.
35. Misiak B, Stramecki F, Gawęda Ł, Prochwicz K, Szaśiadek MM, Moustafa AA, et al. Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: A systematic review. *Mol Neurobiol.* 2018;55(6):5075-5100.
36. Ursini G, Cavalleri T, Fazio L, Angrisano T, Iacovelli L, Porcelli A, et al. BDNF rs6265 methylation and genotype interact on risk for schizophrenia. *Epigenetics.* 2016;11(1): 11-23. DOI: [10.1080/15592294.2015.1117736](https://doi.org/10.1080/15592294.2015.1117736)
37. Wegelius A, Pankakoski M, Tomppo L, Lehto U, Lönnqvist J, Suvisaari J, et al. An interaction between NDE1 and high birth weight increases schizophrenia susceptibility. *Psychiatr Res.* 2015;230(2):194-199.
38. Haukvik UK, Saetre P, McNeil T, Bjerkan PS, Andreassen OA, Werge T, et al. An exploratory model for G×E interaction on hippocampal volume in schizophrenia; obstetric complications and hypoxia-related genes. *Prog Neuro Psychopharmacol Biol Psychiatry.* 2010;34(7):1259-1265. DOI: [10.1016/j.pnpbp.2010.07.001](https://doi.org/10.1016/j.pnpbp.2010.07.001).
39. Nicodemus KK, Marengo S, Batten AJ, Vakkalanka R, Egan MF, Straub RE, et al. Serious obstetric complications interact with hypoxia-regulated/vascular-expression genes to influence schizophrenia risk. *Mol Psychiatry.* 2008;13(9):873-877.
40. de Kluiver H, Buizer-Voskamp JE, Dolan CV, Boomsma DI. Paternal age and psychiatric disorders: A review. *Am J Med Genet B Neuropsychiatr Genet.* 2017;174(3):202-213.
41. McGrath JJ, Petersen L, Agerbo E, Mors O, Mortensen PB, Pedersen CB. A comprehensive assessment of parental age and psychiatric disorders. *JAMA Psychiatry.* 2014;71(3): 301-309.
42. Miller B, Messias E, Miettunen J, Alaräisänen A, Järvelin M-R, Koponen H, et al. Meta-analysis of paternal age and schizophrenia risk in male versus female offspring. *Schizophr Bull.* 2011;37(5):1039-1047.