scientific reports

Check for updates

OPEN

The effect of childhood trauma on bipolar depression

Hernán F. Guillen-Burgos[1,2,7]✉, Juan F. Gálvez-Flórez[2], Sergio Moreno-López[4], María C. Solano[4], Angela T. H. Kwan[5,6], Hernando Santamaria-Garcia[3], Carlos Gómez-Restrepo[7,8] & Roger S. McIntyre[6]✉

Childhood trauma (CT) is associated with an earlier onset and a more severe course of bipolar disorder (BD). However, the specific impact of CT on bipolar depression remains unclear. Herein, this study aimed to investigate the effect of CT using depressive episode frequency as a threshold for disease burden and severity. A cohort of 146 participants with BD was followed for 3 years. The effects of CT on mood episodes, hospital readmissions, suicidal ideation, and behavior were analyzed. A high number of depressive episodes were identified in participants with BD and CT exposure, with the effect being more pronounced in BD II than in BD I. A threshold of ≥4 depressive episodes serves as a sensitivity cutoff point to detect associations with severe outcomes, such as early readmission and suicidal ideation and behavior. The presence of CT increases the risk of experiencing at least one severe outcome by 80%. In our cohort, a cutoff point of ≥4 depressive episodes mediated the effect of CT on at least one severe outcome (early readmission or suicidal ideation and behavior). The study is limited by its non-probabilistic sample, recall bias, and moderate receiver operating characteristic curve value. The findings reinforce the association between CT and BD severity, highlighting the significantly higher number of depressive episodes in individuals with CT. This underscores CT as a risk factor for depressive predominant polarity and more frequent mood episodes in BD.

Keywords Childhood trauma, Bipolar disorder, Bipolar depression, Mood episodes, Depressive episodes, Trauma, Abuse, Neglect, Depression polarity, Mood stabilizer

Adverse childhood experiences (ACEs), including childhood trauma (CT), abuse, and neglect, are strongly linked to various mental health disorders, particularly mood disorders[1–4] Among individuals with bipolar disorder (BD), CT has been associated with earlier onset, greater severity, and a more challenging disease course. This includes higher rates of hospital readmissions, frequent mood episodes, comorbidities, and suicidality[3,5–9] Despite this, further research is needed to fully understand the complex relationship between ACEs and clinical outcomes in BD.

Individuals with BD and a history of CT often report more depressive episodes and shorter intervals of euthymia[10] These individuals may feel significantly unwell approximately 45% of the time during follow-up,[11] with depressive symptoms accounting for 70–81% of their mood episodes[11–16] The predominance of recurrent depressive symptoms, or a depressive predominant polarity throughout the course of BD, might lead clinicians to misdiagnose patients with major depressive disorder instead of BD[17] Understanding the pathways underlying bipolar depression and its association with CT could aid in risk stratification during periods of depressive polarity in individuals with BD.

Research indicates that CT is a significant risk factor for bipolar depression,[18] with affected individuals experiencing more severe depressive symptoms[19] and greater cognitive impairment[20] Therefore, CT exposure should be considered a measurable risk factor in BD, necessitating a comprehensive understanding of its impact on the frequency, characteristics, and severity of depressive episodes.

[1]Center for Clinical and Translational Research, Centro de Investigaciones en Ciencias de la Vida, Universidad Simón Bolívar, Carrera 54 # 64-22, Barranquilla, Colombia. [2]Faculty of Medicine, Center for Clinical and Translational Research, Universidad El Bosque, Bogotá, Colombia. [3]PhD Neuroscience Program, Department of Psychiatry and Mental Health, Centro de Memoria y Cognición, Intellectus, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogotá, Colombia. [4]Faculty of Medicine, Universidad de Los Andes, Bogotá, Colombia. [5]Faculty of Medicine, University of Ottawa, Ottawa, ON K1H 8L1, Canada. [6]Department of Psychiatry, University of Toronto, Toronto, ON M5T 1R8, Canada. [7]Department of Psychiatry and Mental Health, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogotá, Colombia. [8]Department of Clinical Epidemiology and Biostatistics, Pontificia Universidad Javeriana, Bogotá, Colombia. ✉email: hernan.guillen@unisimon.edu.co; roger.mcintyre@bcdf.org

The number of mood episodes plays a pivotal role in determining the illness trajectory of BD, serving as a predictor of relapse or recurrence,[21–23] functional impairment,[24–26] and reduced quality of life[24] Evidence from the Systematic Treatment Enhancement Program for BD (STEP-BD) highlights that a history of a higher number of mood episodes correlates with slower recovery, prolonged remission, and persistence of subthreshold symptoms[22]. Furthermore, an increased number of mood episodes is associated with reduced treatment efficacy during both acute and maintenance periods.

Relapse precipitating factors in BD have been extensively studied, with proximal triggers such as pharmacotherapy, fasting, sleep disruption, and acute stressors identified[27–30] However, CT, a distal risk factor, has lasting effects that predispose individuals to increased sensitivity to proximal triggers. CT exposure alters neurobiological pathways, including hypothalamic-pituitary-adrenal (HPA) axis dysregulation, heightened emotional reactivity, and long-term changes in neuroplasticity and cognitive processing[31] These changes create vulnerability to stress and a lower threshold for relapse in the presence of proximal triggers.

This study hypothesizes that CT's enduring impact amplifies the risk of proximal factors, culminating in a cumulative predisposition to depressive episodes and severe outcomes in BD. There is currently no established threshold for the number of mood episodes required to classify BD as severe. Di Marzo et al.[26] previously suggested that individuals with > 10 episodes are likely to experience more severe outcomes. Similarly, Solomon et al.[12] reported a mean of 5.5 mood episodes per subject during a 25-year prospective follow-up. However, few studies have replicated this proposed threshold or examined the specificity and sensitivity of the number of depressive episodes associated with severe outcomes. This gap persists despite evidence that depressive episodes in BD are common and prone to recurrence[32] Establishing a specific threshold for depressive episodes offers considerable clinical and research benefits. A well-defined threshold enables clinicians to stratify patients by risk level, identify those requiring intensive monitoring or intervention, and standardize severity criteria across studies. Moreover, thresholds support mechanistic investigations, such as mediation analyses, to explore pathways linking risk factors like CT to adverse outcomes.

Existing literature highlights that individuals with BD who experience more lifetime depressive or mixed episodes face a 20- to 40-fold higher risk of suicidal behavior than those in euthymic states[33] However, it remains unclear whether depressive episodes mediate the relationship between prior CT exposure and suicidal ideation or behavior.

While prior research establishes a link between CT and severe BD outcomes,[1,3,34] the mechanisms underlying this association remain poorly understood. We hypothesize that depressive episodes serve as mediators, acting as a pathway through which the long-term effects of CT exposure manifest in adverse outcomes such as early readmission and suicidal ideation or behavior. Specifically, CT exposure disrupts the HPA axis, impairs stress reactivity, and heightens emotional sensitivity, collectively increasing vulnerability to depressive episodes[2,31] These episodes, in turn, exacerbate the risk of severe outcomes by prolonging illness duration, reducing treatment efficacy, and intensifying functional impairment.

In this study, we aim to investigate the mediating role of depressive episodes by identifying a threshold for depressive episode frequency predictive of severe outcomes. This mediation model provides a framework for understanding how distal risk factors like CT interact with illness trajectories to influence the severity and course of BD. Our approach offers novel insights into the mechanisms underlying CT's impact on BD and identifies potential intervention targets to mitigate adverse outcomes.

Methods

We conducted an observational, prospective longitudinal cohort study involving participants diagnosed with BD who completed a 3-year follow-up. Recruitment occurred between 2017 and 2022 at the Center for Clinical and Translational Research in Barranquilla, Colombia.

Participants

A cohort of participants with BD completed 3-year follow-up. Inclusion criteria were as follows: participants aged 18–65 years and diagnosed with bipolar spectrum disorder based on DSM-5 criteria, verified through the Structured Clinical Interview for DSM-5 Clinician Version (SCID-5-CV). Exclusion criteria included diagnoses of unipolar depression, attention deficit hyperactivity disorder, significant cognitive or physical disabilities interfering with assessment, schizophrenia, schizoaffective disorders, other psychotic disorders, personality disorders, or neurological disorders that served as primary diagnoses or comorbidities affecting BD diagnosis or management.

The recruitment was performed in outpatient and inpatient services in two teaching hospitals affiliated at the Center for Clinical and Translational Research in Barranquilla and Bogota D.C, Colombia. A program of follow-up for severe mental disorders was concerned with the insurance companies to guarantee the follow-up for clinical and research purposes.

At enrollment, participants completed a questionnaire detailing demographic and clinical characteristics, as described in "Outcomes". Inclusion criteria were verified by psychiatrists and clinicians trained in mental health. Follow-up visits were scheduled as follows: (a) 1 month after intake and (b) every 3 months thereafter, with additional visits arranged for acute episodes. Assessments during follow-up included clinical outcomes, functionality, health-related quality of life, biological markers, and cognitive function, providing comprehensive data to evaluate BD progression and severity.

Exposure

Demographic and clinical data were collected through a detailed questionnaire, capturing variables such as age, gender, marital status, education level, ethnicity, occupation, socioeconomic status, and ACEs (e.g., CT). Clinical data included age at onset, first mood episode, predominant polarity, diagnosis date, and treatment history.

CT exposure was assessed using the CT Questionnaire-Short Form (CTQ-SF), a 28-item Likert-type self-report scale evaluating CT across five domains: emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN). Each item was scored from 1 (*never true*) to 5 (*very often true*). Participants with scores in the moderate-to-severe range on at least one subscale (EA ≥ 13, PA ≥ 10, SA ≥ 8, EN ≥ 15, and PN ≥ 10)[35] were categorized as having a history of CT exposure. These cutoff points, validated in prior studies, effectively distinguish between CT and non-CT exposure[3,6] Multiple studies have used this instrument to evaluate CT in individuals with BP[36].

Outcomes

Primary outcome

The primary outcome of this study was defined as the number of depressive episodes experienced by participants over the 3-year follow-up period. This outcome was assessed using the self-reported version of the National Institute of Mental Health Life Chart Method–Self/Prospective (NIMH-LCM-S/P) and the DSM-5 criteria. Participants independently completed the NIMH-LCM-S/P, with additional entries recorded during acute mood episodes. Research staff reviewed and verified these data at each visit to ensure accuracy and completeness. The NIMH-LCM-S/P is a validated psychometric tool available in both patient and clinician versions, designed for longitudinal monitoring of mood-related functional impairment[37] Severity ratings were categorized as follows: 0 (*normal*), 2.5 (*minimally ill*), 5 (*low moderate*), 7.5 (*high moderate*), and 10 (*severely ill*). The number of mood episodes was determined based on DSM-5 criteria and the "leap-frog rule," as described by Denicoff et al.[38] The leap-frog rule has been shown to prevent the overestimation of mood episodes compared with using DSM-5 criteria alone[39] Previous studies have utilized this combined approach to accurately establish the number of mood episodes[40–44,38,45,46].

Secondary outcomes

Early readmission was defined as readmission to a psychiatric unit or hospital within 30 days of discharge from the index hospitalization or subsequent admissions. The index admission referred to the first psychiatric hospitalization after the participant's enrollment in the study. Admission and readmission data were obtained from the NIMH-LC and electronic medical records.

Participants with only one hospitalization during the study were not classified as having early readmission. In cases of multiple hospitalizations, readmissions occurring more than 30 days after discharge from the index hospitalization were excluded from the early readmission category. The number of participants with early readmission are detailed in Table 1.

Suicidal ideation and behavior were assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). The scale was administered at baseline to evaluate participants' history of suicide risk and at each follow-up visit (conducted every 3 months) to ensure continuous monitoring and timely intervention when necessary. The C-SSRS evaluates four constructs: severity of ideation, intensity of ideation, suicidal behavior, and lethality[47].

Suicidal ideation was defined as any self-harming thoughts or death wishes, as both have been linked to an increased risk of suicidal behavior[48–50] Any reported suicide attempt (including interrupted or abandoned attempts) or preparations for an attempt were classified as suicidal behavior[51] The C-SSRS has demonstrated high sensitivity and specificity as well as responsiveness to changes over time[47] This scale has been previously validated for use in populations with BP[52,53].

Data management

All collected data were encrypted and anonymized before being recorded into Research Electronic Data Capture (REDCap, licensed by Vanderbilt University). At each study visit, participants completed a comprehensive questionnaire capturing all study variables, following standardized research assessment protocols.

Statistical analysis

Statistical analysis was conducted in accordance with the study's objectives. CT was the primary exposure variable, defined as the presence of any positive CT subtype based on previously established cutoff points. The primary outcome, the number of depressive episodes, was treated as a continuous variable, while secondary outcomes—early readmission and suicidal ideation and behavior—were analyzed as dichotomous categorical variables.

Univariate and bivariate analyses were performed. Continuous variables were presented as means ($\bar{x}$) with standard deviations (*SD*) or as median (M) and interquartile ranges (IQRs), depending on the distribution. Categorical variables were reported as frequencies and percentages. Group comparisons of categorical variables were conducted using Chi-square or Fisher's exact test, while the Mann–Whitney *U* test was used for non-normally distributed variables. For numerical variables, *t* tests were employed.

An index of disease burden and severity was created based on two outcomes: early readmission and suicidal ideation and behavior. Participants experiencing one or more of these outcomes were categorized as having severe bipolar depression. Based on the index of disease burden and severity, a threshold classification performance model was used to calculate the cutoff point for the frequency of depressive symptoms to best identify participants during the follow-up period. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (LR+), negative likelihood ratio (LR−), and receiver operating characteristic (ROC) curves were calculated.

In addition, Poisson regression models were used to estimate the relative risk (*RR*) of experiencing a higher number of depressive episodes and severe outcomes (defined as one or more severe outcomes, multiple severe outcomes, or individual outcomes). CT exposure was the primary predictor, with adjustments for confounders,

Sociodemographic characteristics				
Characteristic	Total	Bipolar disorder		*p* value
		Non-CT	CT	
Total of participants	146 (100)	73 (50.00)	73 (50.00)	
Age (median, IQR)	31 (37–24)	28 (36–22)	33 (37–26)	0.046
Gender				
Male	43 (100)	23 (53.49)	20 (46.51)	0.586
Female	103 (100)	50 (48.54)	53 (51.46)	
Personal status				
Single	79 (100)	42 (53.16)	37 (46.84)	0.238
Married	53 (100)	22 (41.51)	31 (58.49)	
Divorced	14 (100)	9 (64.29)	5 (37.71)	
Education				
Elementary	4 (100)	0 (0.00)	4 (100)	0.039
High school	77 (100)	45 (58.44)	32 (41.56)	
Technician	54 (100)	22 (40.74)	32 (59.26)	
Graduate/Postgraduate	11 (100)	6 (54.55)	5 (45.45)	
Ethnicity				
Hispanic	118 (100)	57 (48.31)	61 (51.69)	0.400
Afro descent	28 (100)	16 (57.14)	12 (42.86)	
Occupation				
Employed	53 (100)	32 (60.38)	21 (39.62)	0.058
Unemployed	93 (100)	41 (44.09)	52 (55.91)	
Socioeconomic				
Low	99 (67.81)	52 (71.23)	47 (64.38)	0.376
Middle	47 (32.19)	21 (28.77)	26 (35.62)	
Childhood trauma (median, IQR)				
Total score	36 (49–31)	31 (33–29)	49 (58–42)	< 0.001
Emotional abuse	8 (10–5)	7 (9–5)	10 (14–6)	< 0.001
Physical abuse	7 (11–5)	5 (7–5)	11 (15–7)	< 0.001
Sexual abuse	7 (11–5)	5 (6–5)	11 (13–8)	< 0.001
Emotional neglect	7 (9–5)	7 (8–5)	8 (10–5)	0.009
Physical neglect	5 (8–5)	5 (6–5)	7 (11–5)	< 0.001
Early age onset (year)				
<18	105 (100)	39 (37.14)	66 (62.86)	< 0.001
≥18	44 (100)	34 (77.27)	10 (22.73)	
Early readmission (within 30 days after discharge)				
No	119 (100)	64 (53.78)	55 (46.22)	0.055
Yes	27 (100)	9 (33.33)	18 (66.67)	
Suicide ideation or behavior				
No	99 (100)	62 (62.63)	37 (37.37)	< 0.001
Yes	47 (100)	11 (23.40)	36 (76.60)	
Total of depressive episodes (mean, *SD*)	4.17 (3.40)	3.31 (1.80)	6.12 (4.02)	< 0.001
Total of mania/hypomania episodes (mean, *SD*)	1.91 (1.99)	1.52 (1.73)	2.30 (2.17)	0.017
Polarity predominance (n, %)				
Depressive	114 (100)	55 (48.25)	59 (51.75)	0.548
Manic	32 (100)	18 (56.25)	14 (43.75)	

Table 1. Baseline and follow-up characteristics of study participants ($n = 146$). CT, childhood trauma; IQR, interquartile range.

including age, gender, early age of onset, and rapid cycling. Assumptions of linearity, outliers, collinearity, and model fit were evaluated to ensure robustness.

Additionally, a mediation analysis was conducted to evaluate whether the threshold of depressive episodes identified above mediated the relationship between CT and the index of disease burden and severity. The mediation models were adjusted for covariates, including age, gender, early age of onset, and rapid cycling. Statistical significance was set at a two-tailed probability value of 0.05, with results reported using a 95%

confidence interval (CI). All statistical analyses were performed using Stata v18.0 SE-Standard Edition (Stata Corp LLC, College Station, Texas).

Results

A total of 146 participants with BD were included in the study, with equal numbers in the CT ($n=73$) and non-CT ($n=73$) groups. At baseline, the median age of participants with BD and CT exposure was 33 years (IQR: 37–26). Among this group, 51.5% ($n=53$) were females, 55.9% ($n=52$) were unemployed, 51.7% ($n=61$) were identified as Hispanic, and 64.4% ($n=47$) were classified as having low socioeconomic status (Table 1).

Clinically, participants with CT exposure exhibited an earlier onset of BD (62.9%, $n=66$) and a higher proportion of early readmissions (66.7%, $n=18$). Additionally, suicidal ideation and behavior were significantly more prevalent in this group (76.6%, $n=36$; Table 1). The total CT and subscale scores were significantly higher in the BD with CT group than in the non-CT group (Table 1).

Effect of CT on mood episodes during the follow-up

During the 3-year follow-up period, 968 mood episodes were recorded (689 depressive episodes and 279 manic episodes). Participants with CT exposure experienced significantly more depressive episodes than those without CT exposure ($p<0.001$).

For participants with BD I, significant differences were observed in the number of depressive episodes between those exposed to CT and those not exposed ($\bar{x}$ = 5.88, $SD=3.45$ vs. $\bar{x}$ = 3.51, $SD=1.95$; $p<0.001$). A higher number of episodes was evidenced in the subgroup with CT compared with the subgroup non-CT (Fig. 1). Besides, there are statistical differences between the number of depressive episodes in BD II exposed to CT compared with non-CT ($\bar{x}$ = 6.34, $SD=4.51$ vs. $\bar{x}$ = 2.64, $SD=0.93$; $p<0.001$; Fig. 1). Also, there are differences in manic/hypomanic episodes for either BD I or BD II participants based on CT exposure.

Sensitivity analysis to identify a threshold in the number of depressive episodes that correlate with the index of burden disease and severity during 3-year follow-up

A sensitivity analysis was conducted to determine an appropriate threshold for depressive episodes correlating with severe disease outcomes. The analysis used a ROC curve for at least one outcome in the index of disease burden and severity (Supporting Information Tables S1 and S2). A threshold of ≥4 depressive episodes yielded an area under the ROC curve (AUC) of 0.66 (Figure S1a). A cutoff point of ≥4 depressive episodes for discriminating at least one severity outcome (e.g., readmission or suicidal ideation or behavior) were 67.69% and 64.20%, respectively (LR + = 1.89, LR− = 0.50).

For more than one outcome in the disease and severity index, a threshold of ≥4 depressive episodes produced an AUC of 0.65 (Figure S1b). The sensitivity and specificity for predicting more than one severe outcome (readmission and suicide ideation and behavior) were 77.78% and 51.82%, respectively (LR + = 1.61, LR− = 0.42).

CT: Impact on outcomes in BD during 3-year follow-up

A Poisson regression model for cumulative depressive episodes revealed a 53% increased risk (95% CI, 1.26–1.85; $p<0.001$). An unadjusted RR of CT exposure with at least one severe outcome in the severity index was 2.42 (95% CI, 1.58–3.70; $p<0.001$). A Poisson regression model adjusted by confounders showed a risk of 80% ($RR=1.80$; 95% CI, 1.17–2.77; $p=0.008$; Table 2).

An unadjusted *RR* of CT exposure with more than one severe outcome in the severity index was 8.0 (95% CI, 1.02–62.35; $p=0.016$). The adjusted model yielded an *RR* of 5.66 (95% CI, 1.17–37.07; $p=0.070$; Table 2).

Examining individual outcomes, CT exposure was associated with an unadjusted *RR* of 2.0 for early readmission (95% CI, 0.96–4.15; $p=0.055$). In the adjusted model, the risk increased to 2.29 (95% CI, 1.07–4.88; $p=0.031$; Table 2). For suicidal ideation and behavior, the unadjusted *RR* was 3.27 (95% CI, 1.81–5.91; $p<0.001$), while the adjusted *RR* was 1.83 (95% CI, 1.03–3.24; $p=0.037$; Table 2).

A mediator effect of depressive episodes for the index of burden disease and severity

The total effect of CT on at least one severe outcome in the disease burden index was significant ($\beta=0.34$; $RSE=0.07$; 95% CI, 0.19–0.49; $p<0.001$). An indirect effect mediated by a threshold of ≥4 depressive episodes accounted for $\beta=0.10$ ($RSE=0.04$; 95% CI, 0.01–0.19; $p=0.021$). The direct effect of CT beyond this threshold was $\beta=0.23$ ($RSE=0.08$; 95% CI, 0.06–0.40; $p=0.006$). The mediation analysis indicated that 30.8% of CT's effect on at least one severe outcome was attributable to depressive episodes, with the remaining 69.2% attributable to other mechanisms (Fig. 2).

Discussion

Our results highlight the impact of CT on the number of episodes of BD. First, we observed a higher number of depressive episodes in participants with BD and CT compared with those with BD without CT exposure. These differences were more pronounced in participants with BD II than in those with BD I. Second, a threshold of ≥4 depressive episodes was identified as a cutoff point for detecting severe outcomes, including at least one severe indicator or more than one indicator within the index of disease burden and severity. Third, participants exposed to CT exhibited a 53% increased risk of experiencing a cumulative number of depressive episodes. Fourth, increased risk were observed for at least one severe outcome and for individual outcomes when CT exposure was present. However, no significant differences were found between CT exposure and the occurrence of two severe outcomes combined ($p=0.070$). Finally, an indirect effect, accounting for 30.8% of the risk for experiencing at least one severe outcome, was mediated by the threshold of ≥4 depressive episodes over the 3-year follow-up period.

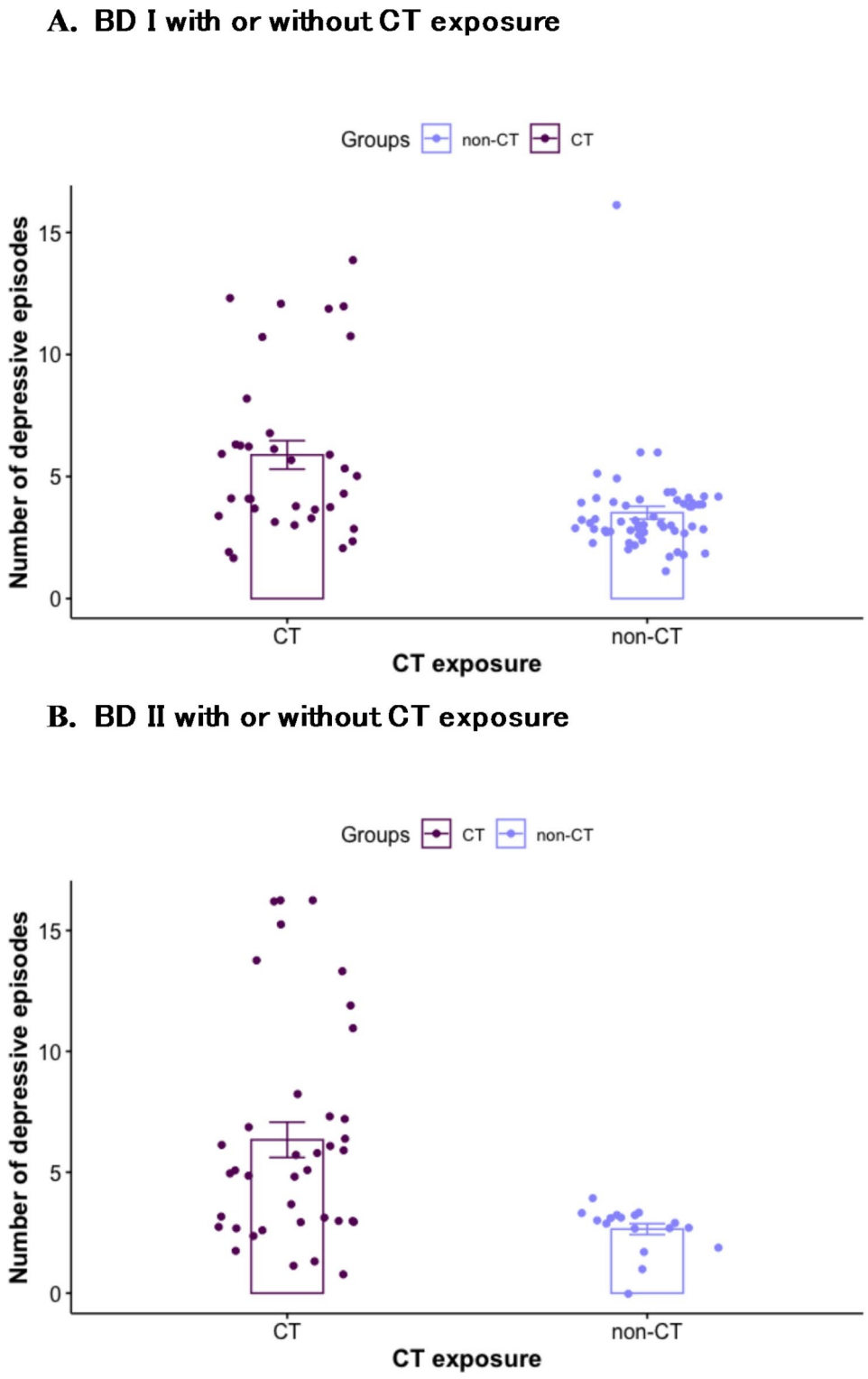

Fig. 1. Differences in the number of depressive episodes between BD with or without CT.

Previous studies report that 50–90% of individuals with BD experience multiple mood episodes throughout their illness[26] Magalhaes et al.[24] highlighted that individuals with recurrent episodes exhibit worse prognoses, impaired functioning, and diminished quality of life, often resulting in treatment resistance. In this sense, recently Bartoli et al. in a meta-analysis found that the number of mood episodes, history of suicide attempts, and depressive onset were associated with depressive polarity in BD. Therefore, exposure to childhood trauma as was identified in our study have contribute to the onset of risk factor associated to depressive polarity. On the other hand, Studies indicate that 50% of individuals with recovered BD experience recurrence within 2 years, with

A risk model of childhood trauma to the cumulative number of depressive episodes and severe outcomes in BD ($n = 146$)								
			95% CI					
Variable	*RR*	Robust *SE*	Min	Max	*p* value	Wald test	*p* value model	Pseudo R^2
Model 1: Cumulative depressive episodes								
Childhood trauma	1.53	0.15	1.26	1.85	< 0.001	174.97	< 0.001	0.21
Model 2: At least one severe outcome in the index of disease burden and severity								
Childhood trauma	1.80	0.39	1.17	2.77	0.008	38.03	< 0.001	0.09
Model 3: More than one severe outcome in the index of disease burden and severity								
Childhood trauma	5.66	5.43	0.86	37.07	0.070	2132	< 0.001	0.17
Model 4: Early readmission within 30 days after discharge								
Childhood trauma	2.29	0.88	1.07	4.88	0.031	10.21	0.031	0.04
Model 5: Suicide ideation and behavior								
Childhood trauma	1.83	0.53	1.03	3.24	0.037	22.21	< 0.001	0.15

Table 2. A risk model of childhood trauma exposure to severe outcomes in BD during 3-year follow-up. 95% CI, 95% confidence interval; BD, bipolar disorder; CT, childhood trauma; max, maximum; min, minimum; *RR*, relative risk; *SE*, standard error. Controlled by age, gender, early age of onset, and rapid cycling.

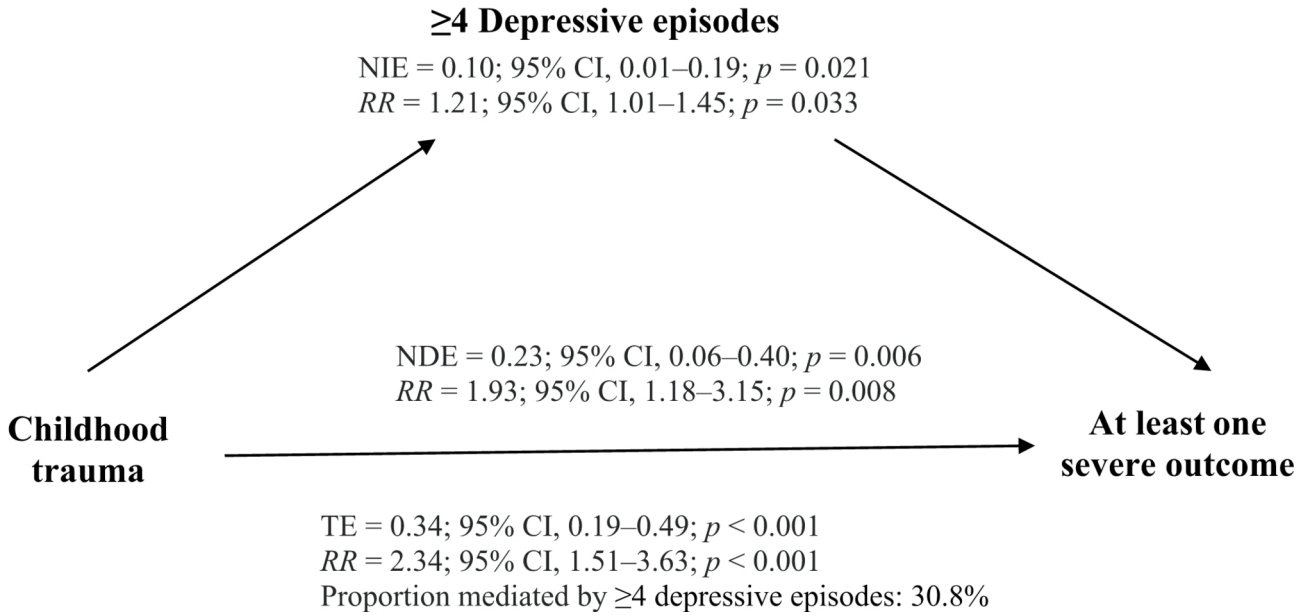

Fig. 2. Mediation analysis examining the relationship between CT exposure, a threshold of ≥4 depressive episodes, and at least one severe outcome (early readmission or suicidal ideation and behavior) (Controlled by age, gender, early age of onset, rapid cycling. NIE: Natural Indirect Effect; NDE: Natural Direct Effect; TE: Total Effect; RR: Relative Risk; CI: Confidence Interval).

depressive episodes being more frequent and associated with greater multidimensional impairments[22,32,54,55] Moreover, the severity of depressive episodes tends to increase over an individual's lifetime[56–58].

Longitudinal studies have shown that the number of mood episodes in BD strongly predicts health outcomes, such as recurrence risk within 2–4 year, increased hospitalizations,[21,22,59] and persistent symptoms between episodes, often resulting in lower recovery rates[22] The cumulative number of prior mood episodes is, therefore, a key marker of illness severity. In this study, we explored whether ACEs, particularly CT, influence these trajectories by exacerbating the frequency and severity of mood episodes. Our findings suggest that CT acts as a risk factor, contributing to more severe illness trajectories by amplifying the recurrence and persistence of mood episodes in BD.

Our results demonstrate that participants with BD, regardless of subtype (BD I or BD II), who were exposed to CT had significantly higher numbers of depressive episodes than those without CT exposure (Fig. 1). Notably, this difference was more pronounced in the BD II group ($p < 0.001$), consistent with prior literature[12,22,24,60,61] Existing research indicates that individuals with BD II spend more time in depressive states than those with BD I[11,16] In our cohort, CT exposure appeared to exacerbate this vulnerability, leading to a higher frequency of depressive episodes, particularly in the BD II group (Fig. 1)[12,22,24,60],6211,[16].

CT plays a critical role in influencing the trajectories and severity of mood episodes, particularly depressive episodes[62] Participants exposed to CT showed a 53% increased risk of cumulative depressive episodes over the 3-year follow-up, aligning with prior research. For instance, Etain et al.[6] reported a 47% increased risk of severe outcomes associated with EA[6], while Haussleiter et al.[63] identified a 38% increased risk linked to PA[63] These findings underscore the impact of specific CT subtypes on depressive episodes in BD. However, variations in the prevalence and associations of BD states with different CT subtypes across studies may reflect socioeconomic and cultural disparities[3,6,64–66].

Rehospitalization is another significant factor in severe BD cases. Early and late readmissions for mental health disorders lead to higher healthcare costs and diminished functionality and quality of life[67] Previous studies have identified predictors of early readmissions,[8] including homelessness, lack of insurance, and ≥3 prior hospitalizations[8] Other studies have found that patient functioning and complex pre-admission polypharmacy predict early readmission within 30 days after discharge[68] In our cohort, CT exposure after adjusted for several cofounders was associated with early readmission (Table 2).

Suicidal ideation and behavior are also closely associated with CT in individuals with BD[3,69] Participants with a history of CT exhibited an 83% increased risk of suicidal ideation or behavior during the follow-up period, consistent with prior findings[3,69–71].

Identifying a specific threshold for depressive episodes provides critical clinical insights beyond merely assessing their cumulative number. While the frequency of episodes independently correlates with illness severity, establishing a threshold allows for standardized definitions and early identification of high-risk individuals. Our findings suggest that ≥4 depressive episodes serve as a reliable predictor of severe outcomes, such as early readmission and suicidal ideation or behavior. Moreover, the threshold facilitates the exploration of mediating pathways, such as the indirect effect of depressive episodes linking CT to severe outcomes. In our study, depressive episodes mediated approximately 30.8% of the total effect of CT on severe outcomes, underscoring their dual role as an illness severity marker and a mediating factor in BD progression. Future studies should validate this threshold in larger cohorts and evaluate its application in clinical practice.

Depressive episodes appear to mediate the relationship between CT and severe outcomes, such as early readmission or suicidal ideation and behavior. This mediation likely reflects the enduring effects of CT on neurobiological systems, including heightened HPA axis activity, which predisposes individuals to recurrent depressive episodes. These episodes, in turn, exacerbate the course of BD by prolonging functional impairment, reducing treatment efficacy, and increasing emotional dysregulation. Although the mediation effect was strongest when considering severe outcomes as a composite index, the limited sample size may have hindered the detection of mediation effects for individual outcomes. Future research with larger cohorts is warranted to explore these pathways and validate the threshold identified in this study.

This study has several strengths. First, it used a prospective longitudinal design with consecutive life charting data collection. Second, CT was assessed using the CTQ-SF, a validated tool widely used in BD research[3,6,34] Third, the study used a combined approach (leap-frog rule and DSM-5 criteria) to minimize the risk of underestimating or overestimating mood episodes[40–44,38,45,46] Finally, robust statistical methods, such as causal mediation analysis, were used to identify mediator effects.

Nevertheless, the study has limitations. These include the use of a convenience cohort, a relatively small sample size, early onset of bipolar diagnosis before cohort entry, potential recall bias in retrospective data collection, and moderate ROC curve values for predicting severe outcomes. Another potential limitation is regarding with mental and physical comorbidities present in the participants with an increased risk for severe clinical course and precipitate mood episodes as well as pharmacological treatment regarding clinical outcomes remission, relapses or recurrences. However, robust follow-up over an extended period with a large sample size may help accurately identify potential thresholds and the effects of CT on mood episodes and illness progression.

Conclusions

CT significantly influences the trajectories of mood episodes, particularly the frequency of depressive episodes, in individuals with BD. CT, along with EA and PA, was associated with an increased risk of cumulative depressive episodes over the 3-year follow-up. A threshold of ≥4 depressive episodes was also a mediational factor between CT and at least one severe outcome under the index disease burden and severity. Future research should include questions about treatment response and evaluate whether CT moderates treatment response in BD in persons with fewer when compared to a greater number of mood episodes.

Data availability

Data supporting the findings of this study are available upon request from the corresponding authors.

Received: 31 May 2024; Accepted: 14 April 2025
Published online: 07 May 2025

References

1. Etain, B. & Aas, M. Childhood maltreatment in bipolar disorders. *Curr. Top. Behav. Neurosci.* **48**, 277–301 (2021).
2. Aas, M. et al. The role of childhood trauma in bipolar disorders. *Int. J. Bipolar Disord.* **4**, 1–10 (2016).
3. Guillen-Burgos, H. et al. Risk of childhood trauma exposure and severity of bipolar disorder in Colombia. *Int. J. Bipolar Disord* **11** (2023).
4. McKay, M. T. et al. Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. *Acta Psychiatr Scand.* **143**, 189–205 (2021).
5. Duarte, D. et al. Childhood-maltreatment subtypes in bipolar patients with suicidal behavior: systematic review and meta-analysis. *Braz J. Psychiatry.* **42**, 558–567 (2020).

6. Etain, B. et al. Childhood trauma is associated with severe clinical characteristics of bipolar disorders. *J. Clin. Psychiatry*. **74**, 991–998 (2013).
7. Agnew-Blais, J. & Danese, A. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry*. **3**, 342–349 (2016).
8. Hamilton, J. E. et al. Predictors of psychiatric readmission among patients with bipolar disorder at an academic safety-net hospital. *Aust N Z. J. Psychiatry*. **50**, 584–593 (2016).
9. Quidé, Y., Tozzi, L., Corcoran, M., Cannon, D. M. & Dauvermann, M. R. The impact of childhood trauma on developing bipolar disorder: current Understanding and ensuring continued progress. *Neuropsychiatr Dis. Treat.* **16**, 3095–3115 (2020).
10. Wrobel, A. L. et al. Childhood trauma and depressive symptoms in bipolar disorder: A network analysis. *Acta Psychiatr Scand.* **147**, 286–300 (2023).
11. Baldessarini, R. J., Vázquez, G. H. & Tondo, L. Bipolar depression: A major unsolved challenge. *Int. J. Bipolar Disord.* **8** (2020).
12. Solomon, D. A. et al. Longitudinal course of bipolar I disorder: duration of mood episodes. *Arch. Gen. Psychiatry*. **67**, 339–347 (2010).
13. Judd, L. L. et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch. Gen. Psychiatry*. **60**, 261–269 (2003).
14. Coryell, W. et al. Long-term stability of Polarity distinctions in the affective disorders. *Am. J. Psychiatry*. **152**, 385–390 (1995).
15. Judd, L. L. et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch. Gen. Psychiatry*. **59**, 530–537 (2002).
16. Forte, A. et al. Long-term morbidity in bipolar-I, bipolar-II, and unipolar major depressive disorders. *J. Affect. Disord*. **178**, 71–78 (2015).
17. Singh, T. & Rajput, M. Misdiagnosis of bipolar disorder. *Psychiatry (Edgmont)*. **3**, 57 (2005).
18. Patella, A. M. et al. Clinical features of differential diagnosis between unipolar and bipolar depression in a drug-free sample of young adults. *J. Affect. Disord*. **243**, 103–107 (2019).
19. Sun, D. et al. The association between childhood trauma and the age of onset in drug-free bipolar depression. *Psychiatry Res.* **310** (2022).
20. Poletti, S. et al. Multidimensional cognitive impairment in unipolar and bipolar depression and the moderator effect of adverse childhood experiences. *Psychiatry Clin. Neurosci.* **71**, 309–317 (2017).
21. Tundo, A. et al. Predictors of recurrence during long-term treatment of bipolar I and II disorders. A 4 year prospective naturalistic study. *J. Affect. Disord*. **225**, 123–128 (2018).
22. Park, D. Y. et al. Episode accumulation associated with hastened recurrence and delayed recovery in bipolar disorder. *J. Affect. Disord*. **227**, 657–664 (2018).
23. Kessing, L. V., Hansen, M. G. & Andersen, P. K. Course of illness in depressive and bipolar disorders. Naturalistic study, 1994–1999. *Br. J. Psychiatry*. **185**, 372–377 (2004).
24. Magalhães, P. V., Dodd, S., Nierenberg, A. A. & Berk, M. Cumulative morbidity and prognostic staging of illness in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Aust N Z. J. Psychiatry*. **46**, 1058–1067 (2012).
25. MacQueen, G. M. et al. Effect of number of episodes on wellbeing and functioning of patients with bipolar disorder. *Acta Psychiatr Scand.* **101**, 374–381 (2000).
26. Marzo, S. et al. The impact of the number of episodes on the outcome of bipolar disorder. *Eur. J. Psychiatry*. **20**, 21–28 (2006).
27. Eddahby, S., Kadri, N. & Moussaoui, D. Fasting during ramadan is associated with a higher recurrence rate in patients with bipolar disorder. *World Psychiatry*. **13**, 97 (2014).
28. Kadri, N., Mouchtaq, N., Hakkou, F. & Moussaoui, D. Relapses in bipolar patients: changes in social rhythm? *Int. J. Neuropsychopharmacol.* **3**, 45–49 (2000).
29. Malkoff-Schwartz, S. et al. Social rhythm disruption and stressful life events in the onset of bipolar and unipolar episodes. *Psychol. Med.* **30**, 1005–1016 (2000).
30. Rodrigues Cordeiro, C. et al. Triggers for acute mood episodes in bipolar disorder: A systematic review. *J. Psychiatr Res.* **161**, 237–260 (2023).
31. Jaworska-Andryszewska, P. & Rybakowski, J. K. Childhood trauma in mood disorders: Neurobiological mechanisms and implications for treatment. *Pharmacol. Rep.* **71**, 112–120 (2019).
32. Perlis, R. H. et al. Predictors of recurrence in bipolar disorder: primary outcomes from the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Am. J. Psychiatry*. **163**, 217–224 (2006).
33. Isometsä, E. Suicidal behaviour in mood Disorders—Who, when, and why?? *Can. J. Psychiatry*. **59**, 120–130 (2014).
34. Palmier-Claus, J. E., Berry, K., Bucci, S., Mansell, W. & Varese, F. Relationship between childhood adversity and bipolar affective disorder: systematic review and meta-analysis. *Br. J. Psychiatry*. **209**, 454–459 (2016).
35. Bernstein, D. & Fink, L. *Childhood Trauma Questionnaire: A Retrospective Self-Report –Manual* (The Psychological Corporation –Harcourt Brace and Company, 1998).
36. Zhang, S. et al. Prevalence of childhood trauma among adults with affective disorder using the childhood trauma questionnaire: A meta-analysis. *J. Affect. Disord*. **276**, 546–554 (2020).
37. Leverich, G. & Post, R. Life charting the course of bipolar disorder. *Curr. Rev. Mood Anxiety Disord*. **1**, 48–61 (1996).
38. Denicoff, K. D. et al. Preliminary evidence of the reliability and validity of the prospective life-chart methodology (LCM-p). *J. Psychiatr Res.* **31**, 593–603 (1997).
39. Koenders, M. A., Nolen, W. A., Giltay, E. J., Hoencamp, E. & Spijker, A. T. The use of the prospective NIMH life chart method as a bipolar mood assessment method in research: A systematic review of different methods, outcome measures and interpretations. *J. Affect. Disord*. **175**, 260–268 (2015).
40. Kupka, R. W. et al. Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. *Am. J. Psychiatry*. **162**, 1273–1280 (2005).
41. Kupka, R. W. et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder1. *Bipolar Disord.* **9**, 531–535 (2007).
42. Post, R. M. et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. *J. Clin. Psychiatry*. **64**, 12282 (2003).
43. Post, R. M. et al. Presentations of depression in bipolar illness. *Clin. Neurosci. Res.* **2**, 142–157 (2002).
44. Nolen, W. A. et al. Correlates of 1-year prospective outcome in bipolar disorder: results from the Stanley foundation bipolar network. *Am. J. Psychiatry*. **161**, 1447–1454 (2004).
45. Denicoff, K. D., Smith-Jackson, E. E., Disney, E. R., Ali, S. O. & Post, R. M. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J. Clin. Psychiatry*. **58**, 3431 (1997).
46. Van Zaane, J., Van Den Brink, W., Draisma, S., Smit, J. H. & Nolen, W. A. The effect of moderate and excessive alcohol use on the course and outcome of patients with bipolar disorders: A prospective cohort study. *J. Clin. Psychiatry*. **71**, 5637 (2010).
47. Posner, K. et al. The Columbia–Suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am. J. Psychiatry*. **168**, 1266–1277 (2011).
48. Szanto, K. et al. Suicide in elderly depressed patients: is active vs. Passive suicidal ideation a clinically valid distinction?? *Am. J. Geriatric Psychiatry*. **4**, 197–207 (1996).
49. Baca-Garcia, E. et al. Estimating risk for suicide attempt: are we asking the right questions? *J. Affect. Disord*. **134**, 327–332 (2011).

50. Greist, J. H., Mundt, J. C., Gwaltney, C. J., Jefferson, J. W. & Posner, K. Predictive value of baseline electronic Columbia–Suicide severity rating scale (eC–SSRS) assessments for identifying risk of prospective reports of suicidal behavior during research participation. *Innov. Clin. Neurosci.* **11**, 23 (2014).
51. Conway, P. M., Erlangsen, A., Teasdale, T. W., Jakobsen, I. S. & Larsen, K. J. Predictive validity of the Columbia-Suicide severity rating scale for Short-Term suicidal behavior: A Danish study of adolescents at a high risk of suicide. *Archives Suicide Res.* **21**, 455–469 (2017).
52. Al-Halabí, S. et al. Validation of a Spanish version of the Columbia-Suicide severity rating scale (C-SSRS). *Revista De Psiquiatría Y Salud Mental (English Edition)*. **9**, 134–142 (2016).
53. Huber, R. S. et al. Detailed assessment of suicidal ideation in youth with bipolar disorder versus major depressive disorder. *Bipolar Disord*. **25**, 200–208 (2023).
54. Altshuler, L. L., Gitlin, M. J., Mintz, J., Leight, K. L. & Frye, M. A. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. *J. Clin. Psychiatry*. **63**, 807–811 (2002).
55. Calabrese, J. R., Hirschfeld, R. M. A., Frye, M. A. & Reed, M. L. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a U.S. community-based sample. *J. Clin. Psychiatry*. **65**, 1499–1504 (2004).
56. Post, R. M. Mechanisms of illness progression in the recurrent affective disorders. *Neurotox. Res*. **18**, 256–271 (2010).
57. Post, R. & Leverich, G. *Treatment of Bipolar Illness: A Case Book for Clinicians and Patients* (WW Norton, Inc, 2008).
58. Kessing, L. V., Søndergård, L., Forman, J. L. & Andersen, P. K. Lithium treatment and risk of dementia. *Arch. Gen. Psychiatry*. **65**, 1331–1335 (2008).
59. Peters, A. T., West, A. E., Eisner, L., Baek, J. & Deckersbach, T. The burden of repeated mood episodes in bipolar I disorder: results from the National epidemiological survey on alcohol and related conditions. *J. Nerv. Ment Dis.* **204**, 87–94 (2016).
60. Berk, M. et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. *Bipolar Disord.* **13**, 87–98 (2011).
61. Berk, M. et al. Staging in bipolar disorder: from theoretical framework to clinical utility. *World Psychiatry*. **16**, 236–244 (2017).
62. Tremain, H., Fletcher, K. & Murray, G. Number of episodes in bipolar disorder: the case for more thoughtful conceptualization and measurement. *Bipolar Disord.* **22**, 231–244 (2020).
63. Haussleiter, I. S., Neumann, E., Lorek, S., Ueberberg, B. & Juckel, G. Role of child maltreatment and gender for bipolar symptoms in young adults. *Int. J. Bipolar Disord*. **8**, 10 (2020).
64. Jansen, K. et al. Childhood trauma, family history, and their association with mood disorders in early adulthood. *Acta Psychiatr Scand.* **134**, 281–286 (2016).
65. Li, X. B. et al. Childhood trauma associates with clinical features of bipolar disorder in a sample of Chinese patients. *J. Affect. Disord.* **168**, 58–63 (2014).
66. Xie, P. et al. Prevalence of childhood trauma and correlations between childhood trauma, suicidal ideation, and social support in patients with depression, bipolar disorder, and schizophrenia in Southern China. *J. Affect. Disord.* **228**, 41–48 (2018).
67. Jencks, S. F., Williams, M. V. & Coleman, E. A. Rehospitalizations among patients in the medicare Fee-for-Service program. *N. Engl. J. Med.* **360**, 1418–1428 (2009).
68. Bozzay, M. L. et al. Predictors of 30-day rehospitalization in a sample of hospitalized patients with bipolar I disorder. *Psychiatry Res.* **281**, 112559 (2019).
69. Hawton, K., Sutton, L., Haw, C., Sinclair, J. & Harriss, L. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *J. Clin. Psychiatry*. **66**, 693–704 (2005).
70. Baldessarini, R. J., Pompili, M. & Tondo, L. Suicide in bipolar disorder: risks and management. *CNS Spectr.* **11**, 465–471 (2006).
71. da Costa, L. Risk factors for suicide in bipolar disorder: A systematic review. *J. Affect. Disord.* **170**, 237–254 (2015).
72. Fiedorowicz, J. G. et al. Depressive symptoms carry an increased risk for suicidal ideation and behavior in bipolar disorder without any additional contribution of mixed symptoms. *J. Affect. Disord*. **246**, 775–782 (2019).
73. Seo, H. J., Wang, H. R., Jun, T. Y., Woo, Y. S. & Bahk, W. M. Factors related to suicidal behavior in patients with bipolar disorder: the effect of mixed features on suicidality. *Gen. Hosp. Psychiatry*. **39**, 91–96 (2016).
74. Marangell, L. B. et al. Prospective predictors of suicide and suicide attempts in 1,556 patients with bipolar disorders followed for up to 2 years. *Bipolar Disord*. **8**, 566–575 (2006).
75. Dev, D. A. et al. Comparing suicide completion rates in bipolar I versus bipolar II disorder: A systematic review and meta-analysis. *J. Affect. Disord*. **361**, 480–488 (2024).

Acknowledgements

The authors extend their gratitude to the participants, their families, and the assistant researchers and clinicians at the Center for Clinical and Translational Research for their invaluable support in managing the cohort of participants with BD.

Author contributions

RSM, HFGB and JFGF: conceived the idea, analyzed the data, wrote the original draft of the manuscript, provided critical feedback over the original draft of the manuscript, and approve final version of the manuscript. SM: analyzed the data and provide critical feedback over the data analysis section.ATHK, MCS, HSM, and CGR: provided critical feedback over the original draft of the manuscript. All authors revised the manuscript and approved the final version of the manuscript.

Funding

This work was supported by funding from Universidad Simón Bolívar, Universidad El Bosque, and the Center for Clinical and Translational Research.

Declarations

Ethics approval and consent to participate

All participants provided informed consent to participate in this research, including consent for future data publication. The study adhered to the principles outlined in the Declaration of Helsinki, CIOMS guidelines, and national regulations, including Act 8430/1993 and Act 2378/2008, in accordance with Good Clinical Practice in Human Research Studies. Ethics approval was granted by the Ethics Committee of Universidad Simón Bolívar (study code: PRO-CIE-USB-CE-0385-00).

Competing interests

H.G.B.: Received research grant support from the Ministry of Science, Technology, and Innovation (MinCiencias) in Colombia and UKRI in the United Kingdom; also received speaker fees from Roche, Pfizer, Abbott, GSK, and Synergy R&D. S.M., M.C.S., A.T.H.K., H.S.M., and C.G.R.: Declare no conflicts of interest. J.F.G.F.: Employed part-time by Universidad El Bosque, Center for Clinical and Translational Research, Bogotá, Colombia. R.S.M.: Received research grant support from CIHR/GACD/National Natural Science Foundation of China and the Milken Institute; also received speaker and consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Neurawell, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie, and Atai Life Sciences. R.S.M. is also the CEO of Braxia Scientific Corp.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-98537-4.

Correspondence and requests for materials should be addressed to H.F.G.-B. or R.S.M.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.