Section: Psychiatry

Original Research Article

METABOLIC SYNDROME IN EUTHYMIC BIPOLAR DISORDER DURING MAINTENANCE TREATMENT WITH LITHIUM VERSUS SODIUM VALPROATE: A CROSS-SECTIONAL COMPARATIVE STUDY

Sidharth Kadganchikar[1], Sindhuri Potluri[2], Sarah Afreen[3], Uma Maheshwari S[4]

[1]Senior Resident, Department of Psychiatry, Government General Hospital, Sangareddy, Telangana, India
[2]Associate Professor, Department of Psychiatry, Osmania Medical College, Telangana, India
[3]Assistant Professor, Department of Psychiatry, Osmania Medical College, Telangana, India

[4]Senior Resident, Department of Psychiatry, Oxford Medical College, Hospital and Research centre, Bengaluru, India

Received *: 10/06/2026*
Received in revised form *: 10/07/2026*
Accepted *: 14/07/2026*

Corresponding Author:
Dr. Sidharth Kadganchikar,
Senior Resident, Department of Psychiatry, Government General Hospital, Sangareddy, Telangana, India.
Email: sidharthck8@gmail.com

DOI: 10.70034/ijmedph.2026.3.95

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (3); 581-585

ABSTRACT

Background: Bipolar disorder is associated with substantial cardiometabolic morbidity. Mood stabilizers may influence weight, glucose regulation, lipids, and blood pressure, but direct comparisons between lithium and sodium valproate remain limited. The objective was to compare the prevalence of metabolic syndrome and its individual components in euthymic adults receiving maintenance lithium or sodium valproate.

Materials and Methods: This hospital-based cross-sectional study included 100 adults aged 18-50 years with DSM-5 bipolar disorder who had been euthymic for at least 2 months and treated for at least 6 months with lithium (n=51) or sodium valproate (n=49). Euthymia was defined as a Young Mania Rating Scale score ≤7 and a Hamilton Depression Rating Scale score ≤8. Metabolic syndrome was identified using the study's modified NCEP ATP III criteria. Waist circumference, blood pressure, fasting glucose, triglycerides, and high-density lipoprotein cholesterol were assessed. Effect estimates included risk difference, risk ratio, odds ratio, 95% confidence intervals, Welch t tests, and Hedges' g.

Results: Metabolic syndrome was present in 20 of 51 lithium-treated participants (39.2%) and 23 of 49 valproate-treated participants (46.9%). The absolute risk difference was 7.72 percentage points (95% CI -11.64 to 27.08), risk ratio 1.20 (95% CI 0.76-1.88), and odds ratio 1.37 (95% CI 0.62-3.03); $\chi^2(1)=0.61$, $p=0.435$. Systolic and diastolic blood pressure, fasting glucose, waist circumference, triglycerides, and HDL cholesterol did not differ significantly; standardized mean differences were small.

Conclusion: Metabolic syndrome was common in both treatment groups, but the study did not demonstrate a statistically significant difference between lithium and sodium valproate. Wide confidence intervals preclude a conclusion of equivalence. Routine cardiometabolic surveillance is warranted regardless of the prescribed mood stabilizer.

Keywords: Bipolar disorder, metabolic syndrome, lithium, sodium valproate, cardiometabolic risk, NCEP ATP III.

INTRODUCTION

Bipolar disorder is a severe recurrent psychiatric illness associated with suicide, disability, reduced social and occupational functioning, and shortened life expectancy.[1-4] Much of the excess mortality is attributable to physical illness, particularly cardiovascular and metabolic disease. Because long-term pharmacotherapy is usually required, systematic physical health monitoring is an essential component of bipolar disorder care.[3,4]

Metabolic syndrome is a clustering of central adiposity, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, elevated

blood pressure, and impaired fasting glucose. Although definitions vary, the syndrome identifies a population at increased risk of type 2 diabetes and cardiovascular disease.[7,8] Meta-analyses indicate that metabolic syndrome affects a substantial proportion of people with bipolar disorder, with prevalence moderated by age, geography, smoking, illness duration, diagnostic criteria, and psychotropic exposure.[5,6]

Cardiometabolic risk in bipolar disorder is multifactorial. Relevant contributors include diet, physical inactivity, smoking, sleep and circadian disruption, socioeconomic disadvantage, endocrine dysregulation, inflammation, genetic vulnerability, and medication. Second-generation antipsychotics are prominent contributors, but mood stabilizers also require attention. Valproate has been associated with weight gain, higher insulin and triglyceride levels, and lower HDL cholesterol in some cohorts.[10] Lithium may cause weight gain in susceptible individuals, yet naturalistic data have not consistently shown an excess prevalence of metabolic syndrome among lithium users.[11]

Direct comparisons between lithium and sodium valproate are limited and frequently confounded by concomitant antipsychotics, treatment duration, illness severity, and nonrandom prescribing. Indian evidence is particularly important because cardiometabolic risk and body composition thresholds differ across populations.[8,9] The present study therefore compared metabolic syndrome and its individual measured components in euthymic adults receiving maintenance lithium or sodium valproate.

AIM

To compare the prevalence of metabolic syndrome in euthymic patients with bipolar disorder receiving maintenance treatment with lithium or sodium valproate at a tertiary care hospital.

OBJECTIVES

To assess and compare the prevalence of metabolic syndrome and its individual components between the lithium and sodium valproate treatment groups.

MATERIALS AND METHODS

Study design, setting, and reporting: A hospital-based cross-sectional comparative study was conducted over 12 months in the Department of Psychiatry at Government General Hospital, Sangareddy, a tertiary care teaching hospital. Participants were recruited by convenience sampling from outpatient services. Reporting was aligned with the STROBE recommendations for cross-sectional studies.[16]

Participants and diagnostic procedures: Adults aged 18-50 years were eligible if they met DSM-5 criteria for bipolar disorder,[2] had remained in clinical remission for at least 2 months, and had received lithium or sodium valproate for at least 6 months. Diagnosis was established through psychiatric clinical assessment. Euthymia was defined as a YMRS score ≤7[14] and a HAM-D score ≤8.[15] Participants provided written informed consent and had adequate vision and hearing.

Exclusion criteria included another current mental disorder, including substance dependence, diagnosed diabetes mellitus or hypertension, neurological comorbidity, and learning difficulty. The exclusion of participants with previously diagnosed diabetes or hypertension may have lowered the observed prevalence of metabolic syndrome. The final sample comprised 51 lithium-treated and 49 sodium-valproate-treated participants. No formal a priori power calculation was documented.

Cardiometabolic measurements and operational definition

Table 1: Modified NCEP ATP III operational criteria used in the study

Waist circumference	**Measured at the iliac process/umbilical level**	>90 cm
Triglycerides	Fasting serum triglycerides	≥150 mg/dL
HDL cholesterol	Fasting serum HDL cholesterol	<40 mg/dL
Blood pressure	Two measurements taken 15 minutes apart	Systolic ≥130 mmHg or diastolic ≥85 mmHg, or antihypertensive treatment
Fasting glucose	Fasting venous serum glucose	≥110 mg/dL or glucose-lowering treatment
Metabolic syndrome	Composite classification	At least three abnormal components

The study used single thresholds for waist circumference and HDL cholesterol. These thresholds differ from sex-specific NCEP and harmonized criteria,[7,8] and should be interpreted as the study's modified operational definition.

Height and weight were measured to calculate body mass index. Waist circumference was measured at the iliac process/umbilical level. Blood pressure was measured twice, 15 minutes apart. Fasting venous blood was centrifuged, and the serum was stored at -70 °C before analysis. Glucose, triglycerides, total cholesterol, and HDL cholesterol were measured; total cholesterol is not a component of metabolic syndrome and was not included in the summarized outcome analysis.

Statistical analysis

The original analysis was conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Publication estimates were independently reconstructed from the reported group summaries using Python 3.13.5, NumPy 2.3.5, and SciPy 1.17.0. Continuous variables are reported as mean ± standard deviation and were compared using Welch's independent-samples t tests. Results include the lithium-minus-valproate mean difference, 95% confidence interval, t statistic

with Satterthwaite degrees of freedom, two-sided p value, and Hedges' g. Metabolic syndrome prevalence was compared using Pearson's chi-square test. Risk differences, risk ratios, and odds ratios for valproate versus lithium were reported with 95% confidence intervals. Baseline categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test. Statistical significance was set at $p < 0.05$. Analyses were unadjusted because participant-level metabolic data were unavailable for multivariable modeling.

Ethics

Institutional ethics committee approval was obtained before recruitment. Participants received study information and provided written informed consent. Participation was voluntary and withdrawal did not affect clinical care.

RESULTS

Participant characteristics

All 100 participants were included in the analysis. The groups did not differ significantly in age, sex, education, socioeconomic status, illness duration, or treatment duration. Marital status differed between groups, with a higher proportion of married participants in the lithium group. Adjusted analysis was not possible.

Table 2: Sociodemographic and clinical characteristics by treatment group

Characteristic	Lithium (n=51)	Sodium valproate (n=49)	Test statistic	p value
Age, years	32.67 ± 9.37	33.59 ± 9.06	t=-0.50; df=98.0	0.619
Duration of illness, years	5.10 ± 2.58	5.40 ± 2.84	t=-0.55; df=96.2	0.582
Duration of treatment, years	5.10 ± 2.93	5.27 ± 2.78	t=-0.30; df=98.0	0.767
Age group, n (%)	18-25: 15 (29.4); 26-35: 14 (27.5); 36-45: 18 (35.3); 46-50: 4 (7.8)	18-25: 12 (24.5); 26-35: 17 (34.7); 36-45: 16 (32.7); 46-50: 4 (8.2)	χ^2=0.70; df=3	0.873
Sex, n (%)	Male: 27 (52.9); Female: 24 (47.1)	Male: 25 (51.0); Female: 24 (49.0)	Fisher's exact test	1.000
Education, n (%)	None: 13 (25.5); Primary: 10 (19.6); Secondary: 9 (17.6); Higher: 19 (37.3)	None: 15 (30.6); Primary: 12 (24.5); Secondary: 9 (18.4); Higher: 13 (26.5)	χ^2=1.41; df=3	0.703
Marital status, n (%)	Single: 9 (17.6); Married: 35 (68.6); Separated: 7 (13.7)	Single: 17 (34.7); Married: 21 (42.9); Separated: 11 (22.4)	χ^2=6.81; df=2	0.033
Socioeconomic status, n (%)	Lower: 25 (49.0); Middle: 9 (17.6); Upper: 17 (33.3)	Lower: 18 (36.7); Middle: 16 (32.7); Upper: 15 (30.6)	χ^2=3.19; df=2	0.203
Occupation, n (%)	Clerk: 8 (15.7); Labourer: 18 (35.3); Manager: 9 (17.6); Professional: 6 (11.8); Unemployed: 10 (19.6)	Clerk: 5 (10.2); Labourer: 9 (18.4); Manager: 10 (20.4); Professional: 16 (32.7); Unemployed: 9 (18.4)	χ^2=8.31; df=4	0.081

Values are mean ± SD or n (%). Tests are unadjusted and two-sided.

Continuous cardiometabolic outcomes

None of the six summarized cardiometabolic measurements differed significantly between treatment groups. All Hedges' g estimates were small, and the confidence intervals were compatible with modest differences in either direction.

Table 3: Continuous cardiometabolic outcomes

Outcome	Lithium mean ± SD	Valproate mean ± SD	Li-VPA difference (95% CI)	Welch t (df)	p value	Hedges' g
Systolic blood pressure, mmHg	122.33 ± 22.84	125.37 ± 22.74	-3.04 (-12.09 to 6.01)	-0.67 (97.9)	0.506	-0.13
Diastolic blood pressure, mmHg	79.88 ± 13.48	83.59 ± 15.99	-3.71 (-9.59 to 2.17)	-1.25 (93.9)	0.214	-0.25
Fasting glucose, mg/dL	110.95 ± 22.20	109.13 ± 25.50	1.82 (-7.69 to 11.33)	0.38 (95.0)	0.705	0.08
Waist circumference, cm	96.65 ± 13.89	94.08 ± 13.70	2.57 (-2.91 to 8.05)	0.93 (97.9)	0.354	0.18
Triglycerides, mg/dL	152.93 ± 55.07	148.97 ± 57.68	3.96 (-18.44 to 26.36)	0.35 (97.3)	0.726	0.07
HDL cholesterol, mg/dL	51.68 ± 17.79	47.54 ± 18.12	4.14 (-2.99 to 11.27)	1.15 (97.7)	0.252	0.23

Positive mean differences indicate higher values in the lithium group. HDL, high-density lipoprotein.

Metabolic syndrome prevalence

Metabolic syndrome occurred in 20 of 51 lithium-treated participants (39.2%) and 23 of 49 sodium-valproate-treated participants (46.9%). The unadjusted difference was not statistically significant. Confidence intervals were wide and did not exclude a clinically meaningful increase or

decrease in risk; the findings therefore should not be interpreted as evidence of equivalence.

Table 4: Effect estimates for metabolic syndrome

Measure	Estimate	Precision or significance	Interpretation
Prevalence in lithium group	20/51 (39.2%)	Reference group	Not applicable
Prevalence in valproate group	23/49 (46.9%)	Observed exposure group	Not applicable
Absolute risk difference	7.72 percentage points	95% CI -11.64 to 27.08	Valproate minus lithium
Risk ratio	1.20	95% CI 0.76 to 1.88	Valproate relative to lithium
Odds ratio	1.37	95% CI 0.62 to 3.03	Valproate relative to lithium
Pearson test	χ^2=0.61; df=1	p=0.435	Two-sided unadjusted comparison

DISCUSSION

This cross-sectional study found a high prevalence of metabolic syndrome in both treatment groups: 39.2% among participants receiving lithium and 46.9% among those receiving sodium valproate. The point estimate was higher with valproate, but the confidence interval was wide and the comparison was not statistically significant. No individual continuous component differed significantly, and all standardized mean differences were small.

The central finding is therefore the cardiometabolic burden across the cohort rather than a demonstrated between-drug difference. Meta-analyses have shown that metabolic syndrome is common in bipolar disorder and is influenced by antipsychotic exposure, age, illness duration, smoking, and the definition used.[5,6] The prevalence observed here is compatible with a high-risk clinical population even though participants with previously diagnosed diabetes or hypertension were excluded.

Prior medication-specific evidence is mixed. Chang and colleagues reported higher insulin, triglyceride, and body mass index values and lower HDL cholesterol among valproate-treated patients compared with drug-free bipolar patients and healthy controls.[10] Conversely, Prillo and colleagues found high rates of obesity and metabolic syndrome in bipolar disorder without a clear excess associated with lithium use.[11] The present estimates are compatible with either a modest valproate excess or no important difference because the confidence intervals are imprecise.

Potential mechanisms of valproate-associated metabolic change include increased appetite and weight, altered insulin sensitivity, adipokine signaling, and hepatic lipid metabolism. Lithium-related weight change may involve appetite, thirst, fluid balance, thyroid effects, and individual susceptibility. These medication effects interact with lifestyle, sleep, illness-related inactivity, and concomitant antipsychotic treatment, making causal attribution difficult in naturalistic cross-sectional samples.

The operational definition deserves particular attention. The study used a single waist threshold of more than 90 cm and a single HDL threshold below 40 mg/dL. Standard NCEP and harmonized criteria use sex-specific HDL thresholds and population-specific waist thresholds.[7,8] The study definition may therefore classify women differently from contemporary criteria and limits direct comparison with other prevalence estimates.

Exclusion of participants with diagnosed diabetes or hypertension probably produced conservative prevalence estimates and may have attenuated between-group differences. Conversely, fasting glucose means were above 100 mg/dL in both groups, emphasizing the need for early preventive care even among patients without established diagnoses. The lack of individual-level data prevented adjustment for age, sex, education, socioeconomic status, antipsychotic exposure, smoking, physical activity, family history, and treatment duration.

Clinically, metabolic monitoring should not be restricted to antipsychotic-treated patients. Baseline and periodic assessment should include weight or body mass index, waist circumference, blood pressure, fasting glucose or glycated hemoglobin, triglycerides, and HDL cholesterol. Abnormalities should prompt lifestyle intervention, medication review, and coordination with primary care. Mood stabilizer selection should balance psychiatric efficacy, suicide prevention, reproductive safety, organ toxicity, and cardiometabolic vulnerability.[3,4]

Metabolic syndrome also has potential neuropsychiatric relevance. It has been associated with poorer executive function and adverse clinical outcomes in bipolar disorder.[12,13] Integrated management of cognitive and metabolic health may therefore improve both physical and functional outcomes.

Future studies should use prospective designs with pretreatment measurements, standardized sex- and population-specific criteria, medication doses and serum concentrations, and detailed documentation of concomitant treatment. Larger samples and multivariable or propensity-score analyses are required to estimate whether lithium and valproate differ independently in metabolic risk.

Strengths and limitations

- The study directly compared two widely used mood stabilizers and assessed all five components of metabolic syndrome.
- The cross-sectional design cannot establish whether metabolic abnormalities preceded or followed treatment, and pretreatment measurements were unavailable.

- The modest sample size resulted in wide confidence intervals, and the study was not designed to demonstrate equivalence or non-inferiority.
- Convenience sampling from a single tertiary-care center limits generalizability.
- Exclusion of participants with diagnosed diabetes or hypertension probably lowered the observed prevalence and limits applicability to patients with established cardiometabolic disease.
- Potential confounders, including antipsychotic use, dose, serum concentration, thyroid function, diet, physical activity, smoking, sleep, family history, and socioeconomic exposures, were not adequately controlled.
- The modified criteria used single thresholds for waist circumference and HDL cholesterol, rather than sex-specific and harmonized thresholds.

CONCLUSION

Metabolic syndrome affected approximately two-fifths of lithium-treated participants and nearly one-half of sodium-valproate-treated participants. The study did not demonstrate a statistically significant difference in prevalence or individual components, but wide confidence intervals prevent a conclusion of equivalence. The findings support systematic cardiometabolic surveillance and prevention for patients receiving either mood stabilizer.

REFERENCES

1. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet. 2016;387(10027):1561-1572. doi: 10.1016/S0140-6736(15)00241-X. Available from: https://doi.org/10.1016/S0140-6736(15)00241-X.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington (VA): American Psychiatric Association; 2013. doi: 10.1176/appi.books.9780890425596. Available from: https://doi.org/10.1176/appi.books.9780890425596
3. Keramatian K, Chithra NK, Yatham LN. The CANMAT and ISBD guidelines for the treatment of bipolar disorder: summary and a 2023 update of evidence. Focus (Am Psychiatr Publ). 2023;21(4):344-353. doi: 10.1176/appi.focus.20230009. Available from: https://doi.org/10.1176/appi.focus.20230009
4. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. CANMAT and ISBD 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97-170. doi: 10.1111/bdi.12609. Available from: https://doi.org/10.1111/bdi.12609
5. Vancampfort D, Vansteelandt K, Correll CU, Mitchell AJ, De Herdt A, Sienaert P, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. Am J Psychiatry. 2013;170(3):265-274. doi: 10.1176/appi.ajp.2012.12050620. Available from: https://doi.org/10.1176/appi.ajp.2012.12050620
6. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry. 2015;14(3):339-347. doi: 10.1002/wps.20252. Available from: https://doi.org/10.1002/wps.20252
7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III. JAMA. 2001;285(19):2486-2497. doi: 10.1001/jama.285.19.2486. Available from: https://doi.org/10.1001/jama.285.19.2486
8. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement. Circulation. 2009;120(16):1640-1645. doi: 10.1161/CIRCULATIONAHA.109.192644. Available from: https://doi.org/10.1161/CIRCULATIONAHA.109.192644
9. Grover S, Malhotra N, Chakrabarti S, Kulhara P. Metabolic syndrome in bipolar disorders. Indian J Psychol Med. 2012;34(2):110-118. doi: 10.4103/0253-7176.101767. Available from: https://doi.org/10.4103/0253-7176.101767
10. Chang HH, Yang YK, Gean PW, Huang HC, Chen PS, Lu RB. The role of valproate in metabolic disturbances in bipolar disorder patients. J Affect Disord. 2010;124(3):319-323. doi: 10.1016/j.jad.2009.12.011. Available from: https://doi.org/10.1016/j.jad.2009.12.011
11. Prillo J, Fotso Soh J, Park H, Beaulieu S, Linnaranta O, Rej S. Obesity and metabolic comorbidity in bipolar disorder: do patients on lithium comprise a subgroup? A naturalistic study. BMC Psychiatry. 2021;21(1):558. doi: 10.1186/s12888-021-03572-w. Available from: https://doi.org/10.1186/s12888-021-03572-w
12. Bai YM, Li CT, Tsai SJ, Tu PC, Chen MH, Su TP. Metabolic syndrome and adverse clinical outcomes in patients with bipolar disorder. BMC Psychiatry. 2016;16:448. doi: 10.1186/s12888-016-1143-8. Available from: https://doi.org/10.1186/s12888-016-1143-8
13. Dalkner N, Bengesser SA, Birner A, Fellendorf FT, Fleischmann E, Grossschadl K, et al. Metabolic syndrome impairs executive function in bipolar disorder. Front Neurosci. 2021;15:717824. doi: 10.3389/fnins.2021.717824. Available from: https://doi.org/10.3389/fnins.2021.717824
14. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429-435. doi: 10.1192/bjp.133.5.429. Available from: https://doi.org/10.1192/bjp.133.5.429
15. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23(1):56-62. doi: 10.1136/jnnp.23.1.56. Available from: https://doi.org/10.1136/jnnp.23.1.56
16. Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology statement: guidelines for reporting observational studies. PLoS Med. 2007;4(10):e296. doi: 10.1371/journal.pmed.0040296. Available from: https://doi.org/10.1371/journal.pmed.0040296.