Ontiveros-Sanchez de la Barquera JA, Perez Silva VA, Nicolini Sanchez H, De la Garza-García LA, Sánchez-Torres MD G, Jezzini-Martínez S. Psychopathology in Relatives of Mexican Patients with Bipolar Disorder. *JNHMA*. 2025;3(2):67-78. doi:10.59867/001c.145918

RESEARCH ARTICLES

Psychopathology in Relatives of Mexican Patients with Bipolar Disorder

Jose Alfonso Ontiveros-Sanchez de la Barquera, MD, MSc, Dr med[1][a], Victor Alfonso Perez Silva, MD[1], Humberto Nicolini Sanchez, MD, MSc[2], Luis Alberto De la Garza-García, MD[1], Guillermo Sánchez-Torres MD, MD[1], Sofía Jezzini-Martínez, MD[1]

[1] Psychiatry, Universidad Autónoma de Nuevo León, [2] Genetics, Instituto de Medicina Genómica

Keywords: bipolar disorder, psychological disorders, relatives, Latino population, Hispanic

https://doi.org/10.59867/001c.145918

Journal of the National Hispanic Medical Association

Vol. 3, Issue 2, 2025

ABSTRACT

Objectives

Our study aims to investigate the prevalence and risk of psychopathology among the relatives of Mexican persons living with bipolar disorder.

Background

Numerous studies have shown a high prevalence of various psychological disorders among the relatives of individuals with bipolar disorder. However, there remains some uncertainty, especially concerning patients of Hispanic origin.

Methods

A cross-sectional study was done with 770 adult relatives (older than 18 years) of bipolar disorder individuals from Mexico City and Monterrey, Mexico (as part of the "Genetics of Bipolar Disorder in Latino Populations"). All participants were diagnosed using the DIGS, FIGS, and medical/psychiatric records, using the best estimation of the diagnosis method and DSM-5 criteria.

Results

A high prevalence of several psychopathologies was found (65.2% n=502) among relatives of bipolar participants. Major Depressive Disorder accounted for 31.9% (n=246) with a higher prevalence in 2nd-degree relatives versus 1st-degree relatives (p=0.013) and in female participants (p=0.01), while bipolar disorder prevalence (21.1% n=163) was more common in first-degree relatives (p=<.001). Substance use disorders were found to be more common in men (p=<.001) and eating disorders in women (p=0.02) in this sample.

[a] Acknowledgments
Michael A. Escamilla, Cynthia Camarillo, Marco Rodriguez, Mercedes Ramirez, Juan Zavala, Regina Armas, Salvador A. Contreras, Javier Contreras, Albana Dassori, Laura Almasy, Deborah Flores.

Conclusions

We found a high prevalence not only of bipolar disorder but also major depressive, anxiety, and substance use disorders among the relatives of Mexican participants with bipolar disorder. Further extensive studies are needed to confirm our findings.

Background

Bipolar disorder (BD) affects approximately 0.4–1.1% of people worldwide, with males and females at equal risk. It is a significant public health issue due to the psychosocial impairment it causes, the substantial costs associated with medical care and disability, and the high suicide rate associated with this disorder.[1] Individuals with BD tend to experience a lower quality of life and diminished work productivity (as lost time and absence costs).[2]

Furthermore, BD is frequently comorbid with several psychiatric (substance-abuse disorders and personality disorders) and medical health issues (hypertension, obesity, endocrine and lipoprotein metabolism disorder).[3-5] Several studies suggest that the prevalence and clinical manifestations of BD may vary according to the gender of the affected individuals.[6-8] For example, substance abuse disorders are more common in males, while females with BD are more prone to experiencing eating disorders.[7,9]

The prevalence of psychopathology among family members of BD individuals has been the focus of global research efforts, revealing a significantly higher occurrence of mood disorders. However, determining an exact figure for this is a challenge due to misdiagnoses and undiagnosed cases within relatives.[8] Studies indicate that the lifetime prevalence of mood disorders among children of parents with BD reaches up to 48-63%.[10,11] Studies compared first-degree relatives of individuals with BD to controls, without a family history of the disorder.[7,11-13] These studies have shown consistently that first-degree relatives (such as parents or siblings) of individuals with BD are more likely to develop depressive, anxiety, and behavioral disorders, or to receive at least two lifetime psychiatric diagnoses and treatment, compared to participants in control groups.[10]

A study by Rasic et al.[14] examined the risk of developing psychiatric disorders in offspring of parents with schizophrenia, BD, and major depressive disorder (MDD). It was found that high-risk offspring were 3.5 times more likely to develop the same disorder as their parents when they were compared to a control group. Research indicates that children of individuals with BD are up to nine times more likely to develop bipolar-type disorders and 2.5 times more likely to experience non-bipolar affective disorders.[15] Moreover, meta-analysis estimated a high incidence of MDD and BD among first-degree

relatives of individuals diagnosed with these disorders.[16] Specifically, the odds of developing MDD were 2.5 times higher, and the odds of developing BD were nearly eightfold compared to control participants.[16]

The reasons for the high incidence of psychiatric disorders among family members of bipolar disorder individuals remain unclear. It appears that a combination of genetic risk factors, environmental influences, and psychosocial dynamics within family relationships may contribute to this phenomenon.[17,18] These findings highlight the significant familial risk associated with BD and underscore the importance of early identification and intervention for at-risk individuals. The present study aims to explore the prevalence of psychopathology among the family members of participants with BD. To achieve this, we analyzed data from two Mexican sites (Mexico City and Monterrey) as part of the "Genetics of Bipolar Disorder in Latino Populations" study, which included direct diagnostic interviews.[19]

Materials and methods

The present cross-sectional study involved families (N=172), which met the previously established ascertainment criteria outlined in Gonzalez et al.[19] study. The study was conducted in the only two Mexican sites of the above study, at Monterrey Nuevo León Mexico (Department of Psychiatry of the University Hospital, UANL and INFOSAME Institute at Monterrey Mexico), and Mexico City (Carraci Institute)**.** While not all relatives could be recruited, the study included available family members (N=770) of participants with BD across two states in Mexico: Mexico City (N=426) and Monterrey (N=344). All families were ascertained through two probands with a history of BD. After obtaining informed consent, all participants underwent interviews using the Diagnostic Interview for Genetic Studies (DIGS)[20] and the Family Interview for Genetic Studies (FIGS),[21] along with a medical and psychiatric history assessment.

Diagnoses were made using the best estimation technique,[22] DSM-5 criteria were applied for psychiatric diagnosis. Data were collected by fully trained psychiatrists, who underwent training for FIGS and DIGS as part of the "Genetics of Bipolar Disorder in Latino Populations" study. Psychiatric History and DIGS interviews mean to take 3–6 hours, while FIGS used to be complete in 45 min. Detailed genogram information was used to collect relative's data.

The study was approved by local IRBs (Department of Psychiatry of the University Hospital, UANL) and granted by NIMH (5RO1MH069856). The participants received meal and travel expenses incentives. Incomplete or not accurate FIGS information were excluded.

We analyzed data from first-degree and second-degree family members of BD participants, with a focus on the prevalence of psychopathology. A comparison was made between first- and second-degree family members.

Statistical Analysis

Descriptive statistics were calculated for all included variables. Comparative analyses were conducted using metric and parametric tests, as appropriate, and the probability of risk for psychopathology was assessed. To examine group differences by diagnosis and sex, Pearson's chi-square test and Fisher's exact test were applied. Age differences were analyzed using Student's t-test. The association between psychopathology and specific family group characteristics was evaluated with multivariate analysis. Unless otherwise specified, a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software, version 17.0.[23]

Results

Demographics

A total of 770 family members of participants with BD were interviewed. Of these, 61.9% (N= 477) were female and 38.1% (N= 293) were male. In terms of employment status, 57.7% (n = 434) were employed and 42.3% (N= 318) were unemployed (disability status was not evaluated). Regarding marital status, 46.1% (N= 348) were married, 39.1% (N= 295) had never been married, and 14.8% (N= 127) were divorced, widowed, or in a cohabiting union. Among the family members, 66.6% (N= 513) were first-degree relatives, while 33.4% (N= 257) were second-degree relatives.

Psychopathology in family members

In our analysis of a sample consisting of 770 family members, we found that 65.2% (502 individuals) exhibited psychiatric pathology. The prevalence rates of various psychiatric disorders were as follows: depressive disorders in 31.9% of the sample (N=246), BD in 21.1% (N=163), anxiety disorders in 12.7% (N=98), abuse and/or alcohol dependence in 14.5% (N=109), substance abuse and/or dependence in 5.9% (N=46), eating disorders in 1.4% (N=11), and psychotic disorders in 3.5% (N=27). (see **Table 1**).

We also analyzed the differences in psychiatric diagnoses among the 502 family members with psychopathology, focusing on variations by sex and the prevalence of psychiatric disorders (see **Table 1**). Our findings indicated a higher prevalence among females for Depressive Disorder ($p = 0.010$) and Anxiety Disorders ($p = 0.026$). No significant differences were found between sexes for BD and Psychotic Disorders. In contrast, males showed a higher prevalence of Alcohol Abuse and/or Dependence ($p < 0.001$) and Substance Abuse and/or Dependence ($p < 0.001$) (see **Table 1**).

Table 1. Psychopathology in 1st and 2nd-degree relatives

Relatives with psychopathology (N=502)	1st-degree (N=359)		2nd-degree (N=143)		*p**
Anxiety(N=98)	**63**		**35**		**0.08**
Female	21	p= 0.66	5	p= .001	
Male	42		30		
Eating Disorders (N=11)	**9**		**2**		**0.73**
Female	9	p= 0.02	1	p= .02	
Male	0		1		
Alcohol abuse (N=109)	**79**		**30**		**0.90**
Female	18	p=<.001	11	p= .003	
Male	61		19		
Substance abuse (N= 46)	**30**		**16**		**0.31**
Female	7	p= <.001	3	p= <.001	
Male	23		13		
Psychotic Disorders (N= 27)	**14**		**13**		**0.02**
Female	8	p= 0.58	6	p= 0.23	
Male	6		7		
Depressive Disorders (N= 246)	**163**		**83**		**0.013**
Female	115	p= .016	55	p= 0.29	
Male	48		28		
Bipolar Disorders (N= 163)	**141**		**22**		**<.001**
Female	84	0.21	14	p= 1.0	
Male	57		8		

While studying the comorbidities of the relatives with psychiatric disorders (N=502), it was found that 28.1% (N=141) had two or more comorbid disorders. Specifically, 22.5% (N=113) had two diagnoses, 4.4% (N=22) had three diagnoses, 1% (N=5) had four diagnoses, and 0.2% (N=1) had five simultaneous diagnoses (bipolar, depressive and anxiety disorders, dependence-abuse of alcohol and drugs).

Psychopathology in first-degree versus second-degree family members

First-degree family members showed a higher prevalence of psychopathology, with 70% (359 out of 513) affected, compared to second-degree relatives, where the prevalence was 55.6% (143 out of 257). This difference was statistically significant (p=0.001). BD showed a higher prevalence among first-degree family members ($p < 0.001$). In contrast, second-degree family members had a higher prevalence of depressive disorder ($p = 0.013$) and psychotic disorder ($p = 0.027$) (see **Table 1** and **Table 3**). No significant differences were found for anxiety disorders, alcohol abuse and/or dependence, or substance abuse and/or dependence (see **Table 2**).

Table 2. Anxiety disorders in 1st and 2nd degree relatives

Anxiety Disorders			
	1st degree (%)	2nd degree (%)	*p**
General (n=98)	53 (54.08)	35 (35.71)	0.082
***Unique disorder** n=70 (71.4%)	44 (62.85)	26 (37.14)	0.085
GAD	2(4.5)	---	0.52
OCD	8(18.2)	3 (11.5)	0.52
Panic Attacks	4(9.1)	2 (7.7)	1.0
Specific phobias	22 (50)	18 (69.2)	0.13
SAD	8(18.2)	3 (11.5)	0.52
*Multiple disorders n=28 (28.6%)	19 (67.85)	9 (32.14)	0.51

Table 3. Psychotic disorders in 1st and 2nd degree relatives

Diagnostic	1st-degree relatives n=14 (%)	2nd-degree relatives n=13 (%)
Not specified psychosis	6(42.8)	8(61.5)
Schizoaffective disorder	3(21.4)	1(7.7)
Schizophrenia	5(35.8)	4(30.8)

Multivariate analysis

The relationship between psychopathology and certain characteristics of family groups was examined. Being a first-degree family member of a participant with BD was found to increase the probability of developing psychopathology by 1.99 times (Odds Ratio, 95% Confidence Interval), with a significance level of $p<.001$. However, no associations were identified between the development of psychopathology and factors such as gender, employment status, or marital status.

Discussion

In this population-based study involving a Mexican cohort with BD, we identified several significant findings. First-degree family members exhibited a higher prevalence of psychopathology when they were compared to second-degree family members, with BD showing a particularly elevated rate. Additionally, second-degree family members showed a greater prevalence of depressive and psychotic disorders. Our study also revealed that depressive and anxiety disorders were more prevalent among females, while alcohol and substance abuse and/or dependence were more common in males. Our findings, based on a Mexican sample, support previous research that highlighted an increased risk for BD among first-degree family members of BD individuals, and a high prevalence of different psychopathology.[13,17,24-26]

Our study found that the rates of BD among first-degree family members reached as high as 18%, a figure surpassing those reported in previous research. Nonetheless, it aligns with the observed increase in psychopathology, which can be as high as 10% among the offspring of

participants with BD.[12,14,17,25] Most published literature primarily focuses on the risk and prevalence of psychiatric disorders in first-degree relatives of BD participants, leaving a gap in knowledge regarding the prevalence of psychopathology in second-degree relatives. In our study, second-degree family members exhibited a higher prevalence of depressive and psychotic disorders compared to first-degree family members. It is interesting that in first-degree family members, MDD was reported as one of the most common disorders in our study; notably, this fact was reversed, with higher prevalence for MDD in second-degree (58%) compared to first-degree family members (45.4%).[27]

Research has consistently shown that gender significantly influences the presentation of psychopathology within families.[28] In line with this, our study shows that depressive and anxiety disorders were more prevalent among females, while alcohol and substance abuse and/or dependence were more common in males.[29,30] It is noteworthy that in bipolar individuals, women are more likely to experience anxiety disorders and more severe depressive episodes. Conversely, men are more prone to develop substance abuse disorders.[1] It has been suggested that sex-specific differences in brain structure and function could contribute to different psychopathological patterns observed in men and women with BD.[31] Interestingly, in children at familial high risk for BD compared with a control group, sex-specific morphometric differences were found,[32] possibly reflecting endophenotypic markers of risk linked to gender. However, genetic and nongenetic factors, as well as influence of culture, may contribute to the sex differences observed in our and other studies.[33]

The presence of certain comorbidities in family members of BP participants suggests that shared etiological factors, beyond just the bipolar disorder itself, contribute to the risk for these related conditions.

First-degree relatives of individuals with BD exhibit an elevated risk for a range of psychiatric and medical comorbidities relative to the general population, including anxiety disorders, personality disorders, substance-use disorders, type 2 diabetes, and ischemic heart disease. These familial associations are largely attributable to the heritability of BD, supporting the hypothesis that shared genetic and etiological mechanisms underlie the increased susceptibility to these conditions among family members.[34]

There is a scarcity of literature on comorbidity among relatives of individuals with BP in the Mexican population. When comparing prevalence rates with those reported in Hispanic/Latino populations living in the United States, it is important to consider that some studies suggest lower rates among recent immigrants similar to those reported in Mexico, compared to those who have resided in the U.S. for longer periods.[35] Other research has documented

persistently high rates of psychiatric comorbidities and related health conditions in Hispanic populations in the U.S., including depression, anxiety, and substance-use disorders, findings that are consistent with our study.[36]

Understanding the key components of psychopathology in relatives of individuals with BD is complex, as it is linked to genetic, psychological, familial, and contextual factors. For instance, children of parents with BD are nine times more likely to develop BD themselves and are also significantly more likely to experience other affective and anxiety disorders compared to children of nonaffected parents.[17] Moreover, living with someone who has BD can create significant psychological and emotional stress for family members, potentially triggering or worsening mental health issues among them. The unpredictable mood cycles associated of BD and the emotionally charged atmosphere it creates can lead to increased anxiety, depression, and other mental health disorders in those close to the affected individual with BD.[37,38] It has been recognized that living with family members with uncontrolled mental health conditions is an adverse childhood experience.[39] This could account for psychopathology found in our and other studies with first-degree family members.[40]

The primary goal of the present study was to examine whether certain psychiatric disorders tend to cluster within family members of BD participants. Our findings indicate that being a first-degree family member carries an odds ratio of 1.99 to exhibit psychopathology. Our finding, with a sample of Mexican participants, reinforces evidence from previous family studies that highlighted the increased risk of psychopathology in first-degree family members of individuals with BD.[41,42] Understanding the risk of psychopathology in family members of participants with psychiatric disorders is crucial not only for early identification but also for potential intervention strategies for at-risk populations.

Limitations

While our study included many participants, there are some limitations in the design. First, the sample in this study was highly selective, as families were chosen based on having multiple relatives affected by BD. Additionally, because we did not conduct a follow-up assessment, it remains uncertain whether more participants in our sample would develop psychopathology over time, including BD. Therefore, it may not be appropriate to generalize our findings to less-selective samples. While an effort was made to obtain data from all family members with detailed genograms, there were some missing data that could influence the final results of the study. While the best estimation method was realized to maximize diagnostic validity in our sample, several limitations are found including subjectivity, inter-rater variability, and lack of true validation due to no actual gold standard to confirm BD. Finally, we did not study past trauma in participants.

Conclusion

Our study with the Mexican population and its results are closely linked to previous research on the prevalence of psychopathology among family members of individuals with BD. These studies show similar findings to ours concerning specific pathologies and the relative risk analysis in these at-risk populations.

Our study, conducted within a Mexican cohort, aims to deepen the understanding of the pathology and its varied presentations in different cultural settings.

Our findings regarding the differences in psychopathology prevalence requires replication in future studies involving the Mexican and Hispanic populations, incorporating controlled analyses of potential associated risk factors. Added to the genetic and neurobiological mechanisms, these studies need to incorporate the impact of sociocultural and environmental factors to understand their contribution to BD. The contribution of future studies of BD presents a complex challenge whose results could impact the treatment and understanding of BD individuals and their families, for medical and behavioral health services.

Published: November 03, 2025 EDT.

REFERENCES

1. Oliva V, Fico G, De Prisco M, Gonda X, Rosa AR, Vieta E. Bipolar disorders: an update on critical aspects. *Lancet Reg Health Eur*. 2024;48:101135. doi:10.1016/j.lanepe.2024.101135

2. Anyayo L, Ashaba S, Kaggwa MM, Maling S, Nakimuli-Mpungu E. Health-related quality of life among patients with bipolar disorder in rural southwestern Uganda: a hospital based cross sectional study. *Health and Quality of Life Outcomes*. 2021;19(1):84. doi:10.1186/s12955-021-01729-5

3. Dragasek J, Minar M, Valkovic P, Pallayova M. Factors associated with psychiatric and physical comorbidities in bipolar disorder: a nationwide multicenter cross-sectional observational study. *Front Psychiatry*. 2023;14. doi:10.3389/fpsyt.2023.1208551

4. Ghanbari Jolfaei A, Ataei S, Ghayoomi R, Shabani A. High Frequency of Bipolar Disorder Comorbidity in Medical Inpatients. *Iran J Psychiatry*. 2019;14(1):60-66. doi:10.18502/ijps.v14i1.424

5. Wang Z, Li T, Li S, et al. Correction to: The prevalence and clinical correlates of medical disorders comorbidities in patients with bipolar disorder. *BMC Psychiatry*. 2022;22:232. doi:10.1186/s12888-022-03871-w

6. Dell'Osso B, Cafaro R, Ketter TA. Has Bipolar Disorder become a predominantly female gender related condition? Analysis of recently published large sample studies. *Int J Bipolar Disord*. 2021;9(1):3. doi:10.1186/s40345-020-00207-z

7. Perich T, Lau P, Hadzi-Pavlovic D, et al. What clinical features precede the onset of bipolar disorder? *Journal of Psychiatric Research*. 2015;62:71-77. doi:10.1016/j.jpsychires.2015.01.017

8. Preisig M, Strippoli MPF, Castelao E, et al. The specificity of the familial aggregation of early-onset bipolar disorder : A controlled 10-year follow-up study of offspring of parents with mood disorders. *Journal of Affective Disorders*. 2016;190:26-33. doi:10.1016/j.jad.2015.10.005

9. Yakovleva YV, Викторовна ЯЯ, Kasyanov ED, Дмитриевич КЕ, Mazo GE, Элевна МГ. Prevalence of eating disorders in patients with bipolar disorder: a scoping review of the literature. *Consortium Psychiatricum*. 2023;4(2):91-106. doi:10.17816/CP6338

10. Helmink FGL, Mesman E, Hillegers MHJ. Beyond the Window of Risk? The Dutch Bipolar Offspring Study: 22-Year Follow-Up. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2025;64(5):593-601. doi:10.1016/j.jaac.2024.05.024

11. Vandeleur C, Rothen S, Gholam-Rezaee M, et al. Mental disorders in offspring of parents with bipolar and major depressive disorders. *Bipolar Disord*. 2012;14(6):641-653. doi:10.1111/j.1399-5618.2012.01048.x

12. Mesman E, Nolen WA, Reichart CG, Wals M, Hillegers MHJ. The Dutch Bipolar Offspring Study: 12-Year Follow-Up. *American Journal of Psychiatry*. 2013;170(5):542-549. doi:10.1176/appi.ajp.2012.12030401

13. Nurnberger JI Jr, McInnis M, Reich W, et al. A high-risk study of bipolar disorder. Childhood clinical phenotypes as precursors of major mood disorders. *Arch Gen Psychiatry*. 2011;68(10):1012-1020. doi:10.1001/archgenpsychiatry.2011.126

14. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. *Schizophr Bull*. 2014;40(1):28-38. doi:10.1093/schbul/sbt114

15. Parry P, Allison S, Bastiampillai T. "Pediatric Bipolar Disorder" rates are still lower than claimed: a re-examination of eight epidemiological surveys used by an updated meta-analysis. *Int J Bipolar Disord*. 2021;9(1):21. doi:10.1186/s40345-021-00225-5

16. Wilde A, Chan HN, Rahman B, et al. A meta-analysis of the risk of major affective disorder in relatives of individuals affected by major depressive disorder or bipolar disorder. *Journal of Affective Disorders*. 2014;158:37-47. doi:10.1016/j.jad.2014.01.014

17. Lau P, Hawes DJ, Hunt C, Frankland A, Roberts G, Mitchell PB. Prevalence of psychopathology in bipolar high-risk offspring and siblings: a meta-analysis. *European Child & Adolescent Psychiatry*. 2017;27(7):823-837. doi:10.1007/s00787-017-1050-7

18. O'Connell KS, Adolfsson R, Andlauer TFM, et al. New Genomics Discoveries Across the Bipolar Disorder Spectrum Implicate Neurobiological and Developmental Pathways. *Biological Psychiatry*. 2025;98(4):302-310. doi:10.1016/j.biopsych.2025.05.020

19. Gonzalez S, Camarillo C, Rodriguez M, et al. A genome-wide linkage scan of bipolar disorder in Latino families identifies susceptibility loci at 8q24 and 14q32. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 2014;165(6):479-491. doi:10.1002/ajmg.b.32251

20. Nurnberger JI Jr, Blehar MC, Kaufmann CA, et al. Diagnostic Interview for Genetic Studies: Rationale, Unique Features, and Training. *Archives of General Psychiatry*. 1994;51(11):849-859. doi:10.1001/archpsyc.1994.03950110009002

21. Maxwell M. Family interview for genetic studies. Clinical Neurogenetic Branch, Intramural Research Program, NIMH. 1992. https://www.nimhgenetics.org/

22. Leckman JF, Sholomskas D, Thompson D, Belanger A, Weissman MM. Best Estimate of Lifetime Psychiatric Diagnosis: A Methodological Study. *Archives of General Psychiatry*. 1982;39(8):879-883. doi:10.1001/archpsyc.1982.04290080001001

23. Bryman A, Cramer D. *Quantitative Data Analysis with IBM SPSS 17, 18 & 19: A Guide for Social Scientists*. Routledge; 2012. doi:10.4324/9780203180990

24. Oquendo MA, Ellis SP, Chesin MS, et al. Familial transmission of parental mood disorders: unipolar and bipolar disorders in offspring. *Bipolar Disorders*. 2013;15(7):764-773. doi:10.1111/bdi.12107

25. Rhee SJ, Abrahamsson L, Sundquist J, Sundquist K, Kendler KS. The risks for major psychiatric disorders in the siblings of probands with major depressive disorder. *Mol Psychiatry*. 2025;30(1):69-75. doi:10.1038/s41380-024-02650-1

26. Wozniak J, Faraone SV, Martelon M, McKillop HN, Biederman J. Further evidence for robust familiality of pediatric bipolar I disorder: results from a very large controlled family study of pediatric bipolar I disorder and a meta-analysis. *J Clin Psychiatry*. 2012;73(10):1328-1334. doi:10.4088/JCP.12m07770

27. Mitchell PB, Frankland A, Hadzi-Pavlovic D, et al. Comparison of depressive episodes in bipolar disorder and in major depressive disorder within bipolar disorder pedigrees. *The British Journal of Psychiatry*. 2011;199(4):303-309. doi:10.1192/bjp.bp.110.088823

28. Piccirilli L, Capuzzi E, Legnani F, et al. Gender Differences in Clinical and Biochemical Variables of Patients Affected by Bipolar Disorder. *Brain Sciences*. 2025;15(2):214. doi:10.3390/brainsci15020214

29. Pavlidi P, Kokras N, Dalla C. Sex Differences in Depression and Anxiety. *Current Topics in Behavioral Neurosciences*. Published online 2022:103-132. doi:10.1007/7854_2022_375

30. Su Z, Yang X, Hou J, Liu S, Wang Y, Chen Z. Gender differences in the co-occurrence of anxiety and depressive symptoms among early adolescents: A network approach. *Journal of Psychiatric Research*. 2024;179:300-305. doi:10.1016/j.jpsychires.2024.09.024

31. Lee MY, Zhu JD, Tsai HJ, Tsai SJ, Yang AC. Investigating sex-related differences in brain structure and function in bipolar I disorder using multimodal MRI. *BMC Psychiatry*. 2024;24(1):855. doi:10.1186/s12888-024-06228-7

32. Madsen KS, Baaré WFC, Hernandez-Torres E, et al. Sex-specific cortical brain differences in children at familial high risk for schizophrenia or bipolar disorder. Published online April 25, 2025. doi:10.1101/2025.04.24.25326262

33. Fullerton JM, Tesfaye M. Global Diversity in Bipolar Disorder: The Role of Cultural and Social Differences With a View to Genomics. *Biological Psychiatry*. 2025;98(4):354-364. doi:10.1016/j.biopsych.2025.02.008

34. Kesebir S, Koc MI, Yosmaoglu A. Bipolar Spectrum Disorder May Be Associated With Family History of Diseases. *J Clin Med Res*. 2020;12(4):251-254. doi:10.14740/jocmr4143

35. Alegría M, Mulvaney-Day N, Torres M, Polo A, Cao Z, Canino G. Prevalence of Psychiatric Disorders Across Latino Subgroups in the United States. *Am J Public Health*. 2007;97(1):68-75. doi:10.2105/AJPH.2006.087205

36. Gattamorta KA, Mena MP, Ainsley JB, Santisteban DA. The Comorbidity of Psychiatric and Substance Use Disorders Among Hispanic Adolescents. *Journal of Dual Diagnosis*. 2017;13(4):254-263. doi:10.1080/15504263.2017.1343965

37. Miklowitz DJ. Family-Focused Treatment for Adolescents and Young Adults With Bipolar Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2018;57(10):S339. doi:10.1016/j.jaac.2018.07.861

38. Phillips R, Durkin M, Engward H, Cable G, Iancu M. The impact of caring for family members with mental illnesses on the caregiver: a scoping review. *Health Promotion International*. 2023;38(3):daac049. doi:10.1093/heapro/daac049

39. Park YM, Shekhtman T, Kelsoe JR. Effect of the Type and Number of Adverse Childhood Experiences and the Timing of Adverse Experiences on Clinical Outcomes in Individuals with Bipolar Disorder. *Brain Sciences*. 2020;10(5):254. doi:10.3390/brainsci10050254

40. Tzouvara V, Kupdere P, Wilson K, Matthews L, Simpson A, Foye U. Adverse childhood experiences, mental health, and social functioning: A scoping review of the literature. *Child Abuse & Neglect*. 2023;139:106092. doi:10.1016/j.chiabu.2023.106092

41. 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 Psychiatry*. 2020;77(8):814-822. doi:10.1001/jamapsychiatry.2020.0223

42. O'Connell KS, Coombes BJ. Genetic contributions to bipolar disorder: current status and future directions. *Psychological Medicine*. 2021;51(13):2156-2167. doi:10.1017/S0033291721001252