Dialogues in Clinical Neuroscience & Mental Health

e-ISSN: 2585-2795 • p-ISSN: 2654-1432
DOI: 10.26386/obrela.v8i3.307
p. 73-84

Multilevel Predictors of Bipolar Disorder Symptomatology: A Cross-sectional Study of Neurodevelopmental and Psychosocial Risk Factors in a Greek Clinical Population

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Abstract

Background: Bipolar disorder (BD) is a complex and often misdiagnosed psychiatric condition associated with high morbidity, suicidality, and functional impairment. Early identification of risk factors is critical for improving clinical outcomes, particularly in settings with limited access to mental health services. *Aim:* This study aimed to identify psychosocial, neurodevelopmental, and behavioral predictors of BD symptomatology using a multidimensional assessment model. *Methods:* A cross-sectional study was conducted with 590 participants recruited from the outpatient psychiatric clinics of the 414 SNEN Military Hospital in Athens, Greece. Participants completed the CISQ-90 psychometric inventory and a structured questionnaire covering psychosocial, demographic, and behavioral variables. Statistical analyses included Spearman correlations, multiple regression models, and structural equation modeling (SEM). *Results:* Significant predictors of BD included maternal history of mental illness, comorbid ADHD, perinatal complications, male gender, and left-handedness. Unexpectedly, parental divorce was negatively associated with BD, potentially reflecting protective effects in high-conflict households. Social support emerged as the strongest protective factor, with higher levels significantly predicting lower BD symptomatology. Financial stressors (e.g., low income, loan default) contributed modestly. Substance use and suicidality showed the highest predictive value, with BD mediating the relationship between substance use and suicidal ideation. *Conclusions:* The findings underscore the importance of adopting a multilevel diagnostic approach to BD that incorporates familial, neurodevelopmental, psychosocial, and behavioral factors. Enhanced screening and early intervention strategies targeting at-risk populations, particularly those with neurodevelopmental vulnerabilities and reduced social support, may help reduce diagnostic delays and improve treatment outcomes.

Keywords

Bipolar Disorder, Neurodevelopmental risk, Social support, Parental divorce, Alcohol abuse, Drag use, Suicidality

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1. Introduction

Bipolar disorder (BD) is a chronic, episodic mood disorder characterized by alternating periods of mania or hypomania and depression. It ranks among the leading causes of disability worldwide, significantly impairing psychosocial functioning and quality of life (1). Despite considerable advances in the understanding of its clinical manifestations, BD remains frequently underdiagnosed or misdiagnosed, resulting in delays in appropriate treatment and increased psychological and functional morbidity (2).

The diagnostic complexity of BD stems from its heterogeneous presentation and symptom overlap with other psychiatric conditions, particularly major depressive disorder (MDD). Individuals often seek clinical help during depressive phases, which tend to be more frequent and persistent than manic episodes. This leads to frequent misclassification of BD as unipolar depression (3,4). Such diagnostic errors are particularly prevalent in bipolar II disorder, where hypomanic episodes may be subtle, underreported, or perceived as normative personality traits (5).

The consequences of misdiagnosis are clinically significant. Inappropriate treatment, such as prescribing antidepressants without mood stabilizers, can exacerbate symptoms by inducing manic episodes, triggering rapid cycling, or fostering treatment resistance (6). Additionally, delayed or incorrect diagnosis is associated with heightened risk for suicidality, substance abuse, and deteriorated psychosocial outcomes (7). Thus, accurate and early diagnosis is critical for mitigating long-term complications.

Currently, BD diagnosis relies heavily on clinical interviews and patient self-reports—methods that are susceptible to recall bias and often fail to capture the episodic and cyclical nature of the disorder. The absence of objective biomarkers or standardized screening instruments contributes further to diagnostic uncertainty (2). Comorbid conditions, including metabolic disorders or ADHD, may further obscure the clinical picture and influence treatment planning (8).

Given these limitations, there is an urgent need to identify robust prognostic and predictive factors that may inform earlier and more accurate identification of BD. These factors span multiple domains—including genetic vulnerability, neurodevelopmental indicators, adverse early life experiences, and psychosocial stressors—and have the potential to enhance clinical risk stratification.

Incorporating such predictors into standardized clinical assessment protocols could improve diagnostic precision, facilitate earlier intervention, and enable more effective treatment personalization. Early detection is consistently associated with reduced relapse rates, improved functional outcomes, and better overall prognosis (9). Furthermore, personalized care models grounded in individual risk profiles are aligned with the evolving paradigm of precision psychiatry.

Taken together, these insights underscore the need for a comprehensive, multidimensional approach to the diagnosis and management of BD. Advancing empirical research in this area may significantly contribute to the refinement of clinical strategies and the improvement of outcomes for individuals living with bipolar disorder.

1.1 Genetic Heritability: Associations with Family History

A positive family history of psychiatric disorders—particularly bipolar disorder (BD)—is one of the most robust and consistently observed risk factors for developing the condition. Parental psychopathology (10) and having first- or second-degree relatives with BD significantly elevate individual risk, with some studies indicating a tenfold increase compared to the general population (11).

Twin studies provide further support for the genetic basis of BD, reporting markedly higher concordance rates in monozygotic twins compared to dizygotic twins (12–15). These findings suggest that heritable genetic influences account for a substantial proportion of vulnerability, beyond what can be attributed to shared environmental factors (16). The lifetime risk for BD among individuals with a close affected relative ranges from 5% to 10%, in contrast to approximately 1% in the general population (15).

Evidence suggests that both maternal and paternal transmission contribute equally to genetic risk. Having a parent or sibling with a mental illness has been associated with an approximately 13.6% increased likelihood of developing bipolar disorder (BD) (17). Overall, the accumulated evidence supports a polygenic, multifactorial model for BD, wherein multiple genetic loci interact with environmental variables to influence disease onset and expression.

1.2 Neurophysiological Factors

A growing body of research suggests that neurophysiological variables—particularly those rooted in early brain development—may be critical in the etiology of BD. Among these, perinatal complications, left-handedness, and comorbid attention-deficit/hyperactivity disorder (ADHD) have garnered significant attention.

Perinatal complications, such as preterm birth (18), perinatal hypoxia (19), low birth weight, and reduced head circumference (20), have been linked to an increased likelihood of developing BD later in life. These adverse events may disrupt normative neural development, potentially resulting in long-lasting structural and functional brain alterations that predispose individuals to mood dysregulation. Additionally, prenatal stress and infections have been shown to impact fetal brain development adversely, further reinforcing the role of early-life biological insults in BD pathogenesis (21). Nevertheless, other researchers have not found a direct link between obstetric complications and BD, indicating the need for more nuanced interpretation (22,23).

Handedness, particularly non-right-handedness, has also been investigated as a neurodevelopmental marker in BD. Motor lateralization in patients with bipolar disorder (BD) has been investigated, with findings suggesting that atypical cerebral lateralization may represent a trait feature (24). Additionally, an increased prevalence of left-handedness among individuals with BD has been reported (25,26). However, the robustness of this association remains debated, with some attributing the link to chance findings or sample heterogeneity (27).

ADHD and BD frequently co-occur, with emerging literature pointing to substantial overlap in their clinical features and underlying neurobiology (28–30). Neuroimaging studies have identified shared dysfunctions in regions implicated in emotion regulation and executive control—particularly the prefrontal cortex—suggesting that these disorders may arise from common neurodevelopmental trajectories (28).

Gender differences also appear to play a role in the clinical presentation and course of BD. Women are more often diagnosed with bipolar II disorder, characterized by depressive episodes and hypomania, whereas men exhibit higher rates of substance use disorders, conduct disorder, and pathological gambling (31,32). Furthermore, BD tends to manifest later in women, particularly during reproductive years, and is often associated with rapid cycling and comorbidities such as anxiety disorders, migraines, and thyroid dysfunction (33,34). These differences underscore the importance of considering gender as a moderating factor in both diagnosis and treatment planning.

1.3 Early Life Experiences

Adverse experiences during early developmental stages have been increasingly recognized as key contributors to the onset and trajectory of bipolar disorder (BD) (35). Childhood trauma—including emotional, physical, and sexual abuse, as well as neglect—has been consistently linked to a heightened risk of BD (36). Emotional and sexual abuse, in particular, appear to exert strong associations with BD onset (37). These adverse events may impair affect regulation, impulse control, and cognitive functioning, increasing sensitivity to stress and reducing resilience to psychosocial challenges later in life (38). Moreover, such early trauma has been associated with earlier age of onset, rapid cycling, and higher rates of suicide attempts among individuals with BD (39).

Another potential developmental risk factor is frequent relocation during childhood and adolescence. Although more robustly associated with schizophrenia, residential mobility has also been implicated in the pathogenesis of BD, particularly when it co-occurs with familial psychiatric history (40). The disruption of social ties, loss of environmental stability, and stress of constant adaptation may contribute to emotional dysregulation. However, this association remains under debate, as other studies have not confirmed a direct relationship (41,42).

Parental divorce during formative years has also been identified as a potential contributor to various mental health outcomes, including mood disorders (43) and specifically BD (44). Children of divorced parents may be at higher risk for emotional distress, behavioral problems, and difficulties with interpersonal relationships (45). While divorce does not uniformly lead to psychiatric conditions, it can act as a critical psychosocial stressor—especially when compounded by other risk factors such as childhood trauma or familial mental illness (46).

1.4 Socioeconomic Factors

In addition to early developmental influences, social determinants have been shown to play a significant role in the manifestation and progression of bipolar disorder (BD). Socioeconomic status, occupational stability, interpersonal relationships, and access to resources are often intricately linked with the course of BD.

Research has demonstrated that individuals with BD are disproportionately affected by social disadvantage. Newly diagnosed bipolar disorder (BD) patients have been found to be significantly less likely to have completed higher education, maintain employment, earn high incomes, or live in stable partnerships compared to non-clinical control groups (47). These social disparities not only reflect the disruptive impact of mood symptoms on daily functioning but may also serve as precipitating or perpetuating factors.

Economic instability is both a cause and a consequence of bipolar symptomatology. Manic episodes often involve impulsivity, including excessive spending or risky financial behavior, leading to financial crises or loan defaults. Conversely, depressive episodes may impair occupational performance and diminish earning capacity, contributing to a feedback loop of financial stress and emotional distress (48). Inadequate treatment adherence further exacerbates this cycle (49), while fear of economic collapse can increase feelings of hopelessness—an established precursor of depressive episodes (50).

Furthermore, individuals with BD frequently struggle to maintain consistent employment due to affective instability, cognitive deficits, and social functioning challenges. These limitations often result in underemployment or unemployment and hinder professional advancement. Bipolar disorder (BD) has been shown to significantly impair work performance and occupational achievement, with employment rates among affected individuals ranging from 40% to 75% (51). The inability to attain vocational goals may subsequently contribute to diminished self-esteem and serve as a psychosocial trigger for further mood episodes (52). Nonetheless, the directionality of these associations remains debated, with socioeconomic disadvantage potentially both a cause and consequence of BD.

1.5 Behavioral factors

Among the various comorbidities associated with BD, alcohol use disorder (AUD) stands out due to its high prevalence and significant influence on the clinical course and prognosis of the illness. The co-occurrence of BD and AUD not only complicates treatment strategies but also substantially elevates the risk of suicidal behaviors (53). A nuanced understanding of this triadic relationship—BD, alcohol use, and suicidality—is essential for developing targeted prevention and intervention strategies.

Recent epidemiological data confirm the high prevalence of AUD among individuals diagnosed with BD. A meta-analysis synthesizing data from 20 studies conducted across 12 countries estimated that approximately 29.12% of individuals with bipolar disorder (BD) meet the criteria for alcohol use disorder (AUD), with 15.87% meeting criteria for alcohol dependence and 18.74% for alcohol abuse (54). These findings highlight the need to routinely screen for alcohol misuse in clinical populations with BD.

The presence of AUD in individuals with BD is associated with a more severe and treatment-resistant course of illness. Alcohol

misuse following the first manic or depressive episode has been shown to intensify symptomatology and increase the frequency of relapses (55,56). Gender differences may further modulate these effects, with men exhibiting greater vulnerability to alcohol-related exacerbation of BD symptoms (55). Furthermore, alcohol use has been found to interfere with the efficacy of pharmacological treatments, reduce treatment adherence, and impair long-term prognosis (55,56). The bidirectional nature of the BD–AUD relationship suggests a reciprocal amplification, whereby each condition intensifies the clinical burden of the other.

Suicidal behavior remains a critical concern in the management of BD. The addition of AUD to the diagnostic profile further amplifies suicide risk. Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicate that individuals with comorbid bipolar disorder (BD) and alcohol use disorder (AUD) exhibit significantly higher rates of suicide attempts compared to those with BD alone (53). Consistent with these findings, AUD has been identified as an independent and significant predictor of suicidal behavior among individuals with BD (57).

Several underlying mechanisms may account for the increased suicidality observed in individuals with comorbid BD and AUD. Alcohol can exacerbate depressive symptomatology, intensify emotional dysregulation, and act as a maladaptive coping strategy in the context of mood instability (58–60). From a neurobiological perspective, both BD and AUD are linked to alterations in neurotransmitter function, including dysregulation of serotonergic, dopaminergic, and glutamatergic pathways. These alterations are often accompanied by chronic low-grade inflammation, elevated levels of proinflammatory cytokines, and hypercortisolemia (61,62), all of which have been associated with heightened risk of suicidal ideation and behavior.

The interaction between BD and AUD constitutes a high-risk phenotype for suicidality, as underscored in longitudinal studies (63). Therefore, it is imperative that both alcohol use patterns and suicidality risk are routinely assessed in clinical evaluations of BD. Addressing these factors is essential not only for diagnostic clarification but also for effective risk management and therapeutic planning.

Among individuals with bipolar disorder (BD), comorbid substance use disorder—particularly involving illicit drugs—has been linked to worse clinical outcomes (64). For instance, BD patients with any lifetime substance use disorder had a suicide attempt rate of 39.5%, compared to 23.8% among those without, representing more than twice the risk (odds ratio = 2.09) (65). These findings suggest that drug use should be considered a core component of the BD clinical phenotype and not merely a comorbidity.

Longitudinal and cohort studies further underscore the impact of both alcohol and illicit drug use on suicidal ideation in BD. A recent longitudinal analysis from the Prechter Program demonstrated that increases in cannabis use intensity and broader alcohol- or substance-related impairment were predictive of heightened suicidal ideation over the following six months, even among individuals without a formal substance use disorder diagnosis (66). Moreover, systemic reviews have consistently reported that up to two-thirds of studies find general substance use to be a risk factor for developing or worsening bipolar symptoms (67).

Ultimately, the intersection of BD with neurobiological vulnerabilities, early life adversity, social instability, substance use, and suicidal ideation illustrates the complex and multifaceted nature of the disorder. A multi-level, integrative approach—encompassing biological, psychological, and social dimensions—is essential for both early detection and the formulation of comprehensive treatment interventions. The present study aimed to examine the predictive contribution of neurodevelopmental and psychosocial factors to BD symptomatology through a multidimensional analytic framework, with a focus on mediation effects.

2. Methodology

This study aimed to investigate multiple factors that may contribute to the prediction of bipolar disorder (BD). Specifically, it examined whether neurophysiological, developmental, socioeconomic and behavioral factors are associated with increased BD symptomatology and may serve as predictors.

2.1 Sample

The study included a convenience sample of 590 voluntary participants affiliated with the Hellenic Armed Forces. Participants were recruited from the outpatient and psychiatric clinics of the 414th Military Hospital in Athens, Greece. The majority were male (N = 552), with smaller proportions of female participants (N = 33) and individuals who did not report gender (N = 5). Ages ranged from 18 to 45 years (M = 26.32, SD = 4.90).

Most participants were single (N = 528), while 41 were married, 6 divorced, 1 widowed, and 14 did not report marital status. Regarding income, 345 participants reported a monthly income between 0–500€, 118 between 501–1000€, 36 between 1001–2000€, and 9 over 2001€.

Educational attainment varied: 40 had completed lower secondary education, 266 were high school graduates, 215 held a university degree, and 49 had obtained postgraduate qualifications. In terms of professional status, 18 were commissioned officers, 15 non-commissioned officers, 69 contracted NCOs, 215 enlisted personnel, and 221 were relatives of military personnel utilizing hospital services. Among active-duty personnel, the average length of military service was 8.86 years (SD = 6.75).

As for psychiatric history, 6 participants had a prior diagnosis of BD, 80 had depression, 33 were diagnosed with psychotic-spectrum disorders, 5 had experienced a psychotic episode, 21 had a personality disorder, 150 had an anxiety disorder, 30 an adjustment disorder, and 11 had a substance use disorder. An additional 110 had an unspecified diagnosis, while 143 had no previous psychiatric diagnosis. Of the total sample, 217 participants were currently receiving psychotropic medication.

2.2 Measurement

Data were collected using a two-part instrument. The first part captured demographic and psychosocial variables, including age,

gender, body mass index (BMI), occupational and financial status, perceived social support, exposure to traumatic life events, personal medical history, substance use, and family psychiatric history.

The second part utilized the Critical Indices Scanning Questionnaire–1 (68), a validated self-report measure designed to assess multidimensional psychopathology. The CISQ-1 consists of 14 subscales: generalized anxiety disorder/panic attacks (α = .94), somatic complaints (α = .70), anxiety/tension (α = .70), sleep disturbance (α = .68), compulsions/obsessions/ideolacies (α = .83), specific phobias (α = .83), social phobia (α = .79), depression (α = .91), paranoid ideation (α = .72), psychotic symptoms (α = .78), hypomanic symptoms (α = .74), suicidality (α = .83), dramatization (α = .79), and defensiveness (α = .68). Items are scored on a three-point Likert scale (Yes, Maybe, No).

Given the elevated risk of misdiagnosis in BD, formal clinical diagnoses were not used as the primary outcome measure. Instead, the study relied on symptom indicators derived from the CISQ-1. Specifically, the depression and hypomania subscales were combined to create a composite BD symptom index (α = .89), which served as the main dependent variable in statistical analyses.

2.3 Inclusion Criteria

Eligible participants were adults (aged 18 and older) who utilized the services of the outpatient psychiatric clinics of the 414th Military Hospital and voluntarily consented to participate.

2.4 Exclusion Criteria

Questionnaires were excluded if they were incomplete, internally inconsistent, or clearly falsified. Participants who withdrew consent during data collection were also excluded from analysis.

2.5 Procedure

The 414 SNEN Military Hospital, located near Athens, serves both active-duty personnel—including enlisted soldiers, contracted and permanent staff—and their family members. Individuals attending the outpatient psychiatric clinics were informed about the study and invited to participate voluntarily.

Those who expressed interest were escorted to a private consultation room by a military nurse or physician and a trained soldier-psychologist. Participants received detailed oral information regarding the study's objectives, the anonymous nature of their participation, their right to withdraw at any point without penalty, and the intended academic use and possible dissemination of the research findings.

Verbal informed consent was obtained from all participants. This consent was formally witnessed and documented. Participants were informed that no personally identifiable information would be collected and that all data would remain strictly anonymous and confidential. The consent process adhered to the ethical standards set forth in the Declaration of Helsinki (1975), as revised in 2013.

After providing consent, participants completed the questionnaire in the presence of the healthcare staff, who remained available to provide clarification or assistance if needed. Data collection continued for a period of fourteen months. All data were subsequently anonymized and analyzed using SPSS version 19 and AMOS for structural equation modeling.

3. Results

To explore the factors associated with bipolar disorder (BD), a series of bivariate correlation analyses were conducted using Spearman's rho coefficient. This non-parametric method was chosen due to the presence of categorical and non-normally distributed variables within the dataset. Statistically significant correlations between BD and psychosocial, neurodevelopmental, and behavioral variables are summarized in Table 1.

Table 1. Spearman's rho correlations between Bipolar Disorder Index and predictor variables across multiple domains (N = 590)

Domain	Variable	Spearman's ρ	p-value
Genetic Heritability	Mother with mental illness (yes - no)	.350	p < .001
	Sibling with mental illness (yes - no)	.266	p < .001
	Father with mental illness (yes - no)	.228	p < .001
Neurophysiology factors	Perinatal problems (yes - no)	.275	p < .001
	ADHD (yes - no)	.262	p < .001
	Gender (male-female)	.222	p < .001
	Dyslexia (yes - no)	.172	p < .001
	Left-handedness (yes - no)	.109	p < .05
Early life Events	Social supportive framework (high - low)	-.625	p < .001
	Parental divorce (yes - no)	-.241	p < .01
	Changes of parental home (yes - no)	.216	p < .001
Economic	Income (low - high)	.277	p < .001
	Loan (yes - no)	.142	p < .01
Others	Suicidality (high - low)	.786	p < .001
	Drag Use (high - low)	.499	p < .001
	Alcohol Abuse (high - low)	.346	p < .001

Note. Spearman's rho (ρ) correlations are used due to the ordinal or non-normally distributed nature of the variables. Positive values indicate direct associations with BD symptomatology; negative values indicate inverse relationships.

In order to better understand the predictive strength of each domain, a series of multiple regression models and structural equation models (SEM) were subsequently conducted. These analyses were structured thematically across five major domains: (a) genetic heritability, (b) neurophysiological indicators, (c) early life events, (d) socioeconomic stressors, and (e) behavioral correlates, including suicidality and substance use. Each domain is presented in detail in the following sections, highlighting both direct and indirect predictors of BD symptomatology.

3.1 Genetic Heritability

Bipolar disorder (BD) was found to be significantly associated with a family history of mental illness. Specifically, positive correlations were observed between BD indicators and the presence of mental illness in the mother (ρ = .350, $p < .001$), sibling (ρ = .266, $p < .001$), and father (ρ = .228, $p < .001$). These findings reflect a moderate positive relationship between familial psychopathology and the expression of bipolar symptomatology, aligning with existing literature that underscores the heritable nature of BD.

To further investigate the predictive value of familial mental health history, a multiple linear regression analysis using the forced entry method was conducted (Table 2). The model yielded a medium effect size ($R^2 = .10$, $R^2_a = .10$), $F(3, 350) = 13.437$, $p < .001$, suggesting that these variables accounted for approximately 10% of the variance in BD symptom scores. Among the predictors, maternal mental illness demonstrated the strongest association with BD (β = .197, $p < .001$), followed by sibling mental illness (β = .128, $p = .015$) and paternal mental illness (β = .122, $p = .025$).

Table 2. Linear Regression Analysis Predicting BD Symptoms from Familial Mental Illness

Predictor	B	SE	Sig.	β
Father with mental illness	.285	.127	.025	.122
Mother with mental illness	.440	.120	<.001	.197
Sibling with mental illness	.374	.154	.015	.128
Constant	.228	.356	.523	-

Note. Variables entered on Step 1: Father, Mother, and Sibling with diagnosed mental illness.

To assess the structural relationship between these hereditary factors and BD, a path model was tested that included maternal, paternal, and sibling mental illness as latent predictors. However, this model failed to achieve acceptable fit indices, indicating that the influence of genetic or familial history alone is insufficient to fully account for the onset or severity of BD. This suggests that additional factors—such as neurodevelopmental, psychosocial, or behavioral variables—may play an equally or more influential role in shaping BD symptomatology.

3.2 Neurophysiological indicators

Bipolar disorder (BD) was found to be positively associated with several neurophysiological variables. Specifically, significant correlations were observed with perinatal complications (ρ = .275), attention-deficit/hyperactivity disorder (ADHD) (ρ = .262), dyslexia (ρ = .172), left-handedness (ρ = .109), and male gender (ρ = .222), all statistically significant at $p < .05$ or better.

To further explore these associations, a multiple linear regression analysis was conducted (Table 3), incorporating all five neurophysiological variables as predictors. The model demonstrated a medium effect size ($R^2 = .23$, $R^2_a = .22$), $F(5, 296) = 17.555$, $p < .001$. Among the predictors, perinatal problems (β = .292, $p < .001$) and ADHD (β = .265, $p < .001$) emerged as the most robust contributors to BD symptoms. Male gender also showed a significant effect (β = .194, $p < .001$), followed by left-handedness (β = .125, $p = .015$). Dyslexia approached significance (β = .099, $p = .062$), suggesting a potential trend that warrants further investigation.

Table 3. Linear Regression Predicting BD Symptoms from Neurophysiological Variables

Predictor	B	SE	Sig.	β
Perinatal Problems	.435	.076	<.001	.292
ADHD	.610	.120	<.001	.265
Dyslexia	.170	.091	.062	.099
Left-handedness	.842	.345	.015	.125
Gender (Male)	.353	.094	<.001	.194
Constant	−1.965	.773	.012	—

Note. Variables entered at Step 1: Perinatal Problems, ADHD, Dyslexia, Left-handedness, and Gender.

To validate the underlying structure of these relationships, a structural equation model (SEM) was constructed and tested. The model demonstrated excellent fit to the data: $\chi^2(6) = 4.09$, $p = .66$; CFI = 1.00; TLI = 1.07; RMSEA = 0.00. As shown in Figure 1, significant direct paths were found from gender (β = .20), perinatal problems (β = .23), ADHD (β = .22), and left-handedness (β = .09) to BD. The model explained 14.7% of the variance in BD symptomatology.

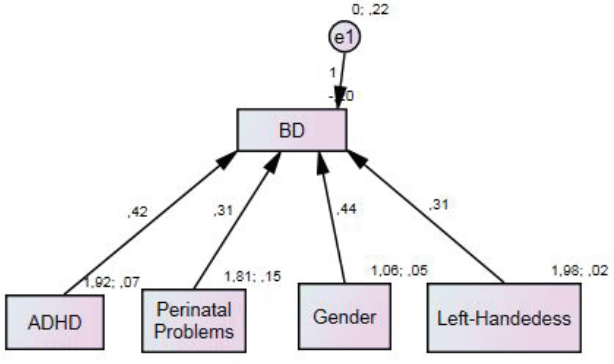

Figure 1: Structural equation model for neurophysiological predictors of BD

3.3 Early Life Events

Early environmental factors were also found to be significantly associated with bipolar disorder (BD). Specifically, BD symptomatology was positively correlated with frequent changes of the parental home during childhood and adolescence (ρ = .216, $p < .001$). In contrast, two variables were inversely associated with BD: parental divorce (ρ = –.241, $p < .01$) and high levels of perceived social support (ρ = –.625, $p < .001$).

To examine the predictive power of these variables, a multiple linear regression analysis was conducted (Table 4). The model yielded a medium effect size ($R^2 = .21$, $R^2_a = .19$), $F(3, 116) = 10.291$, $p < .001$. Among the predictors, both social support (β = –.403, $p < .001$) and parental divorce (β = –.198, $p = .018$) emerged as significant protective factors against BD symptoms. Interestingly, changes in the parental home did not significantly contribute to the model (β = –.004, $p = .960$), despite its positive bivariate correlation.

Table 4. Linear Regression Predicting BD Symptoms from Early Life Events

Predictor	B	SE	Sig.	β
Social Support Framework	–.371	.077	<.001	–.403
Parental Divorce	–.202	.084	.018	–.198
Changes of Parental Home	–.004	.081	.960	–.004
Constant	3.036	.276	<.001	-

To further investigate the interaction between early environmental and genetic influences, a structural equation model (SEM) was developed incorporating familial mental illness (genetic vulnerability), parental divorce, and perceived social support. The model exhibited excellent fit indices: $\chi^2(6) = 6.78$, $p = .342$; RMSEA = .015; CFI = .998.

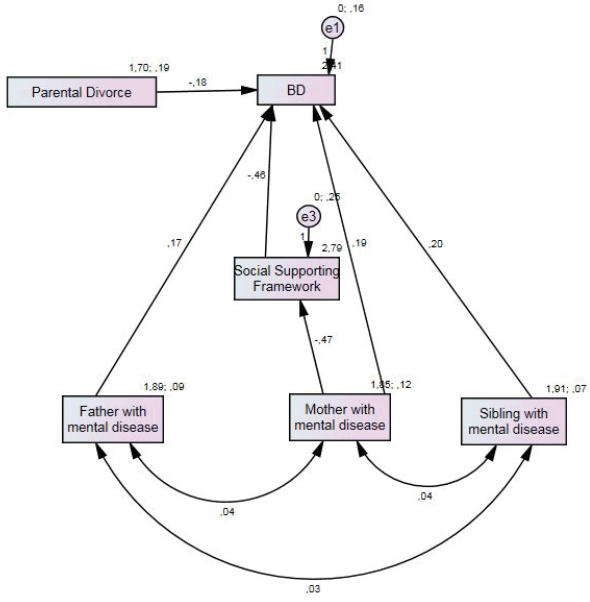

Figure 2: Structural equation model for BD: Early Life Events perspective

Notably, parental divorce demonstrated a small but significant negative direct effect on BD symptomatology (β = –.158, $p = .013$), suggesting a potentially protective role in specific psychosocial contexts (Figure 2). Furthermore, maternal mental illness was negatively associated with perceived social support (β = –.308, $p < .001$), which itself strongly predicted reduced BD symptom scores (β = –.473, $p < .001$). These findings underscore the mediating role of familial emotional climate in shaping psychiatric risk trajectories.

3.4 Socioeconomic stressors

Economic variables were also found to play a role in the expression of bipolar disorder (BD) symptomatology. Specifically, BD was significantly associated with lower monthly income (ρ = .277, $p < .001$) and reported difficulty in repaying a loan (ρ = .142, $p < .01$), indicating that financial instability may contribute to the burden of the disorder.

Table 5. Linear Regression Predicting BD Symptoms from Economic Stressors

Predictor	B	SE	Sig.	β
Monthly Income	.179	.037	<.001	.226
Inability to Repay Loan	.133	.043	.002	.146
Constant	1.648	.131	<.001	-

Note. Variables entered at Step 1: Monthly Income and Loan Repayment Status.

A multiple regression analysis was conducted to assess the predictive capacity of these two economic indicators (Table 5). The model produced a small effect size ($R^2 = .07$, $R^2_a = .07$), $F(2, 414) = 16.092$, $p < .001$. Both predictors were statistically significant: lower income was associated with increased BD symptoms (β = .226, $p < .001$), as was inability to repay a loan (β = .146, $p = .002$). Although modest in effect, these findings suggest that economic stressors are independently associated with bipolar symptomatology and may serve as contextual risk factors.

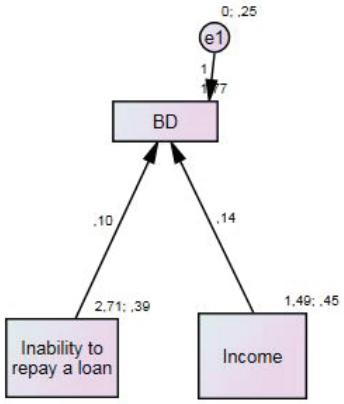

Figure 3: Structural equation model for BD: Economic Stressors perspective

To evaluate the structural influence of financial stressors on BD, a path model was constructed. The model demonstrated excellent fit: $\chi^2(1) = .032$, p = .859; CFI = 1.000; TLI = 1.248; RMSEA < .001. Both predictors contributed significantly: income (β = .19, p < .001) and loan status (β = .12, p = .005). Together, they explained 5.0% of the variance in BD symptomatology, as shown in Figure 3.

3.5 Behavioral risk factors

Substance use and suicidality emerged as particularly strong correlates of bipolar disorder (BD) in the current study. Specifically, BD symptom scores were strongly and positively correlated with suicidality (ρ = .786), drug use (ρ = .499), and alcohol abuse (ρ = .346), all statistically significant at $p < .001$. These findings suggest that behavioral risk factors play a central role in the manifestation and severity of BD.

To further explore these relationships, a multiple regression analysis was conducted (Table 6), including suicidality, drug use, and alcohol abuse as predictors of BD symptoms. The model yielded a large effect size ($R^2 = .60$, $R^2_a = .59$), $F(3, 477) = 30.269$, $p < .001$, indicating that these variables explained a substantial portion of variance in BD. Among them, suicidality emerged as the strongest predictor (β = .684, $p < .001$), followed by alcohol abuse (β = .104, $p = .004$) and drug use (β = .101, $p = .006$).

Table 6. Linear Regression Predicting BD Symptoms from Suicidality and Substance Use

Predictor	B	SE	Sig.	β
Suicidality	.571	.027	<.001	.684
Drug Use	.135	.049	.006	.101
Alcohol Abuse	.133	.045	.004	.104
Constant	.091	.121	.451	-

To examine the interrelations among these variables and their cumulative effect on BD and suicidality, a structural equation model (SEM) was constructed (Figure 4). The model demonstrated excellent fit: $\chi^2(1) = .331$, $p = .565$; CFI = 1.000; TLI = 1.005; RMSEA < .001. In this model, drug use significantly predicted both BD (β = .30, $p < .001$) and suicidality (β = .14, $p < .001$). Alcohol abuse also significantly predicted BD (β = .15, $p = .001$) and was strongly correlated with drug use (r = .553, $p < .001$). Finally, BD symptoms were a strong predictor of suicidality (β = .65, $p < .001$), partially mediating the relationship between substance use and suicidal risk.

Collectively, the model explained 16.1% of the variance in BD and 51.9% in suicidality, underscoring the critical role of behavioral and psychological comorbidities in understanding the clinical complexity of bipolar disorder.

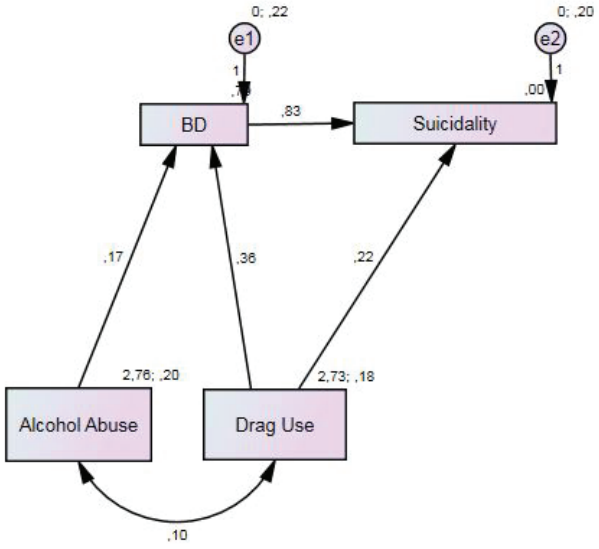

Figure 4: Structural equation model for BD: Suicidality, Drug Use, and Alcohol Abuse

Discussion

The present study offers a comprehensive and multifactorial account of the predictors associated with bipolar disorder (BD), emphasizing the dynamic interplay between genetic predisposition, neurodevelopmental traits, early environmental exposures, economic strain, and behavioral comorbidities. Collectively, these findings reinforce calls within contemporary psychiatry for multidimensional risk assessment models and individualized diagnostic formulations.

The significant association between BD and family history of mental illness -particularly maternal psychopathology- reaffirms existing literature emphasizing heritability as a major etiological factor in BD (16). The significant association between BD and family history of mental illness -particularly maternal psychopathology- reaffirms existing literature emphasizing heritability as a key risk factor (16). However, while bivariate analyses supported this link, regression and structural equation modeling (SEM) revealed that genetic variables alone did not yield an adequate predictive model of BD. Only when these familial mental health indicators were embedded within a broader model of early life experiences -particularly including perceived social support and parental dynamics- did they demonstrate significant indirect effects. This discrepancy highlights a crucial distinction: the predictive utility of familial psychopathology may derive less from pure genetic transmission and more from its interplay with relational and environmental conditions. The stronger effect of maternal mental illness, in particular, may reflect not only inherited vulnerability but also exposure to maternal affect regulation patterns, caregiving behaviors, and attachment-related disruptions during early development (69). The SEM findings suggest that familial mental illness acts as a contextual factor

shaping the emotional environment in which early psychosocial stressors unfold—rather than as a standalone determinant of BD. This underscores the importance of integrating family dynamics and relational stressors into conceptual frameworks of BD vulnerability.

Neurodevelopmental variables also emerged as key predictors. Perinatal complications, ADHD, and left-handedness were all significantly associated with BD symptomatology, supporting neurobiological theories that emphasize early central nervous system disruptions as foundational to later affective instability (70). ADHD's strong predictive value aligns with previous work identifying shared genetic and neurofunctional underpinnings between ADHD and BD (71). These associations were consistent across both regression and SEM models, lending further robustness to these findings.

Male gender also contributed significantly to BD expression, potentially reflecting sex-based differences in neuroendocrine reactivity, impulsivity, and behavioral regulation (32). However, this finding should be interpreted with caution. The BD index used in the present study was derived from the integration of depressive and hypomanic indicators, thereby more closely approximating the clinical profile of bipolar II rather than the full bipolar spectrum. Importantly, the sample was predominantly male, due to the nature of the military population studied, resulting in a relative underrepresentation of female participants. As a result, conclusions regarding gender-based risk for BD -particularly bipolar II- cannot be drawn with confidence. Future studies employing gender-balanced samples and diagnostic differentiation between bipolar subtypes are needed to clarify whether sex-related effects are robust or sample-specific.

One particularly novel and counterintuitive finding was the inverse association between parental divorce and BD. While traditionally conceptualized as a risk factor, divorce may in certain family contexts serve as a protective buffer against chronic conflict and psychological stress (72), suggesting that post-divorce environments may foster healthier relational dynamics when toxic family systems are interrupted. Additionally, maternal mental illness predicted lower levels of perceived social support, which in turn was the strongest negative predictor of BD. These findings align with evidence highlighting the protective role of stable, supportive relationships in mitigating vulnerability to mood disorders (73).

Although earlier studies have proposed that frequent residential relocation during childhood and adolescence may contribute to emotional dysregulation and increase psychiatric vulnerability (40), our results did not confirm a significant association between early-life mobility and BD symptoms. This aligns with more recent evidence questioning the consistency of this relationship (41,42). One possibility is that residential mobility operates not as an independent risk factor, but as a proxy for deeper systemic stressors—such as socioeconomic instability, parental conflict, or low familial support—which may better account for its previously observed effects.

Economic hardship, while a more modest contributor, was still significantly associated with BD. Low income and difficulty repaying loans were both significant predictors, echoing findings from socioeconomic models of mental illness that underscore the chronic stress, reduced access to care, and cumulative adversity often experienced by economically disadvantaged individuals (74).

The strongest predictors of BD were behavioral: suicidality and substance use. Suicidality, in particular, accounted for the largest proportion of variance in BD symptomatology. This is consistent with prior research identifying suicidality not merely as a consequence of BD but as a core component of its clinical expression (75). Both alcohol and drug use were also significantly associated with BD and suicidality, with SEM models confirming partial mediation. These findings support conceptualizing BD not only as a distinct diagnostic entity but also as a central node within a broader affective dysregulation and maladaptive coping network (76).

Clinical Implications

Clinically, the findings support the value of integrative assessment protocols that encompass familial, neurodevelopmental, and psychosocial factors. Early screening for ADHD symptoms, perinatal complications, and family psychiatric history -particularly maternal- may improve early detection and intervention. Additionally, interventions targeting the enhancement of perceived social support may serve as protective buffers. Clinicians should maintain high vigilance for co-occurring substance use and suicidality, not only as consequences of BD but as interacting drivers that may sustain or escalate clinical severity.

Limitations

Several limitations should be acknowledged. First, the cross-sectional nature of the study limits the ability to draw causal inferences. Although SEM offers insights into potential directional relationships, only longitudinal studies can confirm temporal sequences. Second, reliance on self-reported data may introduce recall bias and social desirability effects, potentially impacting data accuracy. Third, while several models demonstrated statistical robustness, the proportion of explained variance in BD remained moderate -indicating the likely influence of unmeasured variables such as genetic polymorphisms, inflammatory markers, or early relational trauma.

Future Directions

Future research should incorporate longitudinal designs and multi-method assessments, including biological markers (e.g., BDNF levels, cytokine profiles), neuroimaging data, and structured diagnostic interviews. Further exploration of resilience-promoting variables -such as emotional intelligence, community engagement, and attachment security- could enhance prevention strategies. Given the high risk of suicidality in BD, integrating dialectical behavior therapy (DBT) principles into early intervention programs may also prove beneficial.

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder
AUD: Alcohol use disorder

BD: Bipolar Disorder
BDNF: Brain-Derived Neurotrophic Factor
DBT: Dialectical Behavior Therapy
SEM: Structural Equation Modeling

Ethics, Consent & Metadata

Ethical Approval

All procedures performed in this study involving human participants conformed to the ethical standards of the 1975 Helsinki Declaration, as revised in 2013. Participants were informed in advance of the study's aims, anonymity protocols, and their right to withdraw at any stage without consequence.

Data Availability Statement Data supporting the findings of this study are available at: https://doi.org/10.5281/zenodo.15654503

Conflict of Interest Statement

The authors declare no competing interests.

Acknowledgments

The authors sincerely thank Researchers Orestis Giotakos and Elias Kassaras for voluntarily and actively presenting the findings at academic conferences. Also acknowledges the editorial and phrasing assistance provided by OpenAI's ChatGPT language model.

Funding Statement

This research received no specific grant from any public, commercial, or not-for-profit funding agency.

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