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Review Article

The centrality of mood symptoms in bipolar disorder: A systematic review of network analysis studies

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The centrality of mood symptoms in bipolar disorder: A systematic review of network analysis studies

Short Title: Centrality of Mood Symptoms in Bipolar Disorder

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Abstract

Background: Network analysis offers a novel framework for understanding the dynamic interconnections among symptoms, moving beyond traditional approaches to identify central symptoms that drive illness courses and treatment response. Recent studies have used this method to examine how symptoms group together and influence one

another in unipolar depression; however, its application to bipolar disorder (BD) remains limited.

Objectives: This review systematically examines literature that applied network analysis methodology to BD to investigate central symptoms and their interrelationships within this condition.

Methods: A systematic search of PubMed, Web of Science, PsycINFO, Embase, and Scopus databases was conducted from inception to January 2026 to identify studies that applied network analysis to examine mood symptom centrality in individuals with BD.

Results: Eleven studies met the inclusion criteria, encompassing diverse BD populations including young adults, and mixed-age samples across different illness phases. Across depressive symptom networks, depressed mood, low energy, and negative self-concept emerged as central nodes, while high energy, pressured speech, and elevated self-esteem were most central in networks of manic symptoms. Methodological and reporting heterogeneity, including variations in network estimation techniques, sample characteristics, and symptom assessment instruments, limited the comparability of findings.

Conclusion: These findings advance understanding of central symptoms and network structures in BD, revealing consistent patterns across depressive and manic symptom networks. Identifying key symptom patterns and their interconnections may inform future symptom-targeted research and enhance understanding of symptom dynamics in BD.

Keywords: *Bipolar disorder; mood disorders; network analysis; symptom assessment; depressive symptoms; manic symptoms.*

1. Introduction

Bipolar disorder (BD) is a chronic mood disorder that affects around 2.4% of the global population.[1] Beyond episodic mood symptoms, individuals with BD frequently experience social, occupational, and interpersonal impairments that persist even during periods of euthymia.[2,3] The burden of BD is further exacerbated by its clinical heterogeneity, including variability in symptom severity, episode duration, treatment

response, and the presence of comorbid conditions like anxiety, substance use, and cardiovascular disease.[5,6] Certain illness characteristics such as early-onset and predominant depression polarity are associated with worse outcomes, including delayed diagnosis and heightened suicide risk. Consequently, these inter- and intra-individual variations contribute to unpredictable illness trajectories and high relapse rates, with up to 60% of individuals experiencing recurrent mood episodes within one year after hospitalization despite appropriate care.[7]

Given this individual heterogeneity, standardized treatment guidelines often fall short. For example, individuals with early-onset BD, psychotic features, or comorbidities often require more intensive monitoring and integrated care.[8,9,]**Erro! Fonte de referência não encontrada.** Effective management typically involves a multi-modal approach, combining mood stabilizers and/or antipsychotics with evidence-based psychotherapies.**Erro! Fonte de referência não encontrada.** However, even with guideline-concordant care, relapse remains common, and only around 30% of patients achieve full symptomatic and functional recovery over two years.[11,12] **Erro! Fonte de referência não encontrada.**

Network analysis offers a promising framework for understanding the multifaceted symptom structure of BD. Drawing from network theory, which conceptualizes complex systems as sets of interconnected elements (nodes) linked by relationships (edges), this approach models individual symptoms as directly interacting components of a system. Within this framework, mental disorders emerge from symptom-symptom interactions rather manifestations of an underlying latent disease process (see Figure 1).**Erro! Fonte de referência não encontrada.**[13,14] BD is particularly well suited to network approaches because symptoms cluster differently across mood states, and may reflect alternative stable patterns - known as attractor states - that are sustained by symptoms reinforcing one another.[15,16]

Traditional statistical approaches to symptom assessment, aggregate symptoms into total scores, which can obscure individual differences in symptom interrelationships and hinder identifying patterns that drive relapse or poor outcomes.[17]**Erro! Fonte de referência não encontrada.** For example, fatigue and impaired concentration may reinforce each other in a given individual; targeting one may disrupt the network and improve functioning.[17]

Importantly, symptom centrality in a network should be interpreted as a statistical property indicating how strongly a symptom is connected to others within the network structure.[18] **Erro! Fonte de referência não encontrada.**By mapping these structural features, network analysis may help explain common patterns of symptom organization associated with illness severity or persistence.

Emerging evidence suggests that central symptoms may not be consistent across individuals; instead, networks appear more stable within patients than between patients over time.[19,20] [1920] This aligns with the idea that BD involves interacting symptoms that form person specific patterns and can change over time. It also highlights the potential value of longitudinal and person-specific network approaches in BD, which could support personalized monitoring or adaptive interventions that better track shifting symptom drivers over time. Ultimately, targeting central symptoms holds promise for improving treatment precision,[20,21] though empirical evidence supporting their effectiveness as intervention targets remains limited.[21,22] Given the complexity of BD and the prevalence of episode recurrence, it is a priority to enhance our understanding of symptom interconnectivity. This systematic review aims to synthesize existing literature on the application of network analysis in BD, with a focus on understanding interconnectivity of mood symptoms. By integrating findings across studies, this review provides the first systematic synthesis of symptom-level centrality patterns in BD network research, identifying commonalities and inconsistencies across methodologies.

Figure 1. Overview of the symptom network analysis workflow
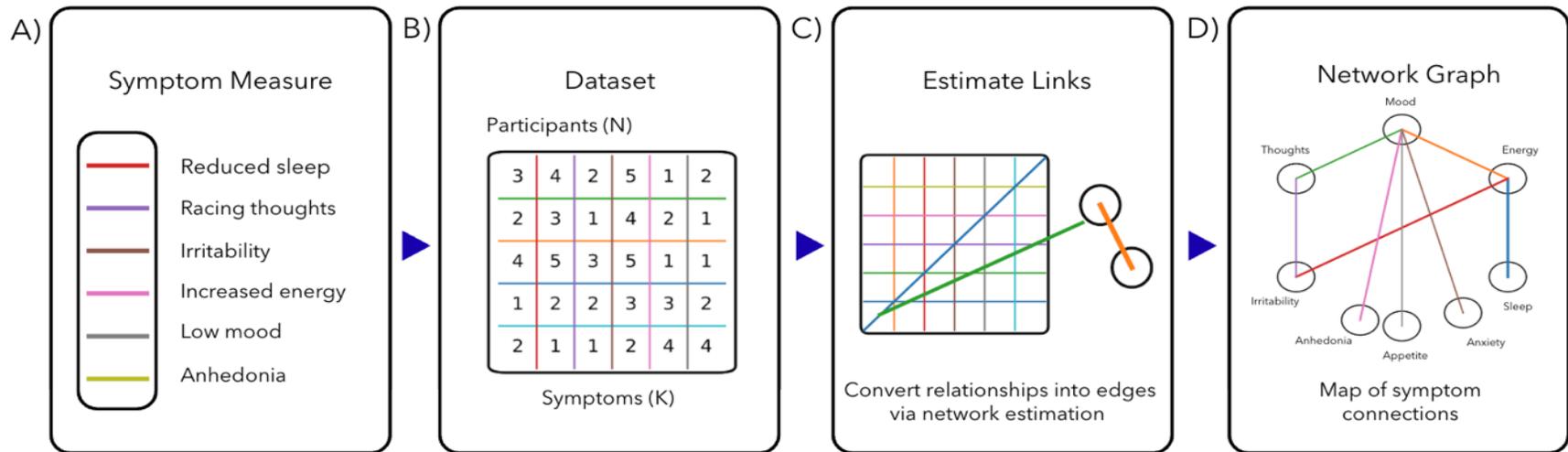
Workflow: questionnaire → dataset → estimated symptom associations → symptom network visualization

(A) Symptoms are assessed using a standardized measure. (B) Symptom scores are organized into a dataset with participants (N) by symptoms (K). (C) Symptom-symptom relationships are estimated using a network modeling approach to derive edges. (D) Estimated associations are visualized as a network graph, where nodes represent symptoms and edges represent statistical associations between symptoms.

2. Methods

2.1 Search Protocol

The review protocol was preregistered on Open Science Framework (OSF; https://osf.io/t7wfc/overview). Studies were searched, screened, and selected for inclusion following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Supplementary Material, Table S1) guidelines.[23] **Erro! Fonte de referência não encontrada.** A systematic literature search was conducted on 5 scientific databases (Web of Science, PubMed, PsycINFO, Embase, and Scopus) from inception to January 2026. The search strategy incorporated terms relating to network analysis and bipolar disorder (see Supplementary Material, Section 1.1). The reference lists of included studies were also screened to identify additional relevant studies.

2.2 Definition of Mood Symptoms

For the purposes of this review, we focus on the core mood episode symptoms as defined by *the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), which includes manic, hypomanic, and major depressive episodes[24,25]. Given the variability in symptom assessment across bipolar network studies, we restricted inclusion to networks modeling core DSM-5 mood symptoms to improve comparability and focus on centrality patterns most directly tied to bipolar clinical phenomenology.

2.3 Eligibility and Population Criteria

Articles were considered eligible if they used network analysis as a primary method to examine mood symptom interrelationships or symptom-level centrality in individuals with BD. Only original, peer-reviewed empirical articles published in English were included. Studies were excluded if they focused on non-BD populations, did not report symptom-level network models, or examined biological, neuroimaging, or non-mood variables (i.e. sleep, cognition, psychosocial functioning). Detailed inclusion and exclusion criteria are provided in the Supplementary Materials (Section 1.2 and Section 1.3). Notably, DSM-5 mood criteria that overlap with cognitive functioning (e.g., distractibility, concentration difficulties) were included when assessed within

standardized mood scales (e.g., MADRS, YMRS); studies examining separate cognitive domains or neuropsychological batteries were excluded.

2.4 Network Analysis Metrics

The most influential symptoms in network analysis are identified using centrality metrics (see Figure 2). In this review, symptom centrality rankings were used descriptively to summarize which mood symptoms appeared most strongly interconnected across studies. Strength centrality served as the primary metric given its common use and relative stability. Betweenness and closeness were also reviewed to explore whether similar symptom patterns emerge across these alternative measures. Network stability was assessed to evaluate the robustness and consistency of the estimated network structure using the correlation stability (CS) coefficient. A CS coefficient < 0.25 suggests low stability, between 0.25 and 0.5 indicates moderate stability, and values > 0.5 indicate strong stability, with higher coefficients indicating estimates are robust and less susceptible to sampling variability.[26] [26]Edge weights estimate the strength of the association between symptoms at a given timepoint. Examining robust edges may identify patterns of symptom co-occurrence that characterize the structure of the disorder.

2.5 Methodological Quality Assessment and Synthesis Strategy

We appraised methodological quality and risk of bias using predefined domains tailored to recommended reporting practices for psychiatric symptom network analyses (e.g., node validity, sample/design adequacy, model specification, stability/uncertainty, interpretability, and transparency). Studies were rated as low/moderate/high concern (Supplementary Table S2), and ratings were used to contextualize centrality findings in the narrative synthesis. Given heterogeneity in estimation approaches, symptom operationalization, centrality metrics, and samples, quantitative pooling was not feasible.[27]

Figure 2. *Description of Network Analysis Metrics[28]*

NETWORK FEATURE	DEFINITION	INTERPRETATION	EXAMPLE
STRENGTH (centrality)	Sum of a symptom's associations with all others in the network.	The degree to which a symptom is statistically interconnected with other symptoms within the network. High strength reflects greater connectivity.	E.g., low mood
BETWEENESS (centrality)	Number of instances a symptom lies on the shortest path between other symptoms in a network, reflecting potential connectivity between symptom groups	Describes the extent to which a symptom bridges another one within the network *(e.g., depressive and manic).*	E.g., decreased need for sleep positioned between grandiosity and goal-directed activity in a manic symptom
CLOSENESS (centrality)	Calculated as the inverse of the average distance from one symptom to all others.	How proximally a symptom is positioned relative to others in the network based on path length.	E.g., sleep disturbance with high closeness
EDGE (association)	Connection between two symptoms in the network. Visualized through line thickness or colour intensity.	The statistical association between two symptoms after controlling for the other ones in the network; edge strength reflects association magnitude.	E.g., a strong edge between insomnia and fatigue.

A summary of key symptom network metrics, organized by network feature, definition, interpretation, and a brief example. The figure describes strength, betweenness, and closeness, as well as one edge-level feature (edges/associations). A symptom example accompanies each metric.[28]

3. Results

Database searches yielded 17,738 records, with 3,809 duplicates removed and 13,929 articles screened (Figure 3). After screening and full-text review, 11 studies met inclusion criteria and were retained for data extraction.

Figure 3. PRISMA flow diagram illustrating the screening, eligibility assessment, and study selection process.
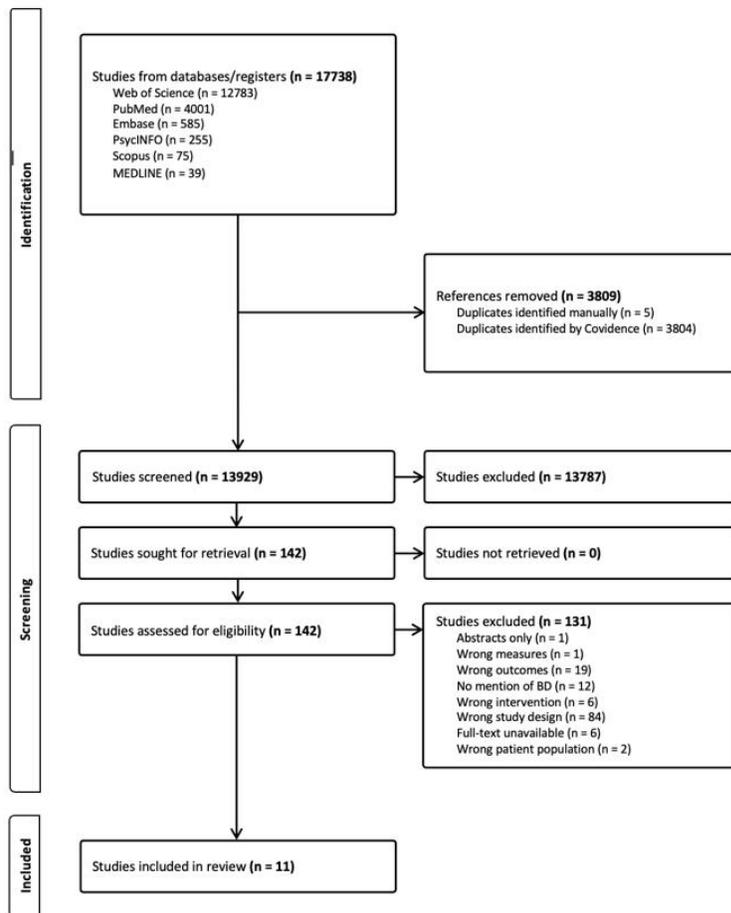
3.1 Network Study Characteristics

3.1.1 Sample characteristics

Across studies, samples were primarily recruited from clinical settings. Sample sizes ranged from 100 to 898 and mean participant age ranged from 26.4 to 50.6, with younger samples potentially capturing earlier illness stages compared to older cohorts. Gender distribution varied considerably (35.0% to 72.2% female), though most studies did not examine sex-specific network differences. Table 1 summarizes key demographic and clinical characteristics of the included samples.

Table 1. *Study Characteristics of Included Samples*

Source					Study Characteristics						
	Sample				Study Design	Age (M)	% female	Education		Employed	Marital Status	Family Psychiatric History
	BD(*n*)	Subtype	Other	Site		Years		Years	%	%	%	%
Liu et al.[29]	898	BD-I	N/A	Wuhan Mental Health Center	Cross-Sectional	39.4	NR	13.1	NR	52.4	54.1	26.5
Bai et al.[30]	423	BD-I *n=191* BD-II *n=232*	N/A	Guangdong Mental Health Center	Cross-Sectional	35.4	62.6	NR	NR	NR	NR	NR
Yang et al.[31]	120	BD-I *n= 92* BD-II *n= 28*	N/A	Hospital of Guangzhou Medical University	Cross-sectional	26.5	35.0	BD-I 12.36 BD-II 12.25	NR	53.3	NR	NR
Lee et al.[32]	516	BD-I BD-II	MDD *n=322*	Seoul National University Bundang Hospital	Cross-Sectional	34.4	72.2	NR	High school/ Below 29.5; Other 68.3	56.6	26.7	52.1
Corponi et al.[33]	718	BD-I BD-II	MDD *n=2040*	BRIDGE-II-MIX study	Longitudinal	44.4	64.2	NR	NR	NR	NR	NR
Briganti et al.[34]	100	BD-I	N/A	University Hospital Brugmann, Brussels	Cross-Sectional	44.5	47.0	NR	NR	NR	NR	NR

	BD(n)											
Wrobel et al.[35]	476	BD-I BD-II	N/A	Bipolar CHOICE trial	Longitudinal	38.9	59.2	NR	NR	NR	NR	NR
McNally et al.[36]	486	BD-I *n=333* BD-II *n=153*	N/A	Bipolar CHOICE trial	Cross-Sectional	39.0	59.0	NR	NR	NR	NR	NR
Koenders et al.[37]	125	BD-I BD-II	N/A	Leiden University Medical Center	Longitudinal	50.6	60.0	NR	Primary 20; Secondary 32; Higher 47.2	NR	NR	NR
Wrobel et al.[38]	543	BD-I BD-II BD-NOS	Schizoaffective disorder (bipolar subtype)	Heinz C. Prechter Longitudinal Study of BD	Cross-Sectional	50.3	67.2	NR	NR	NR	NR	NR
Li et al.[39]	312	BD-I BD-II	N/A	Changchun Mental Hospital	Cross-sectional and longitudinal	Manic = 38.1 Depressive = 40.7	Manic = 54.4 Depressive = 49.1	NR	Manic = Elementary or below 5.4; Secondary 62.5; Post-secondary 32.2 Depressive = Elementary or below 13.2; Secondary 57.5; Post-secondary 29.3	NR	Manic: 36.9 Depressive: 43.4	NR

Legend: BD = bipolar disorder; BD(n) = number of participants with BD; BD-I = Bipolar I Disorder; BD-II = Bipolar II Disorder; BD-NOS = Bipolar Disorder Not Otherwise Specified; MDD = Major Depressive Disorder; N/A = Not Applicable; NR = Not Reported; M = Mean.

3.1.2 Diagnosis and Assessment

All included studies confirmed a diagnosis of BD-I and/or BD-II, using either the DSM or International Classification of Diseases (ICD) criteria. Several studies also used validated structured interviews, such as the Mini-International Neuropsychiatric Interview (MINI) [32,35,31], and Structured Clinical Interview for DSM (SCID).[31,36 25]

Symptom assessment tools varied considerably, with important implications for network comparisons. Manic symptoms were most frequently assessed with the Young Mania Rating Scale (YMRS), a well-validated, clinician rated measure that appeared in three studies.[29,34,37] Two studies used the Bipolar Inventory of Symptoms Scale (BISS) [40] which captures both depressive and manic symptoms [35,36]. Other studies employed a range of clinician-rated and self-report measures, including the Hypomania Checklist (HCL-32) [30] Zung Self-Rating Depression Scale, and structured DSM-based assessments. [30,31,32,33,38,39] Table 2 summarizes diagnostic frameworks, symptom measures, network estimation methods, and stability metrics across studies. Further methodological details on network estimation, stability, and reproducibility are reported in Supplementary Material (Sections 1.8-1.10), and additional information on the psychometric properties of included measures is provided in Supplementary Material (Sections 1.7, 2.3, and Table S2).

Table 2. *Network Analysis Parameters of Included Bipolar Disorder Samples*

Source	BD Symptoms			Network Analysis							Open Access
	Measure	Diagnostic Manual	Mood State	Characteristics		Estimation				Stability	
				Centrality Measures	Structure Differences	Parameters	Correlation Technique	Analytical Model	CS Coefficient	Boot Strapping	
Briganti et al.[34]	YMRS	DSM-IV	Mania	Strength	p = 0.0014	None	Spearman	GGM, GVAR (temporal)	NR	Node predictability and NCT w/ bootstrapping	Yes
Liu et al.[29]	YMRS PANSS-AG	ICD-10	Mania	Strength Expected Influence	Not significant	LASSO + EBIC	Polychoric	GGM	0.75	Case-dropping bootstrap	Yes
Bai et al.[30]	HCL	DSM-IV/ ICD-10	Hypomania	Strength	p = 0.02	LASSO + EBIC	Dichotomous	Ising	BD-I: 0.126 BD-II: 0.362	Case-dropping bootstrap	Yes
Lee et al.[32]	Zung Self Rating Scale	DSM-V + MINI	Depression	Strength Betweenness Closeness	Not significant	EBIC	Partial Correlation	GGM via glasso	0.595	Case-dropping bootstrap	Yes
Corponi et al.[33]	RBDC mixed features	DSM-IV-R for MDE	Depression	Strength	Not significant	LASSO + EBIC	Spearman	Ising	0.75	Case-dropping bootstrap	No
Wrobel et al.[38]	PHQ-9 HAMD-17	DSM-IV	Depression	Strength Expected Influence	Childhood trauma (with vs without): p = 0.042	LASSO	Polychoric	GGM	0.36 (Any childhood trauma) 0.44 (emotional trauma) 0.13 (no childhood trauma) 0.20 (sexual abuse)	Bootstrapped CIs	Yes
Wrobel et al.[35]	BISS	DSM-IV-TR + MINI	Mania/ Depression	Strength Expected Influence	Not significant	LASSO	Polychoric	GGM	Mania: 0.28 (child abuse) 0.20 (no child abuse) Depression: 0.44 (any child abuse)	Bootstrapped CIs	Yes
McNally et al.[36]	BISS	DSM-V + SCID	Mania/ Depression	Strength Expected Influence	NR	GGM, DAG (Baysein), EBIC	Polychoric	GGM, DAG	Mania: 0.52 Depression: 0.75	Bootstrapped CIs	Yes

Koenders et al.[37]	QIDS-SR YMRS	DSM-IV-R + MINI- PLUS	Mania/ Depression	Strength Betweenness	Cycling: p = 0.250 Depressed: p = 0.171 Stable: p = 0.186	No Regularization	Spearman	Weighted Undirected Network	NR	Bootstrapped CIs	Yes
Yang et al.[31]	BPSS-R	DSM-IV-TR + SCID	Mania/ Depression	Strength Betweenness Closeness	NR	LASSO + EBIC	Dichotomous	Ising	0.675	Case-dropping bootstrap	No
Li et al.[39]	BRMS HAMD HAMA	DSM-V	Mania	Strength Betweenness	Not significant	LASSO + EBIC	Polychoric	GGM	NR	Case-dropping bootstrap	No

Legend: YMRS = Young Mania Rating Scale; PANSS-AG = Positive and Negative Syndrome Scale–Aggression subscale; HCL-32 = Hypomania Checklist (32-item); BISS = Bipolar Inventory of Symptoms Scale; PHQ-9 = Patient Health Questionnaire–9; HAMD-17 = Hamilton Depression Rating Scale–17 item; HAMA = Hamilton Anxiety Rating Scale; BRMS = Bech–Rafaelsen Mania Scale; BPSS-R = Bipolar Prodrome Symptom Scale–Retrospective; QIDS-SR = Quick Inventory of Depressive Symptomatology–Self Report; MINI/MINI-PLUS = Mini-International Neuropsychiatric Interview/MINI-PLUS; SCID = Structured Clinical Interview for DSM; MDE = Major Depressive Episode; RBDC = Rapidly Cycling Bipolar Disorder; GGM = Gaussian Graphical Model; DAG = Directed Acyclic Graph; GVAR = Graphical Vector Autoregression; EBIC = Extended Bayesian Information Criterion; LASSO = Least Absolute Shrinkage and Selection Operator; glasso = graphical lasso; CS = correlation stability (coefficient); NCT = Network Comparison Test; CI/CIs = confidence interval(s); NR = Not Reported.

3.1.3 Centrality stability

Network stability varied substantially across studies and appeared to be linked to sample size and network density. CS coefficients ranged from 0.126 (BD-I hypomanic network, n=191) [30] to 0.75 (depression networks, n=898) [29], with only four studies reporting coefficients meeting the recommended threshold of >0.5[31,32,33,36] (see Table 2).

Smaller samples demonstrated lower network stability (CS<0.25) [30], whereas larger samples achieved at least moderate stability (CS>0.35)[35]. This pattern may reflect that current sample sizes may be insufficient for stable estimation of manic symptom networks, which tend to be more sparsely connected than depressive networks.

Notably, four studies identifying central symptoms in manic networks had CS coefficients below 0.25 or unreported,[30,34,35,39] meaning their centrality rankings should be interpreted cautiously. In contrast, studies examining depressive networks in BD populations demonstrated stronger stability, with some achieving CS values approaching 0.60.[32] This suggests that bipolar depression networks may be more reliably estimated than mania networks, potentially reflecting more consistent symptom patterns during depressive states.

3.1.4 Study Heterogeneity

Network estimation methods varied substantially, likely contributing to the heterogeneity in symptom centrality across studies. Some studies estimated regularized partial correlation networks with LASSO, while others applied Ising models for binary symptom data (see Table 2). These approaches reflect fundamentally different network frameworks: LASSO regularization is typically applied to Gaussian graphical models (GGM) to estimate partial correlations between continuous symptom scores, whereas Ising models estimate associations between binary (present/absent) symptom states.

When comparing Table 2 and Table 3, studies using GGM with LASSO more frequently identified affective symptoms as most central, while studies using Ising models more often found behavioural activation symptoms as most central. This pattern

may reflect how binarization of symptom data emphasizes the presence or absence of observable behaviours over subjective mood states, though this relationship is not absolute. For example, Bai et al.[30] used Ising models and still found self-confidence central in BD-I, suggesting that the estimation method alone does not determine centrality findings and likely interacts with sample characteristics and other methodological factors.

Centrality indices also varied across studies. All studies reported strength as the main centrality measure, while betweenness (n=4)[31,32,37,39] and closeness (n=2)[31,32] were reported less consistently. Where reported, these metrics provided further insight into different properties of symptom connectivity.[41]

3.1.5 Symptom Strength Centrality Rankings
Depression Symptoms

Across studies including participants experiencing a depressive episode (n=8), depression symptom networks commonly demonstrated depressed mood, low energy, and self-evaluative symptoms as highly connected nodes (hubs). These symptoms formed the core structure of most depression networks. Depressed mood was reported among the three most central symptoms in six studies, [31,32,35,38] ranking as the most central node in three [32,35,38]. Low energy/anergia was similarly reported among the top three central symptoms in four studies, [31,35,37] with three studies ranking this symptom as the most central node.[35-37] Symptoms reflecting low self-esteem, such as feelings of inadequacy, were frequently ranked second or third in centrality, indicating their role as highly connected but secondary nodes within the depression network organization.[35-37] From a systems perspective, these symptoms may represent high-connectivity components of depressive attractor states, contributing to the stability of the depression network. The centrality rankings of the remaining symptoms (e.g. suicidal thoughts, feelings of emptiness) varied by study. Table 3 presents a direct comparison of the most central symptoms of depression and mania across included networks.

The network structure of depression symptoms varied across groups defined by childhood trauma and abuse history. [35,38] One study compared central symptoms of

depression in individuals with BD who had a history of child abuse to those without such history.[35] Among participants without a history of childhood abuse, depressed mood was the most central symptom, with low energy ranked second, and anhedonia third. For individuals with a history of childhood abuse, low energy was ranked as most central, followed by feelings of inadequacy and pessimism. Another study stratified network results by childhood trauma history (any vs. no trauma and assessment type (clinician-rated vs. self-rated).[38] In contrast to the previous study[35], centrality patterns were largely consistent with respect to the highest-ranked node, with depressed mood occupying the most central position across all trauma-defined networks. The only exception was the clinician-rated network for individuals without childhood trauma, in which the work and activity engagement node, derived from the Hamilton Depression Rating Scale (HAMD), emerged as most central. More distinct differences emerged for the second- and third-most central nodes, with centrality patterns shifting according to childhood trauma history and assessment type. For instance, in the self-rated network of participants without childhood trauma, loss of interest was the second most central symptom, while feelings of worthlessness occupied this position in the self-rated network of participants with childhood trauma. Centrality patterns from these studies suggest an impact of early-life trauma on depression network organization, with negative self-evaluative nodes demonstrating slightly higher centrality in participants with childhood trauma histories, and depressed mood remaining a high-connectivity node in most networks.

Mania/Hypomania Symptoms

Across studies that included participants in a manic/hypomanic state (n = 9), symptoms related to increased energy/motor activity, psychomotor arousal, and elevated self-esteem occupied core positions within most mania/hypomania network configurations. Increased motor activity and energy appeared among the most central symptoms of mania in the largest number of networks (n=6) [29,31,34-36,39], with four studies highlighting these symptoms as the most central node.[29,35,36,39] Additional symptoms related to psychomotor arousal, such as pressured speech, were identified among the

three most central symptoms across four studies. [33,35-37] Specifically, pressured speech was reported in three studies[33,35,36] and increased speech rate/amount was reported in one[31]. These symptoms often ranked in the second or third positions of centrality, following energy-related symptoms. In patient populations with and without childhood abuse histories, high energy remained the most central node, with pressured speech ranking second, reflecting a stable network organization in which core manic symptoms maintained strong connectivity across groups with varying trauma backgrounds [35]. Symptoms reflecting elevated self-esteem, such as grandiosity or excessive self-confidence, appeared as one of the three most central symptoms in four studies, ranking in the second or third position of centrality within these studies.[30,31,35,36] These centrality patterns show a relatively stable core of highly connected mania symptoms that may act as central nodes within manic attractor states, influencing network dynamics and supporting the persistence of manic mood states.

Some studies examined the centrality of mania symptoms across bipolar disorder episode stages. One study compared mania symptom networks across hospitalization phases (start, middle, and end) and found that elevated mood was the most central and highly connected symptom during the early stages of manic episodes, with its connectivity declining as patients stabilized[34]. The notably high centrality of elevated mood was unique to this study's mania network and may reflect greater mania severity in the study population. A second study observed similar shifts over the course of pharmacological treatment, where the symptom with the highest node strength at baseline, motor activity, decreased in centrality as treatment progressed, while other symptoms, such as interpersonal contact, increased in connectivity.

Distinct Clinical Features in BD

Corponi and colleagues[33] used network analysis to examine interactions between mixed symptoms in acutely depressed MDD and BD patients, using the Research-Based Diagnostic Criteria (RBDC) to capture these symptoms. In BD patients experiencing a major depressive episode (MDE), network results indicated that mixed symptoms were highly central, while core depression symptoms had lower overall

connectivity in the network, despite being frequently observed in the sample. The most central mixed symptoms included impulsivity, pressured speech, and psychomotor agitation. Core depression symptoms, including low energy or fatigue and loss of concentration had low connectivity and the highest thresholds, emerging only at higher overall depression severity, and appearing as isolated nodes in the BD network. This study was the only one to include mixed symptoms in the BD depression network and examine their impact on network dynamics. The core MDE criteria of depressed mood and loss of interest were excluded from this BD symptom network due to their high endorsement and limited variability in the study sample.

Yang and co-authors[31] examined emergent symptoms of mania in remitted BD patients, identifying racing thoughts as the most central node, with high energy or activity and overconfidence ranking as second and third in centrality. Here, it appears that activation-related symptoms maintain high centrality across acute and prodromal phases, consistent with broader network models of psychopathology in which strongly connected symptoms reinforce one another and contribute to the structural stability of symptom networks.

Koenders and colleagues[37] separated BD symptom networks into three disease course groups (stable, depressed, and cycling). The depressed group's centrality patterns were largely consistent with other BD network findings, with psychomotor slowness and low self-esteem emerging as central nodes. The stable group demonstrated central symptoms spanning both depression and mania domains, including increased speech, loss of interest, and depressed mood. In the cycling group, concentration, low energy and low interest, were the most connected nodes. Manic and depressive symptoms in this group were more strongly interconnected than in the depressed or stable groups, indicating that patients who exhibit one symptom are more likely to experience other closely linked symptoms simultaneously. Despite differences in centrality patterns across groups, energy-related symptoms remained highly central across all illness courses in this study.

Among studies (n=9) including both BD-I and BD-II samples, only one study [30] distinguished between the central symptoms of the two disorder subtypes. In the BD-I

network, the most central symptom was increased flirtatiousness or sexual activity, followed by heightened self-confidence. In contrast, the BD-II network was characterized by increased creativity and ideas as the most central symptom, followed by greater activity and project planning. Both BD-I and BD-II shared the same third most central symptom of wanting to meet or meeting more people. These centrality patterns differ from other network findings in this review, likely reflecting the symptom measure used (Hypomania Checklist), as the items from this measure comprised the mania network. Notably, this study was the only one to focus exclusively on hypomania symptoms, which could also account for the distinct centrality patterns observed. Despite these differences, some consistencies with mania networks from other studies were evident, as esteem-related symptoms remained among the top-ranked central symptoms in the BD-I network.

Two studies directly compared symptom centrality between individuals with unipolar and bipolar depression.[32,33] Both studies found no significant differences between unipolar and bipolar depression networks in overall network structure, global strength, or edge weights, suggesting similar underlying connectivity patterns among depressive symptoms across the two disorders.

Table 3. *Rank of Central Symptoms for Manic & Depressive Networks*

Source	Central Symptom Rank						
	Depression			Mania/Hypomania			Other
	Rank 1	Rank 2	Rank 3	Rank 1	Rank 2	Rank 3	
Briganti et al.[34]	NR	NR	NR	Elevated mood	Motor activity/energy	Irritability	NR
Liu et al.[29]	NR	NR	NR	Increased motor activity/energy	Emotional instability	Disruptive/ aggression behaviour	NR
Bai et al.[30]	NR	NR	NR	BD-I: More flirtatious/sexually active BD-II: More creative/ideas	BD-I: More self-confidence BD-II: Plan activities/projects	BD-I & BD-II: Wants to meet/meets more people	NR
Li et al.[39]	NR	NR	NR	Motor Activity	Voice/Noise Level	Verbal Activity	NR
Lee et al.[32]	Depressed affect	Emptiness	Confusion	NR	NR	NR	NR
Corponi et al.[33]	Impulsivity	Pressure to talk	Psychomotor agitation	NR	NR	NR	NR
Wrobel et al.[35]	No child abuse: Depressed mood Any child abuse: Low energy	No child abuse: Low energy Any child abuse: Inadequacy	No child abuse: Anhedonia Any child abuse: Pessimism	No child abuse: High energy Any child abuse: High energy	No child abuse: Pressured speech Any child abuse Pressured speech	No child abuse: Elated Any child abuse: Grandiosity	NR
McNally et al.[36]	Low energy	Inadequacy	Depressed mood	High energy	Grandiosity	Pressured speech	NR
Koenders et al.[37]	Loss of energy	Elevated mood	Decreased self-esteem	NR	NR	NR	Cycling: Concentration Loss of interest Low self-esteem Stable: Increased Speech Loss of interest Depressed Mood
Yang et al.[31]	Thinking about suicide	Depressed mood	Tiredness/lack of energy	Racing thoughts	Extremely energetic/active	Overly self-confident	NR

| Wrobel et al.[38] | No child trauma & Any child trauma (self-rated): Depressed Mood

No child trauma (clinician-rated): Work and interest

Any child trauma (clinician-rated): Depressed Mood | No child trauma (self-rated): Loss of interest

Any child trauma (self-rated): Feelings of worthlessness

No child trauma (clinician-rated): Depressed Mood

Any child trauma (clinician-rated): Work and interest | No child trauma & Any child trauma (self-rated): Insomnia/Hypersomnia

No child trauma (clinician-rated): Retardation

Any child trauma (clinician-rated): General Somatic | NR | NR | NR | NR |
|---|---|---|---|---|---|---|---|

3.1.6 Robust Symptom Connections

Across studies reporting edge weight statistics (n=10), consistent patterns of symptom connectivity emerged. In depression networks, low energy and psychomotor slowing were strongly connected[35,36]. Negative self-evaluative symptoms, such as hopelessness with personal devaluation [32] and guilt with feelings of inadequacy [36], demonstrated strong associations with one another, reflecting tightly connected nodes within the cognitive-affective domain. Depressed mood also shared strong connections with decreased interest and suicidality[38,39.]

In mania networks, energy- and activation-related nodes formed the most stable and strongest connections. These connections included high energy linked with hyperactivity[33,35,36] and elevated mood linked with increased motor activity[29,34]. Irritability was also strongly associated with aggressive or disruptive behaviours in four studies[29,30,33,34], indicating that irritability may act as a bridge symptom linking affective and behavioural symptom clusters. Esteem-related features demonstrated robust connectivity, including grandiosity linked with elatedness[36] and increased self-confidence connected to more flirtatious or sexually active behaviour [30]. Language-thought disorder and abnormal or morbid thought content were also strongly connected in the mania symptom networks of two studies, reflecting co-activation within cognitive symptom clusters[29,34].

Cross-domain connectivity was also observed. One study[31] identified the strongest edge in their network of emergent BD symptoms as the connection between racing thoughts and suicidal ideation, followed by a strong connection between high energy/activity and depressed mood, reflecting the co-activation of depressive and manic symptoms in early episode phases. Several studies also identified bridge connections linking different symptom clusters, such as racing thoughts with suicidal ideation[31] and verbal activity with well-being or social engagement[39].

4. Discussion

This review aimed to systematically synthesize network analytic studies of BD to identify patterns in symptom centrality, examine methodological heterogeneity, and evaluate the clinical and theoretical implications of network approaches for understanding BD. To our knowledge, this report represents the first systematic synthesis of network analysis applied to BD. Across 11 included studies, certain trends emerged within mood states. In bipolar depression, depressed mood, low energy/anergia, and negative self-evaluative symptoms frequently appeared among the top three central symptoms. In mania, increased motor activity/energy, symptoms related to psychomotor arousal (e.g., pressured speech, increased psychomotor speed), and elevated self-esteem most often ranked as the top three central symptoms. From a network perspective, manic and depressive episodes may reflect distinct attractor states, in which these highly central nodes help stabilize patterns of symptom connectivity and shape the organization of the mood-state networks.[13,14] This pattern aligns with theoretical models proposing that mood episodes emerge from self-sustaining feedback loops among interconnected symptoms, where activation of one central symptom increases the likelihood of activating other connected symptoms, stabilizing the system in a particular mood state.[15,16] The consistency of energy-related symptoms as central nodes across both mania and depression reinforces the idea that BD may fundamentally be a disorder of energy regulation.

Findings from subgroup analyses further support the idea that network structure may vary by clinical course. Cycling patients exhibited interconnections between manic and depressive symptoms, with concentration loss and suicidality as central nodes; depressed patients showed networks dominated by depressive symptoms, where loss of self-esteem and psychomotor slowness were most central; and stable patients had networks with elevated mood and increased speech as central symptoms, and weaker connections between manic and depressive symptoms. These differences suggest that manic and depressive symptoms are more interconnected in cycling patients, whereas they cluster more separately in stable patients, potentially reflecting different vulnerabilities for mood state transitions.[36,37,42] This raises questions about whether

these patterns are trait-like features that predict illness course or state-dependent characteristics that change over time. Future research examining whether network structure at illness onset predicts subsequent cycling patterns could clarify whether network analysis offers predictive value beyond traditional clinical markers.

Childhood trauma may meaningfully shape the symptom structure of bipolar depression. In Wrobel and colleagues[35], trauma-exposed individuals showed networks in which self-critical symptoms (e.g., inadequacy, pessimism) were more central, while depressed mood was less central, suggesting that depression in BD may not reflect a uniform network structure across patients.[43,44] This has clinical implications as assessment and intervention targets may need to be tailored to individuals' developmental and psychosocial histories, rather than assuming the same core symptom drivers for everyone. [45,46,47] More broadly, these findings raise the possibility that other social and environmental determinants (e.g., substance use, poverty, housing instability, discrimination) could also reconfigure symptom networks and should be examined as potential moderators of network structure in future studies.[48]

One of the main difficulties in the diagnosis and management mood disorders is differentiating bipolar from unipolar depression. To date, no consistent clinical features reliably distinguish the two.[49] Misdiagnosis is common and often leads to inappropriate treatment, which worsens clinical trajectories and prolongs symptom remission.[50, 51, 52,54] Network analysis may offer a novel approach to this diagnostic challenge by revealing subtle differences in symptom structures. [52,53] However, the included studies comparing MDD to BD found very similar network structures during depressive episodes, which may reflect methodological heterogeneity rather than true equivalence between conditions.[32,33,55] For example, the symptom measures used in most studies were developed for unipolar depression and may not adequately capture the activation-related symptoms that characterize bipolar depression. Instruments such as the Bipolar Depression Rating Scale (BDRS) have been proposed to address these limitations by incorporating a dedicated mixed symptoms subscale that captures agitation, irritability, lability, and racing thoughts, which standard depression scales omit. [56,57] Longitudinal network analysis also offers promise in this regard, as emerging evidence states that

BD has weaker symptom connectivity and greater capacity for state transitions compared to MDD, even during comparable depressive episodes[58]. This approach may capture the inherent instability and cycling nature of BD that cross-sectional analyses miss, potentially revealing diagnostic differences in the temporal evolution of symptom interactions.

5. Limitations

Despite these promising findings, symptom centrality is a statistical feature of the estimated network and should not be interpreted as clinical priority or an intervention target without validation. Most analyses were cross-sectional, precluding causal inference about within-person dynamics or directional symptom effects. The included studies also showed substantial heterogeneity in network estimation and inconsistent reporting, along with differences in symptom operationalization and labeling, which reduces comparability and underscores the need for standardized reporting. Finally, samples were largely young-to-middle-aged; because earlier-onset BD is often more severe and network structure may vary across developmental stages, generalizability to late-onset and older adult populations may be limited.[59,60,61]

This review also has limitations that should be acknowledged. First, the small number of studies and methodological heterogeneity precluded meta-analytic synthesis. Second, restriction to English-language publications may have introduced language bias. Third, reliance on published aggregate data precluded examination of moderators such as medication status, illness duration, or comorbidities that may influence network structure.

6. Future Directions

Given the findings of the present review, several methodological advances are recommended to overcome current limitations. Longitudinal and person-specific network models that use ecological momentary assessment are important for capturing within-person symptom patterns and changes over time.[49,62,63] Advanced temporal network methods, such as graphical vector autoregressive (VAR) models and dynamic time

warping approaches, can then test how symptoms at one time point predict symptoms at later time points.[64,65,66]. Also, standardized reporting practices following established guidelines are critical for comparability.[21,67] Lastly, the inclusion of broader symptom domains beyond core mood symptoms, including sleep, circadian rhythms, cognitive functioning, and psychosocial variables, would provide a more comprehensive understanding of BD as a complex system.[68,69] A study by Platania and colleagues[70] demonstrated that incorporating neurocognitive and psychosocial domains into network models revealed these variables to be highly interconnected and centrally positioned in BD, with mood symptoms more integrated with cognitive and functional processes than in MDD. Therefore, interventions targeting central non-mood domains may have indirect effects on mood symptoms and overall functional outcomes, supporting the need for personalized, multimodal treatment strategies.

7. Conclusion

Network analysis methods facilitate a more comprehensive understanding of BD by focusing on direct symptom interdependencies and have the potential to provide improved treatment targets. Despite current limitations, network analysis holds considerable promise for informing personalized, mechanistically grounded, and dynamically adaptive interventions in BD.

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Supplemental Material

1.Methods

1.1 Search Strategy
The following Boolean search string was used across databases:
(network analysis OR network approach OR network model OR network structure OR network theory OR network estimat* OR symptom network* OR symptom-level network*)
AND
(bipolar disorder OR mania OR hypomania OR affective disorder OR bipolar depression OR manic symptom* OR hypomani* symptom* OR bipolar symptom* OR manic depression OR bipolar I OR bipolar II OR bipolar spectrum).

1.2 Inclusion/ Exclusion Criteria
       Articles were considered eligible if they met the following inclusion criteria: (1) original empirical research; (2) published in English; (3) published in peer-reviewed journals; (4) used network analysis as a primary method to examine symptoms in individuals with BD; (5) focused on mood symptom centrality or interrelationships (e.g., depressed or manic symptoms); and (6) published before January 2026.
       Exclusion criteria included: (1) review articles or meta-analyses; (2) studies not using network analysis as a primary method; (3) no reportable symptom-level network model; (4) samples primarily including non-BD diagnoses (e.g., schizophrenia, unipolar depression); (5) samples of participants outside the 16–65 age range; (6) focus on brain networks or neuroimaging rather than symptom networks; (7) focus on biomarkers or biological mechanisms unrelated to symptom structure; or (8) reported centrality metrics for non-mood variables (e.g., cognitive performance, quality of life, functioning).

1.3 Participant Criteria
       Eligibility criteria for participants included individuals aged 16 to 65 with a clinical diagnosis of BD-I, BD-II, or BD-NOS. The clinical diagnosis of BD had to meet the DSM-V[71] or ICD-11[72] criteria for BD (or earlier editions of these diagnostic guidelines). The tool used for diagnoses had to be a structured diagnostic interview that was created based on the ICD or DSM criteria (e.g., the Mini International Neuropsychiatric Interview) or be based on a clinical assessment where the participant was diagnosed by a trained healthcare professional.[73] If there was an age of participants below 16 years old, but the overall sample included the relevant age range for the inclusion criteria (e.g., 12 to 45), the study was included to ensure comprehensive coverage of the target population. Studies that included participants outside the age range of 16 to 65 were excluded, as they did not meet the inclusion criteria for age. Studies that investigated non-clinical populations or conditions that were not related to BD were excluded .

1.4 Screening Process
       The screening process began with each article being assessed by title and abstract, and was then evaluated using the exclusion and inclusion criteria.
       Title and abstract screening: All citations were uploaded to the Covidence[74] data management software for title and abstract screening and duplicate removal. Three independent reviewers (DG, MC, KM) screened titles and abstracts in duplicate to determine if the studies were eligible for full-text screening. This screening process occurred on the Covidence data management software[74.] Discrepancies were resolved through discussion between the three reviewers.

Full-text screening: The same reviewers (DG, MC and KM) independently screened the studies that moved forward to the full-text screening stage. Discrepancies were resolved through discussion. Studies meeting the inclusion criteria proceeded to the data collection process.

Data collection process: The data collection process was conducted by one trained reviewer (DG) who extracted the data from the included studies. Excel was used to extract and store the data from each of the included studies. This data was verified by a second trained reviewer (MC), and reviewers came to an 81.2% agreement.

The following characteristics were extracted from each study and included in the systematic review: first author's last name, year of publication, study design type (e.g., cross-sectional or longitudinal), sample size diagnosed with BD and subtype, BD sample type (e.g., BD I, BD II, mixed), participants' mean age (with standard deviation, median, or range), percentage of female participants, age of onset (in years), mood state at the time of assessment, and key sample characteristics (e.g., inpatient, outpatient, clinical stability). Studies also reported the diagnostic manual used (e.g., DSM-IV, DSM-5, ICD-10), diagnostic method, and BD symptom measure employed. Regarding network analysis, we extracted the type of analysis (e.g., symptom or temporal network), estimation method (e.g., Gaussian Graphical Model), statistical software and package used (e.g., R, qgraph, bootnet), and details on model stability and reproducibility (e.g., case-dropping bootstrap, correlation stability coefficient). Finally, outcome characteristics included identified central symptoms, bridge symptoms, and centrality metrics (e.g., strength, betweenness, closeness), as well as whether the article was open access.

1.5 Network studies characteristics
Each study's network structure was described, focusing on nodes (symptoms) and edges (symptom associations).

1.6 Sample characteristics
Studies were categorized based on sample type (clinical or community), mean age or age range of participants, and gender distribution.

1.7 BD symptoms
Diagnostic criteria used in each study were documented (e.g., DSM edition, structured interviews, other standardized diagnostic tools). BD symptom assessment tools were also noted.

1.8 Network estimation
Details regarding the estimation method, such as the use of Gaussian graphical models or regularization techniques (e.g., LASSO), were reported where available.

1.9 Network stability
Network stability was assessed in the included studies using various approaches, including examining bootstrapping results to estimate confidence intervals for network parameters and the CS coefficient to evaluate the stability of centrality indices across subsets of the data.

Bootstrapping is a resampling method that repeatedly draws samples, with replacement, from the data to estimate the variability of network parameters. The CS coefficient indicates the maximum proportion of cases that can be removed while still maintaining centrality estimates that strongly correlate with those of the original, full sample.[75]

1.10 Reproducibility
Studies were classified as open access if available to the public free of charge in an open-access peer-reviewed journal. The studies were classified as open data if their datasets were publicly accessible without restrictions through a recognized data repository or supplementary materials.

2. Results

2.1 Recruitment

Several studies used data from existing large-scale research projects. One study recruited from outpatient psychiatric clinics and included participants at various illness stages[37]. Lee and co-authors[32] recruited BD and MDD patients from mental health centres across South Korea. Briganti and colleagues[34] conducted a longitudinal assessment of manic symptoms in a clinical sample. Corponi and colleagues[33] used data from BRIDGE-II-MIX, a multinational, non-interventional study focused on acute depression in BD and MDD.

Furthermore, two studies recruited participants from Beijing Anding Hospital[29,31]. Despite the shared recruitment site, the two studies differed in both sample characteristics and inclusion criteria: one focused on acutely manic patients presenting to emergency care (YMRS $\geq$ 20) without requiring remission[29], while the other recruited remitted patients with a confirmed first mood episode within the past three years[31]. Additionally, different diagnostic approaches were used, with one study applying ICD-10 clinical diagnoses[29] and the other using DSM-IV-TR criteria confirmed by SCID[31]. Information on participant characteristics and distinct inclusion criteria suggests no data overlap.

2.2 Data Overlap

Two studies drew data from the CHOICE trial, a multi-site randomized study focused on treatment outcomes in BD[35,36]. Both studies reported sample sizes of approximately 480 participants and described similar inclusion criteria; demographic characteristics were also closely matched. Given the shared data source and high likelihood of multiple testing on the same participants, results from these studies were interpreted carefully in light of each other.

2.3 Symptom Assessments

Symptom assessment tools also varied considerably, with important implications for network comparisons. Manic symptoms were most frequently assessed with the Young Mania Rating Scale (YMRS), a well-validated, gold-standard measure of manic symptoms[76], appearing in three studies[29,34,37]. Li and colleagues[39] assessed manic symptoms using the Bech-Rafaelsen Mania Scale (BRMS), a clinician-rated measure of mania severity; depressive symptoms using the Hamilton Depression Rating Scale (HAM-D), a clinician-rated measure of depression severity; and anxiety symptoms using the Hamilton Anxiety Rating Scale (HAM-A), a clinician-rated instrument assessing the severity of anxiety symptoms. Wrobel and colleagues[35] also used the PANSS-AG (Positive and Negative Syndrome Scale–Aggression subscale) to assess aggression-related symptoms. This subscale has strong validity in psychotic populations[77], though its psychometric properties in bipolar samples are not as well established. Two studies[35,36] assessed a broad range of mood symptoms in BD using the Bipolar Inventory of Symptoms Scale (BISS), a well-validated measure of both depressive and manic symptoms[78]. The Zung Self-Rating Depression Scale was employed by one study[32]. This scale is a self-report measure shown to be reliable and valid for assessing depression symptoms, though it is not specific to bipolar populations[79]. Other studies included the Hypomania Checklist (HCL-32)[30], a validated self-report screening measure used to distinguish BD from other psychiatric disorders[80]; the Bipolar Prodrome Symptom Scale-Retrospective (BPSS-R)[31], a clinician-rated measure of prodromal bipolar symptoms, with limited evidence on reliability and validity for the retrospective version; and structured assessments based on DSM-IV-TR major depressive episode (MDE) criteria with Rapidly Cycling Bipolar Disorder (RBDC) mixed features[33], which followed standard diagnostic criteria. Table 3 reports all network analysis parameters, including assessment methods for their corresponding study.

Five studies examined additional elements beyond core BD symptoms, using supplementary questions in standardized tools or incorporating unique methodological approaches to explore specific symptomatology. Yang and colleagues[31] used the Bipolar Prodrome Symptom Scale–Retrospective (BPSS-R), a 41-item measure capturing prodromal manic/hypomanic, depressive, and general symptoms.

Liu and colleagues[29] examined testosterone-related behaviours, including aggression, impulsivity, and hypersexuality, to investigate hormonal influences on manic episodes, and additionally computed node-specific predictive betweenness for the testosterone node[29]. Lee et and colleagues[32] expanded symptom assessment by comparing depressive symptom severity across BD and MDD populations. Corponi and colleagues[33] similarly incorporated cross-diagnostic comparisons to analyze symptom overlap and differentiation.

Section and Topic	Item #	Checklist item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Spe
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened eac
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they work
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in e
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describ
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assess
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristi
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or dat
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies in
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study characteristics	17	Cite each included study and present its characteristics.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its pr
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.

Section and Topic	Item #	Checklist item
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precisio
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registere
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing interests	26	Declare any competing interests of review authors.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from inc

Author, Year	Domain 1: Measurement & Node Validity				Domain 2: Sample & Design Adequacy			Domain 3: Model Specification & Statistical Appropriateness	
	Are node definitions clearly described (symptoms/items, timepoint, scale/instrument)?	Is the rationale for node selection reported (theory/DSM-ICD/validated structure vs convenience)?	Are the symptom measures appropriate and validated for the target population, and is scoring described?	If single items are used as nodes, is the rationale for item-level measurement reported?	Is the sample clearly described (BD subtype/diagnosis method, mood state, setting, inclusion/exclusion)?	Is sample size discussed relative to network complexity (number of nodes/parameters) and uncertainty?	Is the study design clearly stated (cross-sectional vs longitudinal), and are claims aligned with that design?	Is the network model fully specified (e.g., GGM/Ising/MGM/VAR/mlGVAR; estimator; regularization/tuning)?	Is the modeling approach appropriate for the ... and design (continuous/categorized; cross-sectional/longitudinal)?
Bai 2022	Y All 32 HCL items are explicitly listed in Table 1 with full text descriptions (e.g., HCL17 "I am more flirtatious and/or am more sexually active")	Y HCL-32 is a validated instrument designed to assess hypomanic symptoms; rationale is theory-driven (DSM-IV/ICD-10 BD diagnosis)	Y HCL-32 is validated in Chinese population with satisfactory psychometric properties explicitly stated; dichotomous yes/no scoring described	Y Authors explicitly state each HCL-32 item represents a hypomanic symptom and justify symptom-level analysis to identify treatment targets	Y BD-I (n=191) and BD-II (n=232) clearly distinguished; DSM-IV/ICD-10 diagnosis confirmed; inclusion/exclusion criteria detailed; age, gender, age of onset reported	N No discussion of sample size adequacy for 32 nodes; no power analysis or justification provided	Y Cross-sectional design clearly stated; authors appropriately avoid strong causal claims in most sections	Y Ising model explicitly stated; bootnet package version 1.4.3 specified; appropriate for dichotomous HCL-32 items	Y Ising model is appropriate for binary/dichotomous cross-sectional design analysis
Briganti 2021	Y All 11 YMRS items explicitly described in Table 1 with full symptom names (e.g., "Elevated Mood," "Increased Motor Activity-Energy"); three time points (t0, t1, t2) clearly specified	Y YMRS is validated, widely used tool for mania assessment; theory-driven (DSM-IV BD-I diagnosis); authors justify YMRS selection due to low number of items (11) for network stability	Y YMRS is validated and widely used for mania severity assessment; scoring described (0-4 scale, though authors modified original 0-8 scoring for some items)	PY Authors justify using YMRS items as nodes for network stability, but modification of scoring (0-8 to 0-4 for some items) is explained only as needed for variance-covariance matrix, not psychometrically justified	Y BD-I with severe manic features (n=100); involuntary commitment; DSM-IV diagnosis; inclusion/exclusion detailed; age (M=44.5, SD=14.5), gender (47% female), setting (specialized psychiatric ward) reported	PY Authors mention 11 items is "relatively low" for network stability "in a reasonable sample," but no formal power analysis or adequacy discussion for 11 nodes with 100 subjects	PY Design includes both cross-sectional (three separate time points) and temporal (GVAR) components; mostly appropriate claims, but some temporal interpretations may overreach given only 3 time points	PY GGM explicitly stated; psychonetrics package for GVAR specified; but authors state they did NOT use regularization (contrary to standard practice), citing Williams & Rast 2019; Spearman's rho used instead of Pearson (acknowledged as limitation)	PN GGM typically assumes Pearson correlation, continuous normally distributed data; authors use Spearman's rho due to distributions and stationarity assumptions (acknowledged limitation; appropriateness questioned)

Corponi 2020	Y All 23 symptoms explicitly described: 7 DSM-IV-TR MDE criteria (disaggregated for opposite conditions) + 14 RBDC mixed symptoms; dichotomous coding clearly stated; timepoint is current MDE	Y Theory-driven: DSM-IV-TR MDE criteria + RBDC for mixed features; rationale provided for disaggregating opposite symptoms (appetite, sleep, psychomotor); exclusion of depressed mood/anhedonia justified (99.4%/98.6% endorsement)	PY DSM-IV-TR criteria are validated; RBDC are research-based but not formally validated as a scale; dichotomous coding described but no psychometric properties reported for this specific assessment	Y Authors justify symptom-level analysis to examine symptom interactions and differential diagnosis between MDD/BD; network approach rationale clearly articulated	Y Large sample (n=2758); MDD (n=2040) vs BD (n=718); DSM-IV-TR diagnosis; acute MDE; international multicenter; inpatient/outpatient; detailed demographics in Table 1; inclusion/exclusion criteria specified	N No discussion of sample size adequacy for 23 nodes; no power analysis or justification provided despite large N	Y Cross-sectional design explicitly stated; authors appropriately acknowledge "cross-sectional design does not allow for causal inferences" in limitations	Y Ising model explicitly stated; IsingFit R-package specified; eBIC for tuning parameter selection; AND-rule for edge inclusion; regularization (L1) clearly described	Y Ising model is appr... binary/dichotomous... data; cross-section... matches contempo... network anal...
Koenders 2015	Y 14 symptom items clearly described from YMRS and QIDS; overlapping items combined and documented in S1 Table; timepoint selection (most symptomatic) explicitly stated	Y Theory-driven: YMRS and QIDS are validated instruments for BD; rationale for combining overlapping items provided; exclusion of 3 items (libido, insight, appearance) due to low variance (≥94% zero responses) justified	Y YMRS and QIDS explicitly stated as having "good (interrater) reliability and validity"; validated instruments for manic and depressive symptoms	Y Authors justify symptom-level network approach to understand "how symptoms are connected when these are actually present in BD patients"; theoretical framework from Borsboom et al. cited	Y BD-I and BD-II (n=125); DSM-IV-TR diagnosis via MINI-PLUS; three course groups defined (minimally impaired n=47, depressed n=42, cycling n=36); 2-year prospective follow-up; outpatient setting; demographics in Table 1	PY Authors acknowledge in limitations: "for the analyses of 14 different variables within three groups of (on average) 40 patients, sample sizes are small" and "results should be interpreted with caution"	PY Design described as 2-year prospective follow-up with cross-sectional symptom assessments; authors acknowledge "cross-sectional character of the data-points" limits temporal interpretation; some claims about symptom dynamics may exceed cross-sectional data	PY Weighted graphs with Spearman's rank correlations specified; igraph 0.7.1 package named; but no regularization used (acknowledged as limitation); no partial correlations; simple correlation network	PY Spearman's corr... justified due to no... distribution and ord... however, authors ac... "different corre... techniques such as p... correlations, partial-... analyses or the... procedure are valua... in future stud...

Lee 2024	Y All 20 Zung SDS items explicitly listed in Figure 1 with symptom descriptions; cross-sectional timepoint clearly stated	Y Zung SDS described as designed to assess "wide range of depressive symptoms, including both unipolar and bipolar depression"; rationale for using self-report severity scale provided	PY Zung SDS is validated and widely used; however, it is primarily designed for unipolar depression assessment, and authors acknowledge it is "used to evaluate depressive symptoms not only in MDD but also in BD" without extensive validation evidence for BD	Y Authors justify network approach to "explore how the symptoms of mental disorders influence each other within a network framework" and assess "contributions of individual symptoms"	Y MDD (n=322) and BD (n=516); DSM-5 diagnosis via M.I.N.I. by board-certified psychiatrists; demographics in Table 1; inclusion criterion (raw score ≥40) specified; significant demographic differences noted	N No discussion of sample size adequacy for 20 nodes; no power analysis or justification provided	Y Cross-sectional design explicitly stated; authors appropriately note "due to the cross-sectional design of this study, the network analysis remains undirected, revealing associations but not establishing causal inferences"	Y Gaussian Graphical Model with glasso regularization explicitly stated; EBICglasso function from qgraph specified; Louvain algorithm for community detection; parametric bootstrapping (1000 samples) described	Y GGM with glasso a for continuous/ordi scale data; cross-s design matches un network anal
Li 2026	Y All scale items explicitly described: BRMS (11 items), HAMD, HAMA (14 items); symptom clusters defined based on prior literature with citations; timepoints clearly specified (baseline, weeks 1, 2, 4)	Y Theory-driven: BRMS, HAMD, HAMA are validated instruments; symptom clustering rationale provided with citations	Y BRMS, HAMD, HAMA explicitly stated as validated instruments with established psychometric properties; scoring systems described (BRMS 1-4, HAMD/HAMA 0-4)	Y Authors justify network approach to examine "dynamic interaction mechanisms among symptoms" and "temporal evolution patterns under pharmacological interventions"	Y Manic (n=206) and depressive (n=106) BD patients; DSM-5 diagnosis via SCID-5; detailed inclusion/exclusion criteria; demographics in Tables 1-2; responder/non-responder classification defined (≥50% BRMS reduction)	N No discussion of sample size adequacy for 11 (BRMS) or 14 (HAMA) nodes; no power analysis; authors acknowledge "relatively modest sample size" only in limitations	Y Prospective longitudinal design (4 weeks, 7-day intervals) clearly stated; cross-sectional and cross-lagged analyses distinguished; temporal claims appropriately aligned with longitudinal data	Y GGM with glasso regularization explicitly stated; EBIC with γ=0.5 specified; qgraph package used; cross-lagged panel network for temporal analysis; NetworkComparisonTest for group comparisons	Y GGM appropri continuous/ordinal cross-lagged ne appropriate for lon panel data with r measures; 7-day la by clinical assessme
Liu 2024	Y All nodes explicitly described: 11 YMRS items, PANSS-AG subscale items (anger, delayed gratification, emotional instability), testosterone, and aggression severity; scoring	Y Theory-driven: YMRS validated for manic symptoms; PANSS-AG for aggression risk profile; testosterone included based on prior literature linking it to aggression and	Y YMRS is validated clinical rating scale; PANSS validated in Chinese population with Cronbach's alpha = 0.84 explicitly stated; testosterone assayed via standardized	Y Authors justify network approach to "elucidate a biological system by anticipating the inter-relationships among multiple syndromes" and identify "central symptoms,	Y Large sample (n=898); BD patients in manic episode (ICD-10 F30-F39, YMRS ≥20); single PED setting; demographics in Table 1; inclusion/exclusion criteria specified; 98.1% response rate	N No discussion of sample size adequacy for number of nodes (~17 nodes); no power analysis or justification provided despite large N	PY Cross-sectional design explicitly stated; authors acknowledge "cross-sectional design precludes establishing causal relationships" in limitations; but some language suggests causal mechanisms (e.g.,	Y GGM with glasso and EBIC explicitly stated; qgraph package used; polychoric correlations for mixed data; flow network for testosterone associations; NetworkComparisonTest for gender comparisons	PY GGM with poly correlations approp mixed ordinal/contin however, comb categorical aggress ordinal YMRS ite continuous testost single network may complexity not fully

systems specified (YMRS 0-4 or 0-8 scales)	BD pathophysiology	chemiluminescence	bridge symptoms and short paths"			"bridge symptoms linking")		
McNally 2022	Y All 12 depression and 13 mania symptoms explicitly listed in Tables 1-2 with BISS item descriptions; DSM-5 criteria mapping provided; scoring system (0-4 ordinal) clearly described	Y Extensive rationale provided: DSM-5 guided selection; disaggregation of criteria justified; exclusion of atypical features explained; topological overlap concerns addressed; distinction between energy (subjective) vs. psychomotor symptoms (behavioral) articulated	Y BISS (Bipolar Inventory of Symptoms Scale) is validated assessor-administered instrument; citations provided	Y Authors explicitly justify symptom-level analysis based on network theory framework; mereological vs. reflective model distinction articulated	Y Large sample (n=486); BD-I (68.5%) and BD-II (31.5%); DSM diagnosis by licensed psychiatrist; current mood states specified (depressed n=271, manic/hypomanic n=58, inter-episode n=76, mixed n=81); demographics provided	PY Authors note this is "the largest study of bipolar disorder symptom networks"; but no formal power analysis or explicit discussion of adequacy for 12-13 nodes	Y Cross-sectional design explicitly stated; authors clearly acknowledge "GGMs are based on cross-sectional analyses and reflect conditional dependence associations among symptoms, not causal relations"	Y Multiple methods specified; packages and versions reported (bootnet v1.1.0, qgraph v1.6.4, GGMnonreg v1.0.0, bnlearn)	Y Polychoric correlat[ion] for ordinal data; complementary m[ethods] (regularized, non-re[g] DAG) provide tria[ngulation] separate networ[k] depression/mania j[oint] avoid topological
Wrobel 2023	Y All PHQ-9 (9 items) and HAMD-17/HAMD-6 (7 items) explicitly described; CTQ subscales and cutoffs specified; cross-sectional timepoint (study entry) stated	Y PHQ-9 and HAMD-17 are validated instruments; HAMD-6 selection justified based on clinimetric equivalence to HAMD-17; suicidality item added based on established trauma-suicide relationship	PY PHQ-9 and HAMD-17 are validated; however, authors explicitly acknowledge "neither the PHQ-9 nor the HAMD-17 were specifically developed to assess the clinical profile of depressive symptoms in BD"	Y Network theory framework cited; rationale for symptom-level analysis to identify central symptoms and inform targeted interventions provided	Y Large samples (PHQ-9: n=543; HAMD: n=529); BD-I, BD-II, BD-NOS, schizoaffective specified; DSM-IV diagnosis via DIGS with best-estimate process; demographics in Table 1; trauma subgroups defined with CTQ cutoffs	PY Authors note HAMD-17 "returned non-positive definite correlation matrices, likely because of the small ratio of cases to number of items"; reduced to 7 items; but no formal power analysis	Y Cross-sectional design explicitly stated; authors acknowledge "present networks were based on cross-sectional data only" in limitations	Y Regularized GGM with graphical LASSO explicitly stated; polychoric correlations for ordinal data; bootnet v1.5, qgraph v1.9.2, NetworkComparisonTest v2.2.1 specified	Y GGM with poly[choric] correlations appro[priate for] ordinal Likert-sca[le] approach "aligns w[ith] guidelines" (Epska...)

Wrobel 2024	Y All 12 depression and 13 mania BISS items explicitly described in Table 1; node selection guided by McNally et al. (2022) with DSM-5 criteria mapping; scoring system (0-4) specified	Y Extensive rationale: "This node selection was guided by the work of McNally et al. (2022)" who used DSM-5 criteria; readers referred to McNally et al. for detailed discussion	Y BISS (Bipolar Inventory of Symptoms Scale) is validated instrument specifically designed for BD; citations provided	Y Network theory framework cited; rationale for symptom-level analysis to identify central symptoms and inform targeted interventions provided	Y n=476 from Bipolar CHOICE trial; BD-I and BD-II via DSM-IV-TR and MINI; demographics in Table 1; mood states specified; childhood abuse subgroups defined (n=251 abuse, n=225 no abuse)	PY Authors acknowledge "comparatively modest sample sizes (maximum n = 251)" as limitation; note larger samples needed for controlling confounders; but no formal power analysis	Y Cross-sectional (baseline) design explicitly stated; authors appropriately note findings are "largely exploratory"	Y Regularized GGM with graphical LASSO explicitly stated; polychoric correlations for ordinal data; bootnet v1.5, qgraph v1.9.2, NetworkComparisonTest v2.2.1, igraph v1.2.4.1 specified	Y GGM with poly... correlations appro... ordinal BISS data; aligns with guid...
Yang 2024	Y All 41 BPSS-R items described across 4 domains (mania 12 items, depression 13 items, general 12 items, psychosis 4 items); dichotomous response format (Yes/No) specified; Table 2 lists all items with centrality values	Y BPSS-R is validated instrument for retrospectively measuring prodromal symptoms; rationale for prodromal symptom assessment provided	Y BPSS-R is semi-structured interview validated in China; Cronbach's alpha = 0.876 reported for present sample; original development citation provided	Y Network theory framework cited; rationale for symptom-level analysis to identify central prodromal symptoms and inform interventions provided	Y n=120; BD-I (n=92) and BD-II (n=28) via DSM-IV-TR and SCID; currently remitted; first episode within 3 years; demographics in Table 1; inclusion/exclusion criteria specified	N No discussion of sample size adequacy for 41 nodes; n=120 is notably small for 41-node network; no power analysis or justification provided	PY Cross-sectional retrospective design stated; authors acknowledge "recall biases may have influenced responses and causal relationships...could not be demonstrated"; but some language suggests causal implications	PY Ising model for dichotomous data specified; 'estimateNetwork' function used; tuning parameter 0.5 stated; but R package versions not specified; limited detail on regularization approach	Y Ising model appro... dichotomous (Yes/... R items; approach a... recommendat...

LEGEND	
Y	YES
PY	PARTIALLY YES
PN	PARTIALLY NO
N	NO
NM/NR	NOT MENTIONED/NOT REPORTED

Reference that Informed Domain Questions:
1. Mondragon KM, Tan-Lim CS, Velasco RJ, Cordero CP, Strebel HM, Palileo-Villanueva L, Mantaring JV. A scoping review of critical appraisal tools and user guides for systematic reviews with network meta-analysis: methodological gaps and directions for tool development. J Clin Epidemiol. 2026;190:112056. doi:10.1016/j.jclinepi.2025.112056.

Domain	Rationale
Domain 1	Ratings of "Y" are assigned when studies explicitly describe node definitions with specific symptom items, timepoints, and validated instruments (e.g., YMRS, QIDS, BPSS-R), and provide theory-driven or DSM/ICD-based rationale for node selection.[1][2] "PY/PN" ratings apply when symptom measures are named but scoring or item-level justification is incomplete, or when node selection appears convenience-based without explicit rationale.[3] "N" is assigned when node definitions are absent, measures are unvalidated, or single items are used without psychometric justification, which increases risk of measurement error and latent confounding.[4]
Domain 2	"Y" is assigned when studies clearly describe BD subtype, diagnosis method, mood state, setting, and inclusion/exclusion criteria, and discuss sample size relative to network complexity.[1][5] "PY/PN" applies when sample description is incomplete (e.g., mood state not specified) or sample size adequacy is not discussed.[3] "N" is assigned when sample characteristics are poorly described or sample size is clearly inadequate for the number of nodes/parameters, increasing uncertainty in network estimates.[6]
Domain 3	"Y" requires full specification of the network model (e.g., GGM, Ising, VAR), estimator, regularization, and tuning parameters, with appropriate matching to data type and design.[1][5] "PY/PN" applies when model type is stated but key details (e.g., regularization, tuning) are missing or unclear.[3] "N" is assigned when model specification is absent or inappropriate for the data, which can fundamentally bias network structure and centrality estimates.[7][8]

Overall Judejment	Rationale
High concern	Centrality stability not tested (N/NM) and centrality is interpreted strongly; model specification is missing/unclear (NM/PN); major assumption violations or causal overreach (PN/N).[6][4]
Moderate concern	Stability partially assessed or reporting has multiple NM but core model is clear.[7]
Low concern	Model, assumptions, stability, and reporting are all mostly Y/PY.[7][5]

Domain 4	"Y" is assigned when studies report bootstrapping for edge weight accuracy, case-dropping bootstrap for centrality stability (with CS coefficient ≥0.25–0.50), and conclusions match reported stability.[5][2] "PY/PN"applies when stability is partially assessed (e.g., edge weights but not centrality) or CS coefficient is not reported.[3] "N" is assigned when stability is not tested, which is a critical concern because unstable centrality metrics can lead to spurious conclusions about symptom importance.[6][4]
Domain 5	"Y" is assigned when authors avoid causal or within-person claims from cross-sectional networks, acknowledge limitations of centrality interpretation, and do not recommend treatment targets based solely on centrality.[5][9] "PY/PN" applies when some caution is expressed but claims occasionally exceed the data (e.g., suggesting intervention targets without supporting evidence).[3] "N" is assigned when authors make strong causal claims or treatment recommendations from cross-sectional centrality alone, which is a major interpretive overreach.[6][10]
Domain 6	"Y" is assigned when software/package/version is reported and code, data, or correlation matrix is shared or sufficient outputs are provided for reproducibility.[5][2] "PY/PN" applies when software is named but version or code is not provided.[3] "N" is assigned when reproducibility information is absent, limiting the ability to verify or replicate findings.[7]

References that Informed Domain & Overall Judgment Rationale:

1. Koenders MA, de Kleijn R, Giltay EJ, et al. A network approach to bipolar symptomatology in patients with different course types. PLoS One. 2015;10(10):e0141420. doi:10.1371/journal.pone.0141420.
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