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ESTIMATION OF C REACTIVE PROTEIN LEVELS AND STUDY OF THEIR SIGNIFICANCE IN PATIENTS OF BIPOLAR DISORDER

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Abstract:

Bipolar disorder is predominantly a regular psychological disorder with recurring periods of (hypocritical) mood changes. Past experiments have shown that multiple neuroscience pathways play a crucial role in BD patients' molecular pathogenesis. There is, still, a shortage of specific biomarkers that better detect or forecast patients with BD. The goal of the research is to determine CRP levels in bipolar patients and equate the results of the study with levels of C - reactive protein in safe controls. Moreover, the present thesis also analyzed whether there was a disparity in CRP degree in bipolar disorder (i.e., acute mania, acute depression and asymptomatic patients and maintenance) Patients attended or admitted to TMM&RC TMU in Moradabad obtained this prospective examination. Inclusion requirements and demographic specifications were then recorded. Patients were included. A total of 86 patients included 46 (53.5%) male patients and 40 (46.5%) female patients. The average ño-SD of patients with CRP with bipolar disorder (6.57 ± 4.05) are substantially greater than the mean ± SD of patients with CRP with non-bipolar disorder (2.26 ± 1.53) (P<0.0001) and this analysis shows that C-reactive protein levels was slightly higher than in the patients with bipolar disorders as compared to controls. However, no such substantial correlation of demographic variables was identified in this analysis of bipolar disorder. More validated and accurate results will be collected from further trials of more patients.

Keywords: C-reactive protein, bipolar disorder, depression, psychotic mood.

Introduction:

The primary clinical diagnosis with bipolar syndrome is characterized by frequent bouts of depressed (hypo-) psychotic mood shifts. Many patients undergo elevated incidence and extreme mood shifts over time and eventually end in lethal conditions along with reduced care responsiveness.

Sometimes defined as bipolar spectrum disorder or simply as BD in the widest context, Bipolar I disorder, Bipolar II disorder and BD are not otherwise stated (BDNOS). Functional deficiency, though, and a decline in the standard of life indicators was slightly smaller than in most psychiatric conditions such as depressive disorders.

In both high and middle- and low-income nations, it poses the fourth biggest responsibility. The morbidity and mortality correlated with this diagnosis were attributed not only to the psychological but also to many co-morbid medical conditions. The strain of health care

expenses and early death is considered to be associated to this. Previous reports also shown that 80% of bipolar patients benefit from co-morbid disorders at large costs of treatment. These patients have higher care rates and less positive reaction to medication relative to other patients without such co-morbid conditions. It is the 12th largest cause in the worldwide age range of individuals with impairment 2. Recent literature has shown that BD is a multifactorial disorder and many environmental, genetic, and developmental risk factors play a key role in disease pathogenesis.

BDI and BDII concern approximately 2% of the world's population. The lifetime frequency of the whole bipolar continuum has been estimated to be between 2.6% and 7.8%, with an annual occurrence of <1%. Nearly 60% are recurrent after the first diagnosis in the first two years, with about 75% recorded in more than five years.

Neuro-inflammation has recently been identified as a major factor in BD pathogenesis. The acute step protein called the C-reactive protein was found to also be generated in patients with BD in addition to IL-2 and IL-6.

Studies suggest that CRP is elevated relative to stable controls in patients with BD. An elevated degree of CRP is also stated to be related to the overall mortality of BD patients. It is known as a biomarker of immune dysregulation for BD patients. Studies have also shown that the mood disturbances are correlated with CRP, especially in patients who have manic episodes. CRP gene polymorphisms are identified in a cohort of patients with psychological disorders. The amount of circulating CRP was also apparently affected by these genetic shifts.

Review of literature:

Background:

Bipolar disorder is a multidimensional psychological disorder with a frequent and severe personality disorder known as bipolar depression as one of the key signs. It constitutes about 11% of the neuropsychiatric disorder and about 1% of the overall disease burden in developed countries. The risk factors, as well as the heavy ethnic affiliation, are both hereditary and environmental. Episodic severe mood swings influencing sleep, movement, decision-making, judgement, actions and capacity to consider are referred to as bipolar disorder.

Epidemiology:

In their study, Rowland et al (2018) showed that bipolar disorder is related to emotional childhood abuse or disturbed childhood, such as family disorder and cannabis abuse. The same study shows the strong biological association with bipolar disorder with toxoplasma gondii infection but the reason behind is not clear. The most common contributing factor for bipolar illness in the community is childhood violence. The bipolar disorder is likely to be triggered by divorce, early parental losses, childbirth, parental neglect, unemployment, major losses and deaths, etc. However, there is a heavy bipolar condition in the family background of mental wellbeing.

Stressful life events have a positive relationship with bipolar disturbance, according to Lex et al (2017). Bipolar disorder is more common in women than men, and the reason for this is likely that women are more stressful than men.

Patho physiology:

In her study, Millett et al (2019) have shown that the positive sign or biomarker for cognitive or cognitive decay (CRP) is c- reactive protein.

The combination of CRP with bipolar disorder is a portal to a new treatment, and usually is linked to inflammatory conditions. Often considered as a multi-system inflammatory disease, bipolar conditions are mainly associated with comorbidities such as cardiovascular disease, diabetes, asthma, autoimmune disorders, HIV and infectious bowel disease. Patients with bipolar disorder need personalised treatment because the symptoms for each person are unique.

Evers et al. (2019) showed that single nucleotide polymorphism (SNPs) was observed and studied with the genes of CRP from CRP patients with bipolar disorders and that the expression of the CRP gene was almost without effect.

In their studies, Misiak et al. (2018) showed that CRP and cytokines elevation are associated with worst cognitive function in both bipolar disorder and schizophrenia, as well as in the same study, and that biomarkers of cognitive impairment in bipolar disorders are CRP (IL 1& IL 6).

In their study Farnandes et al (2016) showed that during the manic phase the CRP level was very high in a bipolar disorder compared to the depressive phase.

In the same study the level of euphoria, euthymia and healthy monitoring was measured and compared. Elevated CRP is therefore proven to be related to the bipolar disorder, including neuronal inflammation, with cognitive deficiencies and inflammations in the body.

Etiology:

There is still no complete understanding of main aetiology of bipolar disorder. Several studies have been carried out in the last few years, which have examined the importance of genetics with this disorder. The underlying genetic risk of developing this condition was shown to be associated with the alleged characteristics of bipolar prodrome.

1. Genetic factors:

Genetic factors have been shown to play a major role in bipolar disorder development process. Craddock and Jones (1999) pointed out that bipolar disorder in the first-degree family is 5% to 10% higher than in the general public, while in the monozygous twin it is 40% to 70% greater.

Fernandes et al. (2015) noted that neurotrophic polymorphism derived from brain often results in bipolar disorder development. Brain-derived neurotrophic factor (BDNF) can also be considered as a biomarker in patients who have bipolar disorder in order to make diagnosis of disease activity.

2. Prenatal complications:

Several studies have shown a combination of prenatal mental disorder viral infections. The association of bipolar with infectious agents was assessed during a recent review by Barichello et al. (2016). The results were contrasting, and no association between human herpesvirus and Epstein-Barr virus has been discovered.

3. Childhood maltreatment:

Another well studied risk factor for the environment that contributes to developing bipolar disorder is childhood abuse.

In a meta-analysis, the incidence of childhood adversity in BD patients was higher than in the controls, according to Palmier-Claus et al (2015). Interestingly, this study found that childhood abuse is associated in the form of bipolar disorder, mental, physical, and sexual. In another study the risk of transition to bipolar after a depressing period has increased because of a history of childhood abuse. It was thus highlighted that childhood abuse presents a certain risk of bipolar disorder developing later in life.

4. Psychological stress factors:

The combination of traumatic activities often contributes to bipolar disorder growth. A research by Kessing et al (2004) found that the initial admission of bipolar mania disorder is correlated with a traumatic incident such as a near relative's suicide. Such traumatic incidents including recent breakup, unemployment and also recent marriage have also demonstrated that the first entry of mania is related. The analysis also showed that a genetic link with the suicide of a parent with bipolar disorder was not correlated with hospitalization owing to death from other means.

The emergence of bipolar depression was also correlated with the early parental failure. Tsucheniya et al (2003) routinely examined the family history of a psychotic disorder as a risk factor. In addition, bipolar disorder was often linked with breastfeeding, difficult life activities and severe brain injuries.

5. Drug Abuse:

The misuse of substances was also correlated with bipolar disorder happening. Cannabis consumption has been found to have a bipolar disorder link. In a comprehensive analysis of cannabis use Gibbs et al (2015) indicated that psychotic symptoms intensify. After you start using weed to avoid psychological morbidity, it may be worse for people with newly identified bipolary conditions.

The non-prescription opioid usage has raised the risk, Schepis and Hakes, (2011), have noted. Another research stressed the risk of having psychotic disorder increased when alcohol and narcotics or some sort of dependency was used in fewer than 25 years. The influence of multiple medications has not been studied well, however.

Association between bipolar disorder and CRP:

This places BD into a cluster of inflammatory diseases, according to Osimo et al. (2018), and in that sense it will aid in designing the associated therapy to recognise the function that inflammation plays in BD subtypes.

Muneer et al proof Evidence (2016). Neuro-inflammation was proposed as a major prediction for bipolar disorder's molecular pathological function (BD). Sometimes, patients with BD have been diagnosed with elevated comorbidity rates such as coronary disease, diabetes mellitus, and autoimmune thyroiditis. These co-morbidities are also linked to BD-related metabolic and immunological dysfunction, often caused by inflammatory responsive subgroups of patients with BD.

CRP can aid in the detection of mood markers in BD and elevated CRP levels can alert of warning signs that maniatric symptoms start. Wium-Andersen et al (2016) notes that moderate levels of CRP can forecast BD initiation and that high levels of CRP can correlate disease incidence in the general population.

In particular, higher levels of C reactive protein (CRP) in contrast with the healthy individuals are known as an inflammatory marker with progressive BD. CRP is also correlated with all-cause mortality in BD patients, indicates Hayes et al. (2015).

Cytokines such as IL-2 and IL-6 are commonly developed as a reaction to infections and inflammation along with CRP. CRP is also a candidate for the identification of BD-associated immune dysregulation.

Aim and Objectives:

This prospective analytical study had the following aims and objectives:

1. To assess CRP levels in patients suffering from bipolar disorder

2. To associate C - reactive protein levels with phases of bipolar disorder (viz, acute mania or acute depression, and in patients who are asymptomatic and in the maintenance phase)

3. To compare the levels of CRP in healthy control and bipolar disorder patients.

Material and Methods:

Setting:

This prospective analytical study was conducted on patients either attending or being admitted in Psychiatry Department, TMM& RC TMU, Moradabad.

Selection of subjects:

The subjects were selected based on the following criteria.

Inclusion criteria:

1. Patients of all gender (18-65 years) with bipolar disorder as per ICD 10 criteria in acute phase (who have not started any treatment or have discontinued treatment for more than a month)

2. Patients of all gender (18-65 years) with bipolar disorder under remission and asymptomatic who are on maintenance treatment

3. All bipolar disorder patients diagnosed and attending OPD/ In patients admitted in psychiatry ward without any medical co morbidity (either follow up or admission)

4. healthy control subjects of all gender without any history of psychiatric illness (comparable age and sex matched relatives or attendants)

Exclusion criteria:

1. Patient having any current somatic illnesses including liver disease, serious un-or underrated heart, lung or neurological disorders

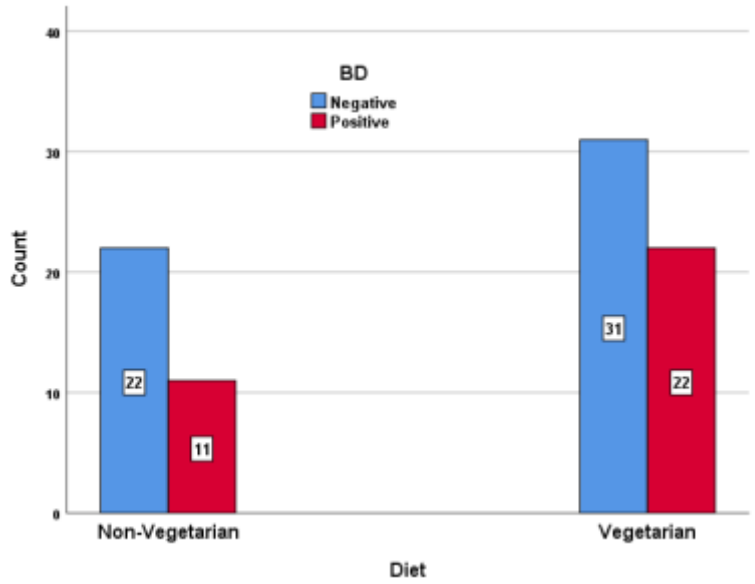
2. Patients suffering from any psychiatric illness, other than bipolar disorder

3. Patients those who refuse to give consent

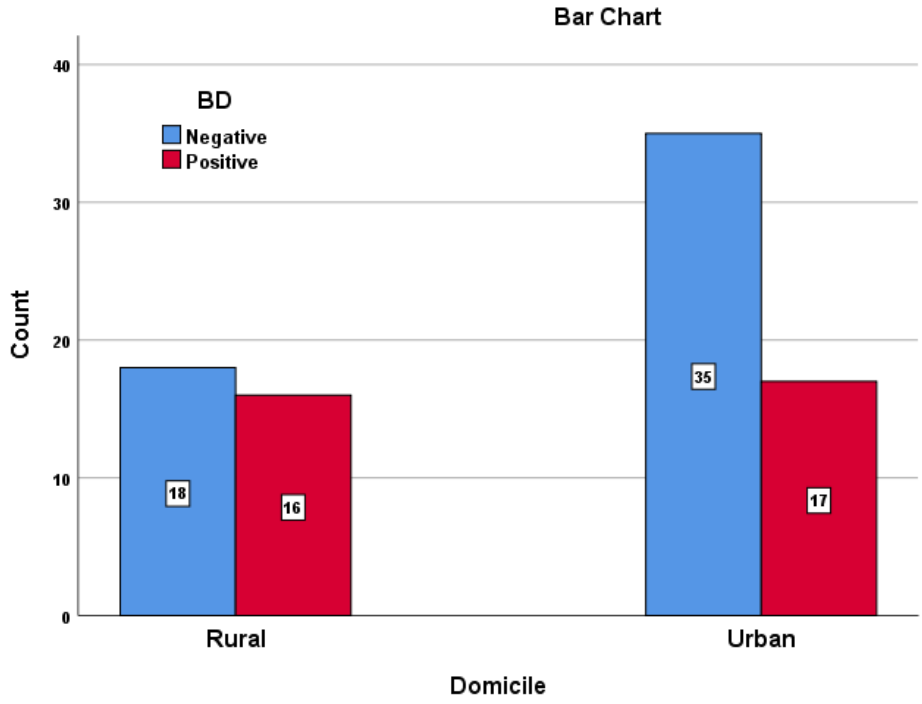
4. Patients below 18 years and above 65 years were not included in order to reduce the possible contaminating effect of concomitant medications and co-morbidity which are substantially increased for these patients

For association between diet and bipolar disorder patients, 22 (66.7%) patients of vegetarian and 11 (33.3%) patients of non-vegetarian were had bipolar disorder patients. However, there is no statistically significant association between diet and bipolar disorder patients (P=0.448).

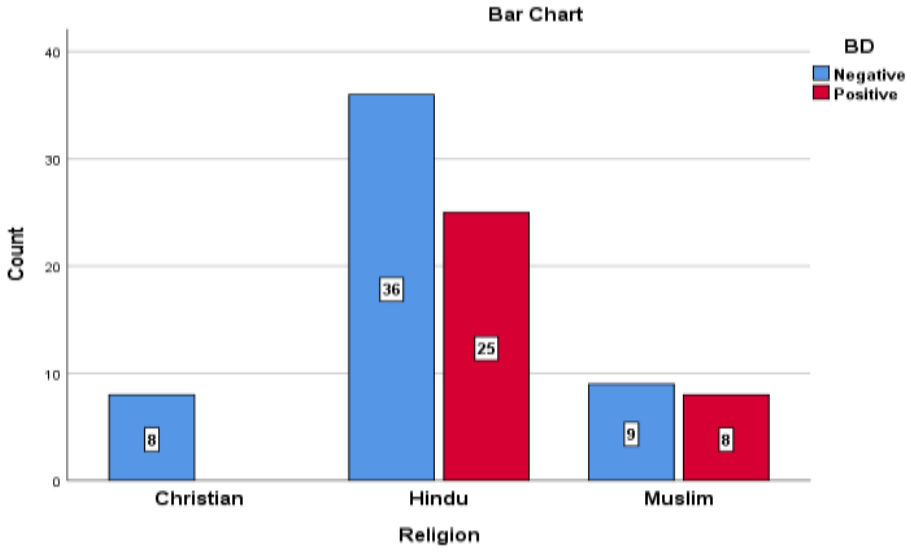
Findings:



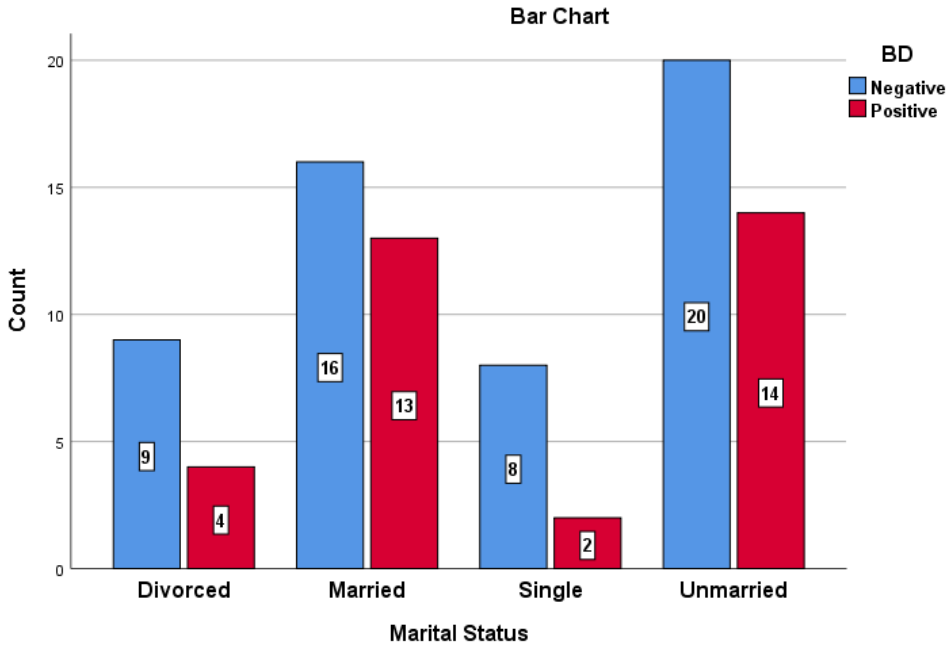
For association between domicile and bipolar disorder patients, 16 (48.5%) patients from rural and 17 (51.5%) patients from urban had bipolar disorder patients. However, there is no statistically significant association between domicile and bipolar disorder patients (P=0.180).



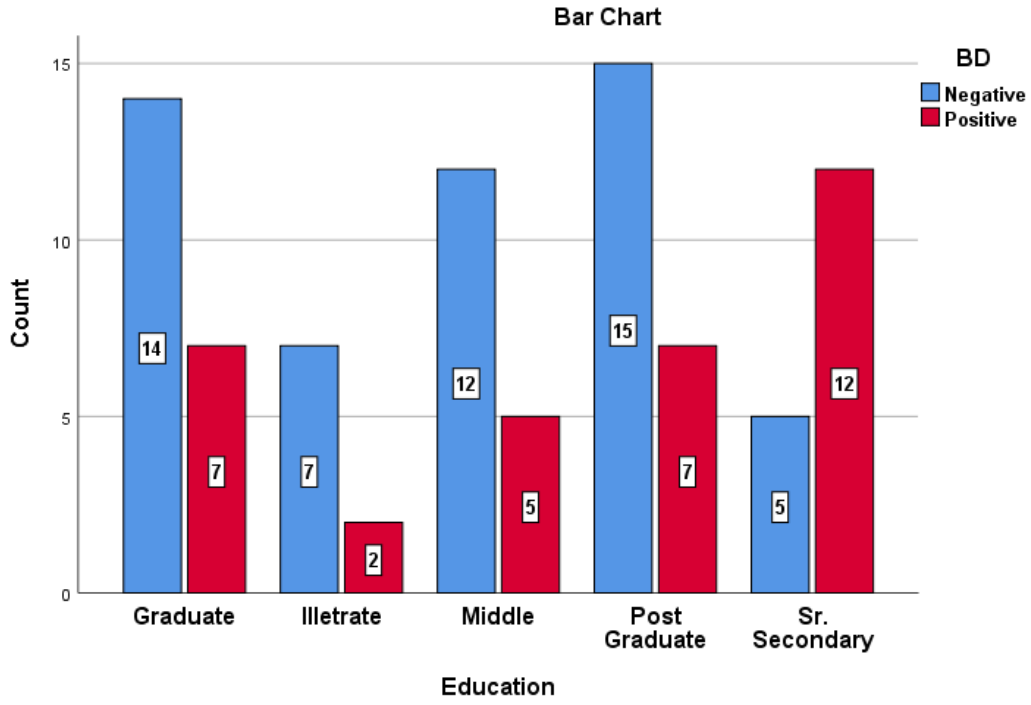
For association between religion and bipolar disorder patients, 25 (75.8%) patients from Hindu religion, 8 (24.2%) patients from Muslim religion, and none of patient from Christian religion had bipolar disorder patients. However, there is no statistically significant association between religion and bipolar disorder patients (P=0.058).



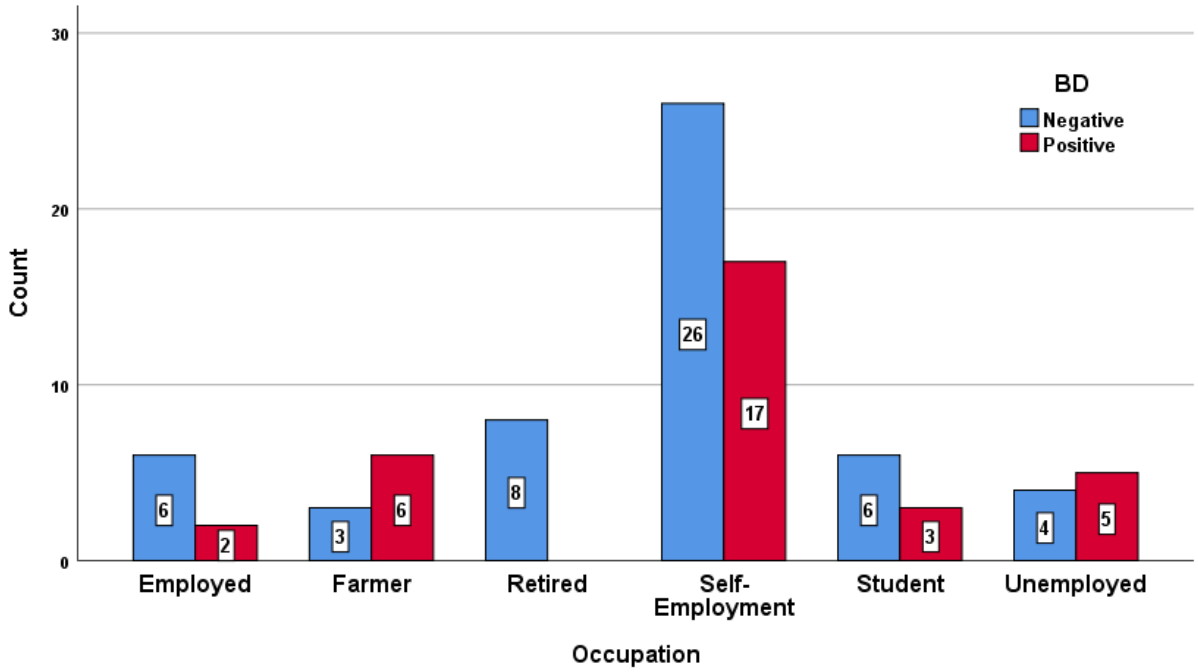
For association between marital status and bipolar disorder patients, 14 (42.4%) patients were unmarried, 13 (39.4%) patients were married, 4 (12.1%) patients were divorced, and 2 (6.1%) patients were single had bipolar disorder patients. However, there is no statistically significant association between marital status and bipolar disorder patients (P=0.499).



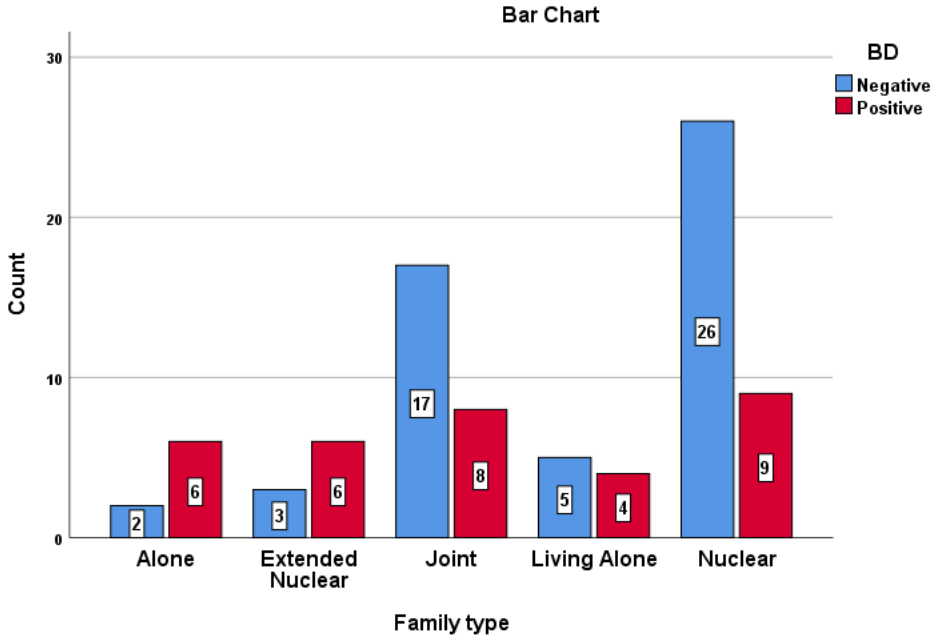
For association between Education and bipolar disorder patients, 12 (36.4%) patients were senior secondary, 7 (21.2%) patients were each Graduation and Post-Graduation, 5 (15.2%) patients were middle, and 2 (6.1%) patients were single had bipolar disorder patients. However, there is a statistically significant association between Education and bipolar disorder patients (P=0.047).



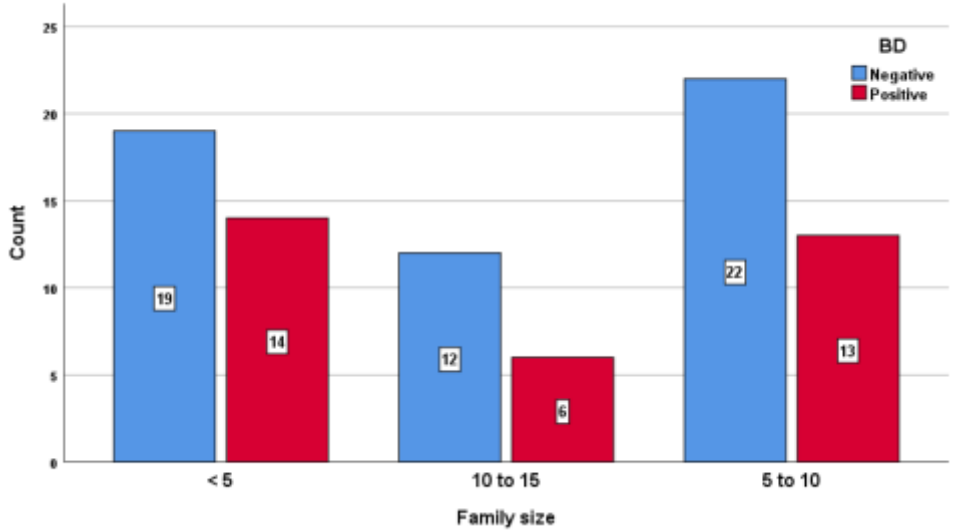
For association between occupation and bipolar disorder patients, 2 (6.1%) patients were employed, 6 (18.2%) patients were farmer, none of patients were retired, 17 (51.5%) patients were self-employment, 3 (9.1%) patients were student, and 5 (15.2%) patients were unemployed had bipolar disorder patients. However, there is no statistically significant association between occupation and bipolar disorder patients (P=0.079).



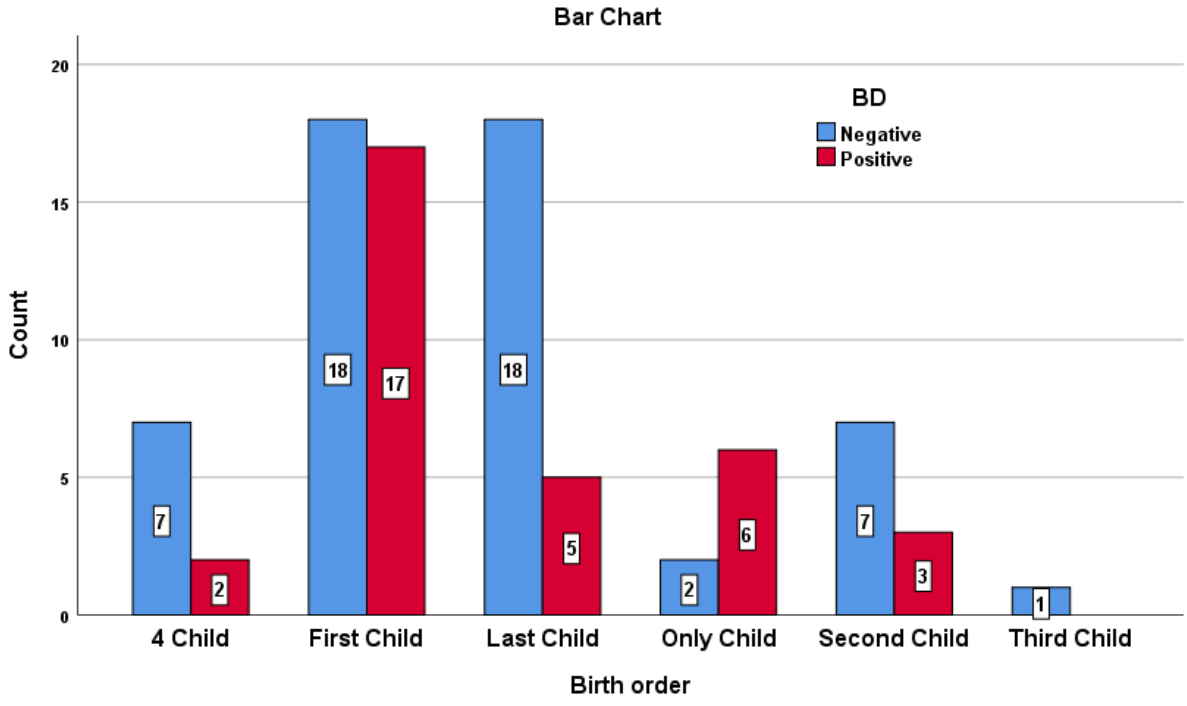
For association between family type and bipolar disorder patients, 6 (18.2%) patients had each of alone and extended nuclear family, 8 (24.2%) patients had joint family, 4 (12.1%) patients were living alone, and 9 (27.3%) patients were nuclear family had bipolar disorder patients. However, there is a statistically significant association between family type and bipolar disorder patients (P=0.032).



For association between family size and bipolar disorder patients, 14 (42.4%) patients had family size of less than five, 6 (18.2%) patients had family size between ten to fifteen, and 13 (39.4%) patients were had family size of five to ten had bipolar disorder patients. However, there is no statistically significant association between family size and bipolar disorder patients (P=0.801).

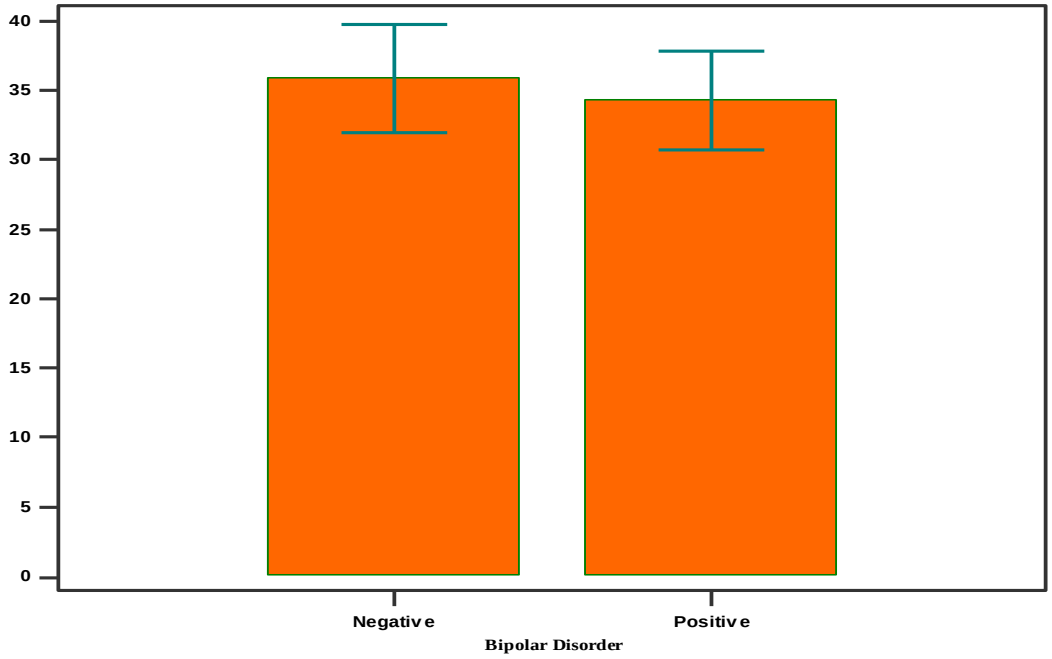


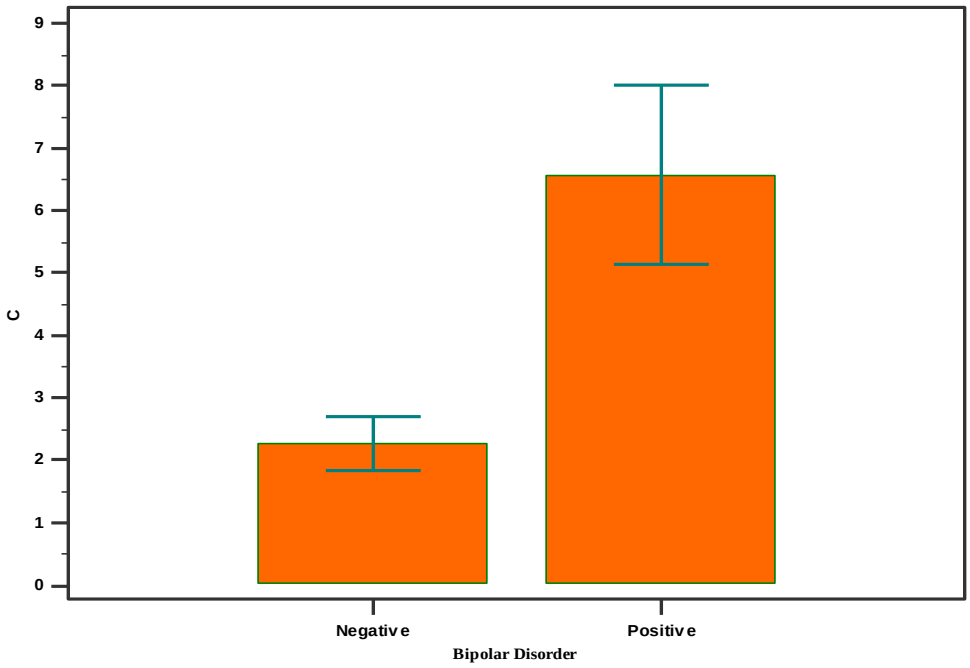
For association between birth order and bipolar disorder patients, 6 (18.2%) patients had only child of birth order, 17 (51.5%) patients had first child of birth order, 3 (9.1%) patients had second child of birth order, none of patients had third child of birth order, 2 (6.1%) patients had fourth child of birth order, 3 (9.1%) patients were student, and 5 (15.2%) patients had last child of birth order had bipolar disorder patients. However, there is no statistically significant association between birth order and bipolar disorder patients (P=0.058).



The mean±SD age of non-bipolar disorder patients (35.91 ± 14.05 years) was higher than the mean age of bipolar disorder patients (34.30 ± 10.12 years). However, it doesn't show any statistically significant difference of ages for bipolar disorder patients (P=0.571, Not Significant).

The mean±SD of CRP levels of bipolar disorder patients (6.57 ± 4.05) was significantly higher than the mean±SD of CRP levels of non-bipolar disorder patients (2.26 ± 1.53) (P<0.0001, Significant).





Discussion:

• A total of 86 patients in the present sample were 46 (53.5%) male and 40% (46.5%) female. There has never been a correlation between the patients with sex and bipolar disorder (P=0.549).

• 53 (61.6%) is vegetarian dieting and 33 (38.4%) were non-vegetarian diets, according to diet. No correlation was identified however amongst patients with a diet and bipolar disorder (P=0.448).

• 52 patients (60,5%) were urban patients and 34 (39,5%) were rural patients, according to the household. No correlation was, however, identified for patients in the home and in bipolar disorders (P=0.180).

• 61 (70.9 percent) of the patients, according to faith, were Hindu, 17 (19.8 percent) Muslim and 8 (9.3 percent) christian. No correlation has been discovered in patients with faith and bipolar disorder (P=0.058).

• 34 (39.5%) patients in the marital status were unmarried, 29 (33.7%) married, 13 (15.1%) divorced and 10 (11.6%) single patients. No correlation was identified among patients suffering from marriage conditions and bipolar disorders (P = 0,499).

• According to college, there was a post-graduation of 22 (25.6%), graduation in 21 patients (24.4%), medium and high school in 17 (19.8%), analphabet in 9 (10.5%). It was considered statistically important (P=0.047).

• 43 (50,0 percent) self-employment patients, nine (10,5%) farmers, students and unemployed patients were self-employed, eight (9,3%) retired and eight (9,2%) employed. There was no correlation between profession and patients with bipolar disorders (P=0.079).

• 35 (40.7 percent) were nuclear couples, twenty-five (29.1%) had a shared family, nine (10.5%) had nuclear extensions and resided alone, and eight (9.3%) patients were alone. • Family form. However, the correlation between the family type and patients with bipolar disorder is statistically relevant (P=0.032).

• 33 patients (38.37%) were under five family members and 35 (40.7%) had between five and ten members and 18 (20.93%) were ten to fifteen members. However, no correlation has been established regarding patients with family size and bipolar disorders (P=0.801).

• In the birth range, 35% (40-40%) patients have their first baby, 23% (26-7%) have their last baby, 8% (9-9%) have only infants, 10% (11-6%) have second baby, 1% (1,2%) have third and 9% (10,5%) have 4 children. However, the correlation of birth order and bipolar disorder patients (P=0.058) is not statistically important.

• In patients with BD, 53 (61.6%) were bipolarly negative, and in 33 (38.4%) patients, bipolarly positive.

• The total ± SD age of patients with non-bipolar conditions (35.91 ± 14.05 years) was greater than the average age of people with bipolar disorder (34.30 ± 10.12 years). However, the variations in age for bipolar patients are not statistically important (P=0.571, No Significant).

• The mean ± SD of the CRP rate of patients with bipolar illness (6.57 ± 4.05) was slightly higher than the average ± SD of non-bipolar CRP (P<0.0001, Significant).

Limitations:

In this analysis, the amount of CRP was calculated in patients admitted or visited the hospital. Therefore, this research is small in number of patients. Further experiments will have verified and more accurate results for a greater amount.

Secondly, this is a prospective review once, and thus only once was carried out and the subjects were not tracked. If patients may be evaluated and a follow-up analysis in a patient population may be done during the pharmacotherapy.

Future scope of the research:

While some shortcomings remain in current studies, this analysis incorporates all the correct and legitimate details with some very interesting results. The research in this study showed new insights and associations among CRP levels in patients with bipolar disorder. This research was also effective in addressing the goals.

Conclusion:

In 80.0% of bipolar cases the clinical treatment expenses related to medical co-morbidity disorders is strongly associated with the incidence. Bipolar illness is predominantly a periodic psychological disease marked by recurring periods of depressed and (hypo-) psychotic mood shifts. Molecular pathogenesis in BD patients is stated to be based on the mechanism of neuroin flammation. There is, still, a shortage of specific biomarkers that better detect or forecast patients with BD.

This research has found that, relative to stable controls, in individuals suffering from bipolar illness, the levels of C-reactive protein dramatically increase. However, no such substantial correlation of demographic variables was identified in this analysis of bipolar disorder. More trials with a broader patient cohort will have confirmed and more accurate results.

References:

1. Ferrari, A. J. et al. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. Bipolar Disord.**18**, 440–450 (2016).

2. Miller, S., Dell'Osso, B. & Ketter, T. A. The prevalence and burden of bipolar depression. J. Affect. Disord.**169**, S3–S11 (2014).

3. Shippee, N. D. et al. Differences in demographic composition and in work, social, and functional limitations among the populations with unipolar depression and bipolar disorder: results from a nationally representative sample. Health Qual. Life Outcomes**9**, 90 (2011).

4. Leboyer, M. et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J. Affect. Disord.**141**, 1–10 (2012).

5. Roshanaei-Moghaddam, B. &Katon, W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. Psychiatr. Serv. Wash. DC**60**, 147–156 (2009).

6. Williams, M. D., Shah, N. D., Wagie, A. E., Wood, D. L. & Frye, M. A. Direct costs of bipolar disorder versus other chronic conditions: an employer-based health plan analysis. Psychiatr. Serv. Wash. DC**62**, 1073–1078 (2011).

7. Landgraf, D., McCarthy, M. J. & Welsh, D. K. Circadian clock and stress interactions in the molecular biology of psychiatric disorders. Curr. Psychiatry Rep.**16**, 483 (2014).

8. Merikangas, K. R. et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch. Gen. Psychiatry**68**, 241–251 (2011).

9. Najafi-Vosough, R., Ghaleiha, A., Faradmal, J. &Mahjub, H. Recurrence in Patients with Bipolar Disorder and Its Risk Factors. Iran. J. Psychiatry**11**, 173–177 (2016).

10. Brietzke, E. et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J. Affect. Disord.**116**, 214–217 (2009).

11. Balukova, S. M., Haarman, B. C. M., Riemersma-van der Lek, R. F. & Schoevers, R. A. Does CRP predict outcome in bipolar disorder in regular outpatient care? Int. J. Bipolar Disord.**4**, 14 (2016).

12. Chang, H. H. & Chen, P. S. C-reactive protein as a differential biomarker of bipolar versus unipolar depression: Response. World J. Biol. Psychiatry**18**, 73–74 (2017).

13. Hayes, J. F., Miles, J., Walters, K., King, M. & Osborn, D. P. J. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. ActaPsychiatr. Scand.**131**, 417–425 (2015).

14. Evers, A.-K., Veeh, J., McNeill, R., Reif, A. & Kittel-Schneider, S. C-reactive protein concentration in bipolar disorder: association with genetic variants. Int. J. Bipolar Disord.**7**, 26 (2019).

15. Becking, K. et al. The association between immune activation and manic symptoms in patients with a depressive disorder. Transl. Psychiatry**3**, e314–e314 (2013).

16. Muneer, A. Bipolar Disorder: Role of Inflammation and the Development of Disease Biomarkers. Psychiatry Investig.**13**, 18–33 (2016).

17. Cunha, Â. B. et al. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci.**258**, 300–304 (2008).

18. Wium-Andersen, M. K., Ørsted, D. D. &Nordestgaard, B. G. Elevated C-reactive protein and late-onset bipolar disorder in 78 809 individuals from the general population. Br. J. Psychiatry**208**, 138–145 (2016).

19. Countries, I. of M. (US) C. on N. S. D. in D. Bipolar Disorder. Neurological, Psychiatric, and Developmental Disorders: Meeting the Challenge in the Developing World (National Academies Press (US), 2001).

20. Harrison, P. J., Geddes, J. R. & Tunbridge, E. M. The Emerging Neurobiology of Bipolar Disorder. Trends Neurosci.**41**, 18–30 (2018).

21. Houghton, K. T. et al. Biological rationale and potential clinical use of gabapentin and pregabalin in bipolar disorder, insomnia and anxiety: protocol for a systematic review and meta-analysis. BMJ Open**7**, e013433 (2017).

22. Rowland, T. A. & Marwaha, S. Epidemiology and risk factors for bipolar disorder. Ther. Adv. Psychopharmacol.**8**, 251–269 (2018).

23. Lex, C., Bäzner, E. & Meyer, T. D. Does stress play a significant role in bipolar disorder? A meta-analysis. J. Affect. Disord.**208**, 298–308 (2017).

24. Blond, B. N., Fredericks, C. A. & Blumberg, H. P. Functional neuroanatomy of bipolar disorder: structure, function, and connectivity in an amygdala–anterior paralimbic neural system. Bipolar Disord.**14**, (2012).

25. MANJI, H. K. et al. The underlying neurobiology of bipolar disorder. World Psychiatry**2**, 136–146 (2003).

26. Clemente, A. S. et al. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. Rev. Bras. Psiquiatr. Sao Paulo Braz. 1999**37**, 155–161 (2015).

27. Millett, C. E. et al. C-reactive protein is associated with cognitive performance in a large cohort of euthymic patients with bipolar disorder. Mol. Psychiatry 1–10 (2019) doi:10.1038/s41380-019-0591-1.

28. Misiak, B. et al. Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: A systematic review. Schizophr. Res.**192**, 16–29 (2018).

29. Fernandes, B. S. et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry**3**, 1147–1156 (2016).

30. Burdick, K. E., Ketter, T. A., Goldberg, J. F. & Calabrese, J. R. Assessing cognitive function in bipolar disorder: challenges and recommendations for clinical trial design. J. Clin. Psychiatry**76**, e342-350 (2015).

31. Duffy, A. Toward a comprehensive clinical staging model for bipolar disorder: integrating the evidence. Can. J. Psychiatry Rev. Can. Psychiatr.**59**, 659–666 (2014).

32. Craddock, N. & Jones, I. Genetics of bipolar disorder. J. Med. Genet.**36**, 585–594 (1999).

33. Fernandes, B. S. et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med.**13**, 289 (2015).

34. Sullivan, P. F. et al. Family history of schizophrenia and bipolar disorder as risk factors for autism. Arch. Gen. Psychiatry**69**, 1099–1103 (2012).

35. Craddock, N. &Sklar, P. Genetics of bipolar disorder. Lancet Lond. Engl.**381**, 1654–1662 (2013).

36. Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat. Genet.**43**, 977–983 (2011).

37. Barichello, T. et al. Exposure to Perinatal Infections and Bipolar Disorder: A Systematic Review. Curr. Mol. Med.**16**, 106–118 (2016).

38. de Barros, J. L. V. M. et al. Is there any association between Toxoplasma gondii infection and bipolar disorder? A systematic review and meta-analysis. J. Affect. Disord.**209**, 59–65 (2017).

39. 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 J. Ment. Sci.**209**, 454–459 (2016).

40. Gilman, S. E., Dupuy, J. M. & Perlis, R. H. Risks for the transition from major depressive disorder to bipolar disorder in the National Epidemiologic Survey on Alcohol and Related Conditions. J. Clin. Psychiatry**73**, 829–836 (2012).

41. Watson, S. et al. Childhood trauma in bipolar disorder. Aust. N. Z. J. Psychiatry**48**, 564–570 (2014).

42. Etain, B. et al. Preferential association between childhood emotional abuse and bipolar disorder. J. Trauma. Stress**23**, 376–383 (2010).

43. Kessing, L. V., Agerbo, E. & Mortensen, P. B. Major stressful life events and other risk factors for first admission with mania. Bipolar Disord.**6**, 122–129 (2004).

44. Tsuchiya, K. J., Byrne, M. & Mortensen, P. B. Risk factors in relation to an emergence of bipolar disorder: a systematic review. Bipolar Disord.**5**, 231–242 (2003).

45. Gibbs, M. et al. Cannabis use and mania symptoms: a systematic review and meta-analysis. J. Affect. Disord.**171**, 39–47 (2015).

46. Schepis, T. S. & Hakes, J. K. Non-medical prescription use increases the risk for the onset and recurrence of psychopathology: results from the National Epidemiological Survey on Alcohol and Related Conditions. Addict. Abingdon Engl.**106**, 2146–2155 (2011).

47. Kenneson, A., Funderburk, J. S. &Maisto, S. A. Substance use disorders increase the odds of subsequent mood disorders. Drug Alcohol Depend.**133**, 338–343 (2013).

48. Osimo, E. F., Cardinal, R. N., Jones, P. B. & Khandaker, G. M. Prevalence and correlates of low-grade systemic inflammation in adult psychiatric inpatients: An electronic health record-based study. Psychoneuroendocrinology**91**, 226–234 (2018).