Symptom Networks of Common Mental Disorders in Public versus Private Health Care Settings in India

Cemile Ceren Sönmez,[*,1,2] Helen Verdeli,[1] Matteo Malgaroli,[3] Jaime Delgadillo,[4] and Bryan Keller[5]

[1] Counseling and Clinical Psychology Department, Teachers College, Columbia University, New York, USA
[2] Department of Psychology, Koç University, İstanbul, Türkiye
[3] Department of Psychiatry at NYU Grossman School of Medicine, USA
[4] Department of Psychology, The University of Sheffield, UK
[5] Department of Human Development, Teachers College, Columbia University, USA

Abstract

We present a series of network analyses aiming to uncover the symptom constellations of depression, anxiety and somatization among 2796 adult primary health-care attendees in Goa, India, a low-and-middle-income country (LMIC). Depression and anxiety are the leading neuropsychiatric causes of disability. Yet, the diagnostic boundaries and the characteristics of their dynamically intertwined symptom constellations remain obscure, particularly in non-Western settings. Regularized partial correlation networks were estimated and the diagnostic boundaries were explored using community detection analysis. The global and local connectivity of network structures of public versus private health-care settings and treatment responders versus non-responders were compared with a permutation test. Overall, depressed mood, panic, fatigue, concentration problems and somatic symptoms were the most central. Leveraging the longitudinal nature of the data, our analyses revealed baseline networks did not differ across treatment responders and non-responders. The results did not support distinct illness sub-clusters of the CMDs. For public health-care settings, panic was the most central symptom whereas in private, fatigue was the most central. Findings highlight varying mechanism of illness development across socioeconomic backgrounds, with potential implications for case identification and treatment. This is the first study directly comparing the symptom constellations of two socioeconomically different groups in an LMIC.

Impact Statement

Depressive disorders, along with anxiety and somatic pain, are among the top leading causes of non-fatal disease burden globally. In 2019, depression was the top leading cause of burden of disease for countries that are at the lower end of socioeconomic development. Especially in low-resource settings, the identification and treatment of these illnesses pose a grand challenge. Although depression, anxiety, and somatic symptoms are highly prevalent and debilitating, the diagnostic boundaries and the mechanism of development of these illnesses are not well understood. One reason for this might be that these illnesses are often comorbid and present a heterogeneous clinical picture. The complex and dynamic relationships between symptoms call for a non-diagnostic and dynamic modeling technique. In this paper, we used the "network approach" to map out the symptoms of depression, anxiety, and somatic drawn from a sample of adult primary care attendees in India. Our work addressed several methodological weaknesses of the symptom network literature by using the composite sub-scale scores of a culturally valid clinical interview with no skip algorithm or overlapping variables. We found "panic" symptom, conceptualized as "intense anxiety/nervousness" or "tension" to be the most central in public health care settings, while "fatigue" was the most central in private health care settings. This indicate some kind of stress/threat response might be the hallmark of common mental disorders among those who are the most economically disadvantaged in India, and potentially in the region. Studying the complexity of the symptom-to-symptom relationships for these highly comorbid conditions can help flag and target the key symptoms that sit at the core of the illness, hence allow for the optimal use of the limited resources. To our knowledge, this is the first study comparing the network structure of common mental disorders of primary care patients from different socioeconomic backgrounds in an low-income country.

Introduction

Globally, mental disorders are the second leading cause of years lived with disability. Depressive and anxiety disorders together account for more than sixty percent of the disability adjusted life years (DALYs) for mental disorders (GBD 2019 Mental Disorders Collaborators 2022). Depression, anxiety, and somatic symptom disorders have high comorbidity rates ranging from 40%-80% (Lamers et al. 2011; Kessler et al. 2005), share similar biological markers (Drysdale et al. 2017; Goodkind et al. 2015), psychological vulnerabilities (Brown and Barlow 2009), and respond similarly to psychotherapy and pharmacotherapy (Cuijpers et al. 2013). Thus, the diagnostic criteria and the illness development are not well understood, particularly in non-Western settings. The present study aims to uncover the symptom constellation and the illness comorbidity in a primary care sample in India, using network analysis.

Our current conceptualization of mental illness, the common cause model (Kendler, Zachar, and Craver 2011), which assumes that a latent factor causes all symptoms of a disorder, has been criticized due to its conceptual, statistical, and clinical limitations. A body of research challenges the idea of distinct disease categories particularly for depression and anxiety (Drysdale et al. 2017; Goodkind et al. 2015; Kessler et al. 2005; Sullivan et al. 2013). The symptom network approach was proposed as an alternative, where psychiatric disorders are thought to consist of a constellation of symptoms connected to each other through a dynamic and mutually reinforcing network (Cramer et al. 2010). Based on this, a direct link between two symptoms (e.g., lack of sleep and somatic symptoms) is assumed to exist outside of what could be explained by an underlying factor. Symptoms that are "central", meaning highly connected to the rest of the symptoms in the network, could inform us about the state of the entire network and potentially serve as good therapy targets (e.g., Fried and Cramer 2017).

Depression and Anxiety Symptom Networks Globally

Growing evidence supports both the statistical appropriateness and clinical usefulness of network models (Cramer et al. 2012; Fried et al. 2015). In a systematic review, alongside depressed mood, fatigue was frequently reported as another central symptom (Malgaroli, Calderon, and Bonanno 2021). Networks of depression have been explored cross-culturally, and in Asian cultures. Recent research with depressed adults from various Asian countries reported sad mood (Park et al. 2020; Wasil et al. 2020) and fatigue (Garabiles et al. 2019) as central symptoms of depression. Different from most findings in Western countries, feeling like a failure was also reported as one of the most central depressive symptoms among adolescents in India (Wasil et al. 2020) and Han Chinese women (Kendler et al. 2018).

Anxiety symptoms were frequently investigated along with depressive symptoms. The first empirical paper on symptom networks of psychopathology examined depression and anxiety symptoms in a national survey from the United States (Cramer et al. 2010). Subsequent studies involving international datasets and and samples from Asian cultures highlighted anxiety as a central symptom in depressive symptomatology. In an international study, the item "I was close to panic" was the most central among the 21-items drawn from the Depression, Anxiety and Stress Scale (Van den Bergh, Marchetti, and Koster 2021). The authors highlighted that one nationality, Malaysian was over-represented in this sample. Two other studies reported anxiety as a central symptom among depressed adults from South Korea. In one, Park and Kim 2020 used the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) and found anxiety symptoms (i.e., lightheadedness, feeling of choking and feeling scared) to be as central as depressive symptoms. In a subsequent nationwide study, Park et al. 2021 reported psychic anxiety to be the most central symptom of the 17-item Hamilton Depression Scale (HAM-D). Overall, while sad mood, lack of interest, and fatigue were central depressive symptoms across cultures, in some international studies, anxiety symptoms were found either as central as (Park and Kim 2020) or more central than depressive symptoms (Van den Bergh, Marchetti, and Koster 2021; Park et al. 2021).

A major methodological limitation in the network literature concerns the assessment of psychological symptoms. The comorbidity networks are typically derived from self-report questionnaires (e.g., PHQ, BDI) or structured interviews (e.g., SCID, MINI; (Malgaroli, Calderon, and Bonanno 2021) mirroring the diagnostic criteria for very specific disorders, such as Major Depressive Disorder and Generalized Anxiety Disorder. While exploring symptom dynamics based on diagnostic categories can be informative, this approach has several limitations. First, symptoms that belong to comorbid conditions (e.g., panic, somatic-related disorders) might be left out limiting our understanding of mental illness to already existing categories. Second, when exploring comorbidity networks, topologically similar symptoms might be included more than once (implicated in both conditions, e.g., sleep disturbance, fatigue). Third, in the case of self-report questionnaires, measurement problems may arise when one symptom domain (e.g., appetite) is assessed via opposite (e.g., diminished and increased appetite) or nested items (e.g., loss of appetite and weight loss) which may lead to biased centrality estimates (Fried and Cramer 2017). Fourth, the use of single-items as nodes could increase measurement error (Fried and Cramer 2017). Fifth, the "skip-out" items (items that are skipped when a core symptom is not endorsed) embedded in many structured interviews may lead to overstated symptom correlations (Hoffman et al. 2019).

The present study addresses these methodological issues in several ways. First, data is drawn from the Revised Clinical Interview Schedule (CIS-R; Lewis et al. 1992) which was developed with an aim to assess Common Mental Disorders (CMDs; Goldberg and Huxley 1992) as one aggregate category capturing all depression, anxiety-related and somatic symptoms listed in the Diagnostic and Statistical Manual (DSM; American Psychiatric Association 1987) and ICD (World Health Organization 2004). The CIS-R is not structured around diagnostic categories. It assesses each symptom only once via multiple items and generates a composite sub-scale score for

each domain (e.g., somatic sub-scale score). As a result, it neither has a skip logic nor overlapping symptoms. Further-more, since the CIS-R has been locally validated and widely used in India, locally relevant symptoms such as irritability are also assessed (Andrew et al. 2012; Weaver 2017). Overall, the CIS-R offers an optimal ground to construct a culturally-valid, comprehensive yet parsimonious symptom network.

The Present Study

The present study consists of secondary analysis of data collected from primary care patients in Goa, India, as part of MANAS (Vikram Patel et al. 2010), a clinical trial aimed at testing the effectiveness of a collaborative stepped-care inter-vention led by lay health counselors. In the MANAS trial, researchers included all primary care patients who screened positive on the 12 item General Health Questionnaire (GHQ-12). There are four aims.

Aim1 In India, the world's most populous low-income country, the health system is heavily privatized and health-care expenditures are a leading cause of poverty (Reddy et al. 2011). High rates of depression, anxiety and somatic symptoms are reported in primary care, ranging between 18.8% to 46% (V. Patel et al. 1998; Vikram Patel et al. 2011; Sen 1987). Yet, little is known about the onset and mechanism of CMDs in adults, and the interplay between the symptoms. The first aim of this current study is to uncover the symptom network of CMDs in an adult primary care patient population in Goa.

Aim 2 Previous symptom network studies found distinct clusters of anxiety and depression with high inter-cluster con-nectivity (O'Driscoll et al. 2021; Park and Kim 2020; Van den Bergh, Marchetti, and Koster 2021). In India, factor an-alytic studies revealed that depression, anxiety and somatic phenomena are not clearly separated among primary care pa-tients. Thus, the second aim is to investigate whether there are distinct communities of illness under the common mental disorder category using network analysis.

Aim 3 Mechanism of illness development and central symp-toms may vary across different socioeconomic levels. One study descriptively compared the symptom networks of pa-tients from countries with different income levels. Park and Kim 2020 found, guilt, fatigue, and suicidality to be more central in high-income countries (Hong Kong, Japan, Korea, Singapore, and Taiwan) and persistent sadness, fatigue, and loss of interest most central in middle-income countries (China, India, Indonesia, Malaysia, and Thailand). While this compar-ison was a unique aspect of this study, the authors explained the differences might be better explained by cultural elements since high-income countries were largely East Asian, whereas middle-income countries were largely South or Southeast Asian. To our knowledge, no study compared networks across different socioeconomic levels within the same culture. Thus, our third aim was to test for the differences in the network structures across different levels of socioeconomic background in India. Earlier findings from the MANAS trial revealed dif-ferential effectiveness of the intervention across public and private health care centers (Vikram Patel et al. 2010), poten-tially indicating public versus private setting might serve as an appropriate proxy for socioeconomic background. Therefore, we used hospital setting as a grouping variable for this study.

Aim 4 Network density, meaning the overall strength of symptom connection, has also been examined in the con-text of prognosis and treatment response. In one study, those with persistent depression at 2-year follow up had "tighter" meaning more connected networks at baseline, compared to remitters (Van Borkulo et al. 2015). Other studies found no such differences in the context of treatment (O'Driscoll et al. 2021; Schweren et al. 2018). Thus, the fourth aim of the present study is to compare the symptom network density of treatment responders at 2, 6, and 12-month follow-up, versus non-responders.

Methods
Participants
The current study draws on baseline and follow-up data from a cluster randomized controlled trial (MANAS trial Vikram Pa-tel et al. 2010) testing the effectiveness of a lay health counselor (LHC) led collaborative stepped care intervention. Eligible participants who screened positive for a CMD using the 12-item General Health Questionnaire (n=2796) were included in the trial. Only baseline data are used to construct the symptom networks for the present study. We used follow-up data col-lected at 2, 6, and 12-months to identify treatment responders versus non-responders.

Measures
The CIS-R has adequate internal consistency (α = 0.82 ; Lewis et al., 1992) and was previously adapted and extensively used in Goa, India (V. Patel et al. 1998; Vikram Patel et al. 2003). The measure assesses the presence and severity (duration, in-tensity, and frequency in the past week or month) of twelve non-psychotic psychiatric symptoms, each captured through multiple-item questions. The following subscales were used in this study; somatic, fatigue, depressed mood, anxiety, worry, phobia, panic, irritability, sleep problems, worry about health, concentration problems, depressive ideas (e.g., hopelessness, suicidal thoughts). While worry subscale captured general wor-ries about things and circumstances, anxiety subscale included items about anxious feelings, nervousness or tension. Depres-sive ideas subscale captured diurnal variation, restlessness, psy-chomotor agitation, feeling guilty, worthlessness, hopelessness, and suicidal ideas.

Each subscale consisted of the sum of four or five binary items. The symptom subscale scores ranged from 0 to 4, except for fatigue and the depressive ideas ranging from 0 to 5. Two additional composite scores (i.e., changes in weight/appetite and functional impairment) were computed for the present study. The appetite and weight change ranged from 0 to 2 and the overall effects variable ranged from 0 to 3. The obsessions and compulsions subscales of the CIS-R have not been part of the interview used in MANAS trial, thus were not included in the analyses. See supplementary material for more detail on the composition of individual variables.

Statistical Analysis

Partial correlation networks (Aim 1)

A network of partial correlations between symptoms (i.e., nodes) was estimated. The partial correlation coefficient (i.e., edge weight) between two focal nodes represents the strength of the linear relationship between them after conditioning on (i.e., partialing out) other nodes in the network (Epskamp and Fried 2018). Partial correlations, as opposed to marginal correlations (i.e., unconditional correlations), are more appropriate for network modeling because under some assumptions they provide information about possible causal relationships. A widely used method to investigate the importance of nodes is called centrality. There are three common centrality indices used: 1) strength refers to the sum of the weights of edges that are connected to a node, 2) closeness refers to the average distance from that node to all other nodes, and 3) betweenness refers to the number of times a node is on the shortest path between two other nodes (Epskamp, Borsboom, and Fried 2018).

The accuracy and stability of the network structures were evaluated in three domains (Epskamp, Borsboom, and Fried 2018). First, the centrality stability (i.e., correlation stability, CS-coefficient) was evaluated. This indicates the maximum proportion of cases that can be dropped to maintain the correlation between the original centrality indices using a case-dropping bootstrap and is recommended to be above 0.5 (Epskamp, Borsboom, and Fried 2018). Second, the edge-weight accuracy and stability was assessed through a nonparametric bootstrap using the bootnet R package (Epskamp, Borsboom, and Fried 2018). Bootnet generates plots showing the bootstrapped CIs of edge-weights, and generally, smaller CIs indicate more accurate edge-weights. Also shown on the plots, if the number of times an edge was estimated to be non-zero is high, the stability of the edge-weights is also considered to be high (Epskamp and Fried 2018). Third, centrality and edge-weight differences are tested with a bootstrap significance test. A bootstrapped confidence interval (CI) is constructed around the difference scores. If the CI overlaps with zero, the centrality of two nodes (or edge-weights) is considered to not differ significantly (Epskamp, Borsboom, and Fried 2018).

Network models were estimated with the R package qgraph using the least absolute shrinkage and selection operator (LASSO; Tibshirani 2011) limiting the number of spurious edges. The lasso tuning parameter controlling the level of network sparsity was selected by minimizing the Extended Bayesian Information Criterion (EBIC; Chen and Chen 2008). The EBIC uses a hyperparameter which is set by the researcher typically between 0 and 0.5 (Foygel and Drton 2010), with higher values indicating more parsimonious models (i.e., fewer edges). For this study, the EBIC hyperparameter was set to 0.25 based on (Hevey 2018) recommendation for exploratory research.

Partial correlation networks, also called Gaussian graphical models (GGM), assume nodes are normally distributed. Because node distributions were skewed for each variable, the source distribution was transformed into a target standard normal distribution (Epskamp and Fried 2018). A nonparametric transformation was used where intermediary cumulative distributions were utilized to create a bijective map between source and target distributions. This was implemented in R using huge package Zhao et al. 2012.

As an alternative solution to skewed data, symptom networks were also estimated using Ising modeling using the IsingFit package in R treating all variables as binary (Epskamp, Borsboom, and Fried 2018), as well as the mixed graphical method (MGM) using the mgm package in R Haslbeck and Waldorp 2020 where only highly skewed variables were treated as binary; namely, anxiety, panic, phobias, appetite and functional impairment. Items were dichotomized based on clinical significance: for anxiety, panic, and phobias, scores equal or greater than 2 were coded as "1", as this has been a typical approach (Jacob et al., 1998). For appetite and functioning, any changes from baseline were coded as "1". Only GGM results are presented due to superior stability and accuracy ((Epskamp, Borsboom, and Fried 2018), see supplementary material for details regarding the MGM and Ising models).

Comorbidity networks (Aim 2)

The community structure was assessed using the walktrap random walk algorithm (Pons and Latapy 2006) within the igraph package (Csardi and Nepusz 2006). The algorithm quantifies the quality of a partition with a measure of modularity. Positive modularity indicated a potential community structure, with higher values of modularity indicating better partitioning. Networks with strong community structures were shown to have modularity indices ranging between 0.3-0.7 (Newman and Girvan 2004).

Group comparisons (Aim 3 and 4)

The challenge when constructing a test of network invariance across groups is that the probability distributions for summary statistics for networks are not analytically tractable. An alternative is to test network invariance using a permutation test (Van Borkulo et al. 2015). Permutation testing was carried out in package NetworkComparisonTest in R (Borkulo et al. 2022) to compare the network structure of treatment responders versus non-responders and public versus private health care settings. The comparison is done in three ways: 1) the global strength, meaning the sum of all edge-weights of permuted data, 2) maximum difference in edge weights, and 3) the Holm-Bonferroni corrected p-values per edge from the permutation test concerning differences in edge weight. For the group comparison that pertained to treatment response, a patient was a "responder" if they 1) were a CMD case at baseline, 2) responded to treatment at 2-months follow-up, and 3) sustained their response over the 6- and 12-months follow-ups. To form a group that is similar in size, a "non-responder" had to be a CMD case at baseline and satisfy one of the following: 1) maintaining the CMD-case status in follow-up assessments, 2) exhibiting a delayed response (at 6 or 12-months follow-up), or 3) response at first but relapse at (6 or 12-months follow-up). Since the network structure comparison based on treatment response might differ across treatment arms, these analyses

were repeated separately for the intervention and control arms.

Results

Demographics

The total number of participants was 2796, with 1648 from 12 public health care facilities (58.9%) and 1148 (41.1%) from 12 private general practitioner facilities. The sample was predominantly female (82%), with a mean age of 46.29 (SD = 13.12), and the mean years of education was 3.67 (SD = 4.14). Based on the CIS-R classification of caseness, a total of 2242 (81%) met criteria for a CMD. Among those, 1032 (46%) had mixed anxiety-depressive disorder, 774 (35%) had depression, and the remaining 436 (19%) had a pure anxiety disorder. A demographic breakdown and rates of CMD and MDD are shown in Table 1.

Table 1. Demographic breakdown and treatment status (n = 2796)

	Frequency	Percentage
Years of Education		
0	1157	41.4
1 to 9	1009	36.1
10 to 14	307	11
15 to 17	35	1.3
Missing	288	10.3
Employment		
Unemployed	1664	59.5
Part time	406	14.5
Full time	374	13.4
Student	10	0.4
Retired	5	0.2
Any other	47	1.7
Missing	290	10.4
Managing Finances		
Living comfortably	254	9.1
Just about getting by	1107	39.6
Difficult to make the ends meet	1145	41
Missing	290	10.4
Debt		
Yes	992	35.5
No	1488	53.2
Don't know	26	0.9
Missing	290	10.4
Treatment Status at follow-up		
Responders	903	32.3
Delayed remission	297	10.6
Relapse	214	7.7
Non-responders	443	15.8
Missing	939	33.6

Network accuracy and stability

The resulting network is presented in Figure 1. The case-dropping bootstrap revealed that the order of node strength

Table 2. The 14 subscale scores across PHC and GP

|	PHC (n = 1648)		GP (n = 1148)		Total (n = 2796)	
	Mean	SD	Mean	SD	Mean	SD
Somatic	1.82	1.65	1.97	1.58	1.88	1.63
Fatigue	3.21	1.65	3.34	1.66	3.27	1.66
Concentration	1.87	1.27	1.71	1.34	1.81	1.3
Sleep	1.95	1.33	2.07	1.27	0.93	1.17
Irritability	0.97	1.21	0.86	1.11	2	1.3
Worry health	1.34	1.5	1.96	1.35	1.6	1.47
Dep. mood	1.63	1.21	1.62	1.22	1.62	1.21
Worry	2.22	1.62	2.02	1.54	2.14	1.59
Dep. ideas	2.17	1.56	2.34	1.54	2.24	1.56
Anxiety	0.69	1.2	0.62	1.04	0.66	1.14
Phobias	0.52	1.02	0.79	1.21	0.86	1.5
Panic	0.92	1.58	0.78	1.35	0.63	1.11
Appetite	0.94	0.74	0.99	0.8	0.96	0.76
Functioning	2.21	0.91	2.07	1	2.15	0.95

PHC = Public Health Care
GP = General Practitioner (Private Health Care)

is interpretable, with a CS-coefficient CS(cor = 0.7) equal to 0.75 meaning the average correlation between the original and bootstrapped indices remains higher than 0.75 even when more than 30% of the cases are dropped. On the other hand, the CS-coefficient indicated that closeness (CS(cor = 0.7) = 0.36) and betweenness (CS(cor = 0.7) = 0.28) remained lower than recommended threshold. Thus, node strength was chosen as the primary centrality index (see supplementary material, Figure 1).

Symptom centrality and edge-weights (Aim 1)

The GGM revealed that the symptom depressed mood had the highest centrality score, though it was not significantly different than centrality scores of the three following symptoms listed in decreasing order; panic, fatigue, and concentration problems (Figure 2). The centrality of the somatic symptom was similar to panic, fatigue, and concentration problems but it was significantly smaller than depressed mood. Sleep problems had the next highest centrality score, followed by anxiety, worry about health, phobias, worry, and functional impairment, in decreasing order. Irritability and appetite problems followed next, with depressive ideas (capturing suicidality and hopelessness) being the least central symptom. The edges phobia-panic, anxiety-panic, and somatic-fatigue were reliably the three strongest, since their bootstrapped confidence intervals (CIs) had no overlap with the CIs of the remaining edges. Visual inspection of the edge differences table revealed several other edges that are significantly stronger than most of the rest: depressed mood-worry, fatigue-concentration, concentration-depressed mood, functional impairment-concentration, and worry-anxiety. The edge anxiety-phobias was significantly smaller than the rest, however, this edge was estimated non-zero only in 61% of the bootstraps, meaning that it was not
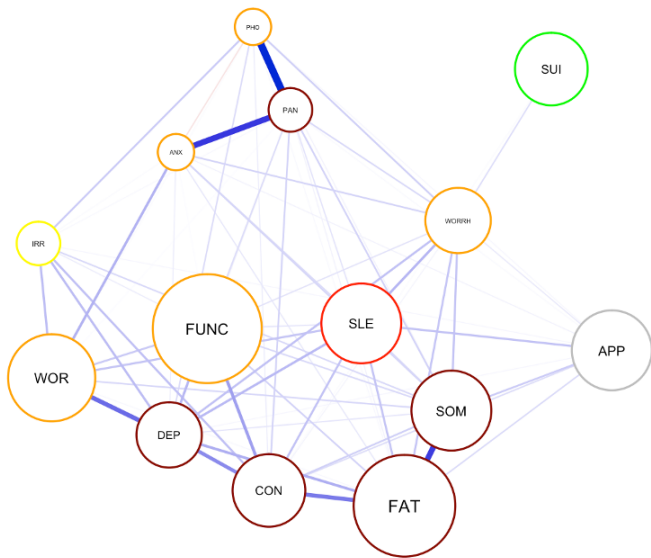
Figure 1. The Gaussian graph model (GGM) network of the 14 CMD symptoms
Note: The size of the nodes represent the mean value. The colors represent node centrality in decreasing order; dark red, red, orange, yellow, green. APP: Appetite and weight changes, ARM: Arm, ANX: Anxiety, CON: Concentration, DEP: Depression, FAT: Fatigue, FUNC: Functional impairment, IRR: Irritability, PAN: Panic, PHO: Phobia, SOM: Somatic, SLE: Sleep problems, SUI: Depressive ideas, WOR: Worry, WORRH: Worry about health.
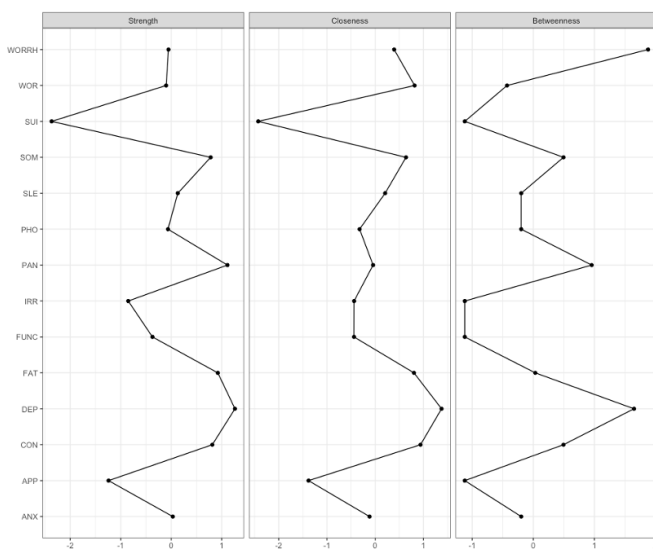
Figure 2. The centrality indices of the GGM network

stable. The boodstrapped differences of centrality scores, edge-weight accuracy, stability and differences are shown in the supplementary material.

Comorbidity networks (Aim 2)

The community detection using the walktrap random walk algorithm did not show strong evidence for a community structure; the modularity was only 0.043, too small to indicate partitioning (Newman and Girvan 2004).

Public versus private health care settings (Aim 3)

The GGM was run for public and private health care patients (Figure 3). The CIS-R total scores, GHQ total scores, and the 12 CIS-R subscale scores across public and private settings are shown in Table 2. Strength centrality indices for both public and private settings were stable (CS-coefficient = 0.75 for both groups). The network densities were not significantly different ($p = 0.157$), with descriptively higher values for public health care patients (4.73, $n = 1648$) than the private health care (4.34, $n = 1148$). The edges anxiety-panic and depression-worry were significantly stronger in the public network than the private health care network ($p < 0.001$), while the edge between somatic-fatigue was significantly stronger in the private network ($p < 0.001$). The NCT does not compare node centralities across groups. Yet, the centrality indices were stable for both groups, meaning bootstrapped differences of centrality indices within each group is reliable. A visual inspection of the black boxes for centrality differences in each group separately (see supplementary material, Figures 9 and 14) revealed that in public settings, the strength centrality scores of panic and depressed mood were the highest centrality indices, while in private settings, it was fatigue, depressed mood, and somatic symptoms.

Responders versus non-responders (Aim 4)

The global strength of the networks from treatment responders ($n = 903$) and non-responders ($n = 954$) were not significantly different ($p = 0.688$), with values of 2.203, 2.556, respectively. The results were similar when the analyses were repeated separately for the intervention arm and control arm. No significant differences were found in the permutation test concerning the maximum difference in edge-weights.

Discussion

This study examined individual symptoms of CMDs in 2796 patients from public and private healthcare settings in India. Our goal was to investigate symptom-to-symptom relationships and diagnostic boundaries of CMDs in a non-Western country across diverse socioeconomic strata using network analysis. Results from the study indicate that, in line with most of the existing literature (e.g., Malgaroli, Calderon, and Bonanno 2021), depressed mood and fatigue were among the most central CMD symptoms. More interestingly, across all models (including Ising and MGM, see additional models in the supplementary material), panic was at least as central as depressed mood and fatigue.

In line with our findings, panic was most central in a large online survey study using the DASS capturing symptoms of depression, anxiety and stress in one single measure (Van den Bergh, Marchetti, and Koster 2021). While the participants of that study were predominantly from Western high-income-countries (US, UK, Canada, and Australia altogether accounted for about 64% of the sample), a Southeast Asian middle-income country Malaysia was overrepresented (25% of the sample). Another study found clinician-assessed psychic anxiety of the HAM-D to be the most central symptom among clinically
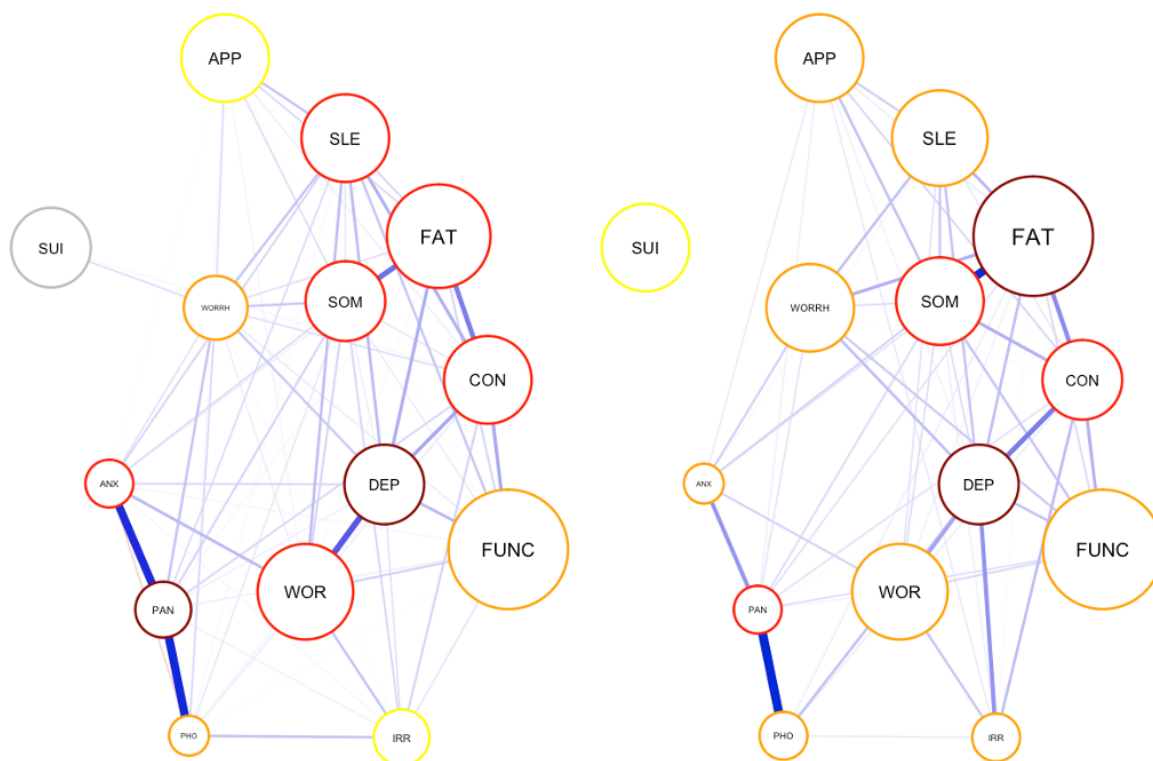
Figure 3. The GGM of the 14 symptoms across public (*n* = 1648, on the left) and private (*n* = 1148, on the right) settings Note: The size of the nodes represent the mean value of the node. The colors represent node centrality in following decreasing order; dark red, red, orange, yellow, green. APP: Appetite and weight changes, ARM: Arm, ANX: Anxiety, CON: Concentration, DEP: Depression, FAT: Fatigue, FUNC: Functional impairment, IRR: Irritability, PAN: Panic, PHO: Phobia, SOM: Somatic, SLE: Sleep problems, SUI: Depressive ideas, WOR: Worry, WORRH: Worry about health.

depressed adults in South Korea (Park and Kim 2020). Both studies used a unified measure to assess depression and anxiety symptoms, had female-majority samples (63% to 82%), and included Asian participants, either entirely or partially. It has been argued previously that typical pathways of depression might differ across men and women, such that an anxiety–pathway could be more plausible for women (Kessler 2003). Similarly, different pathways might be at play across different cultures or income levels.

These findings are corroborated by qualitative studies con–ducted in the region. In an ethnographic study, the authors reported that "tension" as a local idiom could be a central feature of psychological distress in South Asia, with most com–mon features being anger, worry, nervousness or restlessness (Weaver 2017). In fact, in a previous qualitative study nested within the same MANAS trial (Vikram Patel et al. 2010), half of the 117 primary care patients named their health problem as "tension" (Andrew et al. 2012). In CIS-R, panic was con–ceptualized similar to a sense of extreme anxiety or tension: "Thinking about the past month, did your anxiety or tension ever get so bad that you got in a panic, for instance make you feel that you might collapse or lose control unless you did something about it?" Our findings indicate intense anxiety or panic might play an important role in illness development in some groups.

Panic/extreme anxiety is differentiated from other symp–toms (such as worry, worry about health) through its ties with sympathetic activation, potentially indicating that a threat/stress response is activated. Thus, this finding could be truly about the context-specific presentation of the CMDs, changing across different levels of perceived environmental threat, one source possibly being financial distress. In fact, the centrality score of panic might be driven by public health care attendees who constitute the majority in this sample. Health care in India is heavily privatized and related expenditures are a leading cause of poverty (Reddy et al. 2011). Only those with higher resources (both assets and social networks) could access private health care. Thus, one hypothesis generated from this study is as follows: for primary care patients who suffer from the lack of health care resources, a sense of panic is quickly triggering the rest of the network compared to those who have sufficient resources, and this might be the mechanism through which the system is shifting from a healthy to an unhealthy state. A second hypothesis might be that when the patient does not have sufficient resources to access private health care, any acti–vation in the network might more quickly trigger a sense of panic, whereas when the patient has

The density of the responder network, although descrip–tively weaker, was not significantly different than the network of those who did not show sustained response. This might be due to the heterogeneity of the non-response category. For in–stance, those who responded late (at 6-months or 12-months) could have been more similar to the responders group, thereby serving as a confounder. Yet, the lack of significant differ-

ence is in line with others (O'Driscoll et al. 2021; Schweren et al. 2018) and might indicate that in the treatment context, strong edges could in fact serve some patients who began experiencing improvements, by starting a favorable activation in the overall network.

The current study found little evidence to support the notion that anxiety and depression are distinctive conditions. The modularity index being too small to indicate distinct communities for anxiety and depression-specific symptom subscales, there was more evidence for the unidimensionality of the CMDs measured by the CIS-R. This might support the idea that these conditions could not be separated from each other clearly, when a non-diagnostic approach is taken, particularly among primary care attendees in a non-Western, primary care setting.

Strengths, limitations and Implications for Future Research

The study had two major methodological strengths. First, the sample consisted of all primary care patients who screened positive on a health questionnaire as opposed to only depressed or anxious participants as it has typically been done. Including only diagnosed patients would have limited our ability to question the diagnostic categorization, reduced variability and potentially led to erroneous network estimation (De Ron, Fried, and Epskamp 2021). Second, the assessment had a symptom-focused approach rather than a diagnostic focus, where all culturally-relevant symptoms were assessed, and they were assessed only once with more than one item, in a structured interview.

Some methodological challenges existed. First, a decision needed to be made about how to treat the variables given the skewed data distribution. This paper only presents the findings when the variables are treated as continuous, though different models are also examined treating the variables as binary and mixed of binary and continuous. Second, this study might have missed important symptoms and/or have included topologically similar symptoms. The use of composite scores might have overshadowed the importance of some symptoms like guilt and self-blame. Third, while the notion of centrality seems intuitive, its predictive value is unclear. A symptom might be central because it is the "causal endpoint" of a pathway, in which case, intervening on that symptom may not lead to changes in the system (Fried et al. 2018). Strong edges are potentially loaded with information pertaining to the mechanism of change. Finding a strong edge might be a good start though will offer limited clinical implications without knowing the causal mechanism and other factors behind it. Important external factors (latent or observed), however, might contribute to the links between symptoms, including weakened social support, adaptive coping skills, genetic predisposition, and/or neural correlates. Thus, experimental data and longitudinal within-person designs are required to infer a causal chain between symptoms. However, even such research design is not without limitation: isolating one target symptom for intervention is almost impossible clinically, previously referred to as the "fat-hand" problem (Bringmann et al. 2019), where a psychosocial intervention might cause changes in more than one symptom.

To move beyond these limitations, a suggestion for future research is to focus on the "network as a whole" (Bringmann et al. 2019) rather than centrality alone. The "network connectivity/density" (i.e., the global strength) and identification of symptom hubs might have better prognostic value (Cramer et al. 2016). With that perspective, the fact that no specific communities were found in our analyses suggest that all CIS-R symptoms could play an equal role in illness development.

This study examined the CMD symptom networks in a South Asian low-income country and explored the differences in network constellation across different treatment response groups and socioeconomic backgrounds. The findings highlighted the importance of intense anxiety/panic particularly among public health care patients. If this is true, a major public health care implication might be about screening for panic symptom, or "intense anxiety/tension" in primary care settings, to identify those that are at risk of developing or have developed a CMD. However, future studies investigating causality through repeated measures or experimental designs are required before any public health recommendations could be made. Rather than exclusively focusing on the "centrality" of individual symptoms, examining network density, identifying clusters of symptoms with strong reciprocal relationships, and the mechanisms through which symptoms exacerbate each other (i.e., unpacking the edges) is recommended for future studies.

References

American Psychiatric Association. 1987. *Diagnostic and statistical manual of mental disorders.* 3rd ed., R. Washington, DC: American Psychiatric Association.

Andrew, Gracy, Alex Cohen, Shruti Salgaonkar, and Vikram Patel. 2012. The explanatory models of depression and anxiety in primary care: A qualitative study from India. *BMC Research Notes* 5. ISSN: 17560500. https://doi.org/10.1186/1756-0500-5-499.

Borkulo, Claudia D. van, Riet van Bork, Lynn Boschloo, Jolanda J. Kossakowski, Pia Tio, Robert A. Schoevers, Denny Borsboom, and Lourens J. Waldorp. 2022. Comparing Network Structures on Three Aspects: A Permutation Test. *Psychological Methods* 28 (6). ISSN: 1082989X. https://doi.org/10.1037/met0000476.

Bringmann, Laura F, Timon Elmer, Sacha Epskamp, Robert W Krause, David Schoch, Marieke Wichers, Johanna T W Wigman, and Evelien Snippe. 2019. What do centrality measures measure in psychological networks? *Journal of Abnormal Psychology* 128, no. 8 (November): 892–903. ISSN: 1939-1846. https://doi.org/10.1037/abn0000446. https://doi.apa.org/doi/10.1037/abn0000446.

Brown, T A, and D H Barlow. 2009. A proposal for a dimensional classification system based on the shared features of the DSM-IV anxiety and mood disorders: implications for assessment and treatment. *Psychological assessment* 21 (3): 256.

Chen, Jiahua, and Zehua Chen. 2008. Extended Bayesian information criteria for model selection with large model spaces. *Biometrika* 95 (3). ISSN: 00063444. https://doi.org/10.1093/biomet/asn034.

Cramer, A O, C D van Borkulo, E J Giltay, H L van der Maas, K S Kendler, M Scheffer, and D Borsboom. 2016. Major depression as a complex dynamic system. *PloS one* 11 (12): e0167490.

Cramer, A O, D Borsboom, S H Aggen, and K S Kendler. 2012. The pathoplasticity of dysphoric episodes: differential impact of stressful life events on the pattern of depressive symptom inter-correlations. *Psychological medicine* 42 (5): 957–965.

Cramer, A O, L J Waldorp, H L van der Maas, and D Borsboom. 2010. Complex realities require complex theories: Refining and extending the network approach to mental disorders. *Behavioral and Brain Sciences* 33 (2-3): 178–193.

Csardi, G, and T Nepusz. 2006. The igraph software package for complex network research. *InterJournal, Complex Systems* 1695 (5): 1–9.

Cuijpers, P, M Sijbrandij, S L Koole, G Andersson, A T Beekman, and C F Reynolds III. 2013. The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: A meta-analysis of direct comparisons. *World psychiatry* 12 (2): 137–148.

De Ron, J, E I Fried, and S Epskamp. 2021. Psychological networks in clinical populations: Investigating the consequences of Berkson's bias. *Psychological Medicine* 51 (1): 168–176.

Drysdale, A T, L Grosenick, J Downar, K Dunlop, F Mansouri, Y Meng, A F Schatzberg, et al. 2017. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature medicine* 23 (1): 28.

Epskamp, S, D Borsboom, and E I Fried. 2018. Estimating psychological networks and their accuracy: A tutorial paper. *Behavior Research Methods* 50 (1): 195–212.

Epskamp, S, and E I Fried. 2018. A tutorial on regularized partial correlation networks. *Psychological methods* 23 (4): 617.

Foygel, R, and M Drton. 2010. Extended Bayesian information criteria for Gaussian graphical models. *Advances in neural information processing systems,* 604–612.

Fried, E I, C Bockting, R Arjadi, D Borsboom, M Amshoff, A O Cramer, M Stroebe, et al. 2015. From loss to loneliness: The relationship between bereavement and depressive symptoms. *Journal of abnormal psychology* 124 (2): 256.

Fried, E I, and A O Cramer. 2017. Moving forward: Challenges and directions for psychopathological network theory and methodology. *Perspectives on Psychological Science* 12 (6): 999–1020.

Fried, Eiko I., Marloes B. Eidhof, Sabina Palic, Giulio Costantini, Hilde M. Huisman-van Dijk, Claudi L.H. Bockting, Iris Engelhard, Cherie Armour, Anni B.S. Nielsen, and Karen Inge Karstoft. 2018. Replicability and Generalizability of Posttraumatic Stress Disorder (PTSD) Networks: A Cross-Cultural Multisite Study of PTSD Symptoms in Four Trauma Patient Samples. *Clinical Psychological Science* 6 (3). ISSN: 21677034. https://doi.org/10.1177/2167702617745092.

Garabiles, M R, C K Lao, Y Xiong, and B J Hall. 2019. Exploring comorbidity between anxiety and depression among migrant Filipino domestic workers: a network approach. *Journal of affective disorders* 250:85–93.

GBD 2019 Mental Disorders Collaborators. 2022. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* 9:137–50.

Goldberg, D P, and P Huxley. 1992. *Common mental disorders: a bio-social model.* New York, US: Tavistock/Routledge.

Goodkind, M, S B Eickhoff, D J Oathes, Y Jiang, A Chang, L B Jones-Hagata, S M Grieve, et al. 2015. Identification of a common neurobiological substrate for mental illness. *JAMA psychiatry* 72 (4): 305–315.

Haslbeck, Jonas M.B., and Lourens J. Waldorp. 2020. MGM: Estimating time-varying mixed graphical models in high-dimensional data. *Journal of Statistical Software* 93. ISSN: 15487660. https://doi.org/10.18637/jss.v093.i08.

Hevey, D. 2018. Network analysis: a brief overview and tutorial. *Health Psychology and Behavioral Medicine* 6 (1): 301–328.

Hoffman, Michaela, Douglas Steinley, Timothy J Trull, and Kenneth J Sher. 2019. Estimating transdiagnostic symptom networks: The problem of "skip outs" in diagnostic interviews. *Psychological Assessment* 31 (1): 73–81. ISSN: 1939134X. https://doi.org/10.1037/pas0000644.

Kendler, K S, S H Aggen, J Flint, D Borsboom, and E I Fried. 2018. The centrality of DSM and non-DSM depressive symptoms in Han Chinese women with major depression. *Journal of affective disorders* 227:739–744.

Kendler, Kenneth S, Peter Zachar, and Carl Craver. 2011. What kinds of things are psychiatric disorders? *Psychological medicine* 41 (6): 1143–1150.

Kessler, R C. 2003. Epidemiology of women and depression. *Journal of affective disorders* 74 (1): 5–13.

Kessler, R C, W T Chiu, O Demler, and E E Walters. 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry* 62 (6): 617–627.

Lamers, Femke, Patricia Van Oppen, Hannie C. Comijs, Johannes H. Smit, Philip Spinhoven, Anton J.L.M. Van Balkom, Willem A. Nolen, Frans G. Zitman, Aartjan T.F. Beekman, and Brenda W.J.H. Penninx. 2011. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: The Netherlands Study of Depression and Anxiety (NESDA). *Journal of Clinical Psychiatry* 72 (3). ISSN: 01606689. https://doi.org/10.4088/JCP.10m06176blu.

Lewis, G, A J Pelosi, R Araya, and G Dunn. 1992. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychological medicine* 22 (2): 465–486.

Malgaroli, M, A Calderon, and G A Bonanno. 2021. Networks of major depressive disorder: A systematic review.

Newman, M. E.J., and M. Girvan. 2004. Finding and evaluating community structure in networks. *Physical Review E - Statistical, Nonlinear, and Soft Matter Physics* 69 (2 2). ISSN: 1063651X. https://doi.org/10.1103/PhysRevE.69.026113.

O'Driscoll, C., J. E.J. Buckman, E. I. Fried, R. Saunders, Z. D. Cohen, G. Ambler, R. J. DeRubeis, et al. 2021. The importance of transdiagnostic symptom level assessment to understanding prognosis for depressed adults: analysis of data from six randomised control trials. *BMC Medicine* 19 (1). ISSN: 17417015. https://doi.org/10.1186/s12916-021-01971-0.

Park, Seon Cheol, Eun Young Jang, Yu Tao Xiang, Shigenobu Kanba, Takahiro A. Kato, Mian Yoon Chong, Shih Ku Lin, et al. 2020. Network analysis of the depressive symptom profiles in Asian patients with depressive disorders: Findings from the Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD). *Psychiatry and Clinical Neurosciences* 74, no. 6 (June): 344–353. ISSN: 14401819. https://doi.org/10.1111/pcn.12989.

Park, Seon Cheol, and Daeho Kim. 2020. The Centrality of Depression and Anxiety Symptoms in Major Depressive Disorder Determined Using a Network Analysis. *Journal of Affective Disorders* 271. ISSN: 15732517. https://doi.org/10.1016/j.jad.2020.03.078.

Park, Seon Cheol, Yaeseul Kim, Kiwon Kim, Young Sup Woo, Jung Bum Kim, Eun Young Jang, Hwa Young Lee, et al. 2021. Network analysis of the symptoms of depressive disorders over the course of therapy: Changes in centrality measures. *Psychiatry Investigation* 18 (1). ISSN: 19763026. https://doi.org/10.30773/pi.2020.0367.

Patel, V., J. Pereira, L. Coutinho, R. Fernandes, J. Fernandes, and A. Mann. 1998. Poverty, psychological disorder and disability in primary care attenders in Goa, India. *British Journal of Psychiatry* 172 (JUNE). ISSN: 00071250. https://doi.org/10.1192/bjp.172.6.533.

Patel, Vikram, Daniel Chisholm, Sophia Rabe-Hesketh, Fiona Dias-Saxena, Gracy Andrew, and Anthony Mann. 2003. Efficacy and cost-effectiveness of drug and psychological treatments for common mental disorders in general health care in Goa, India: A randomised, controlled trial. *Lancet* 361 (9351). ISSN: 01406736. https://doi.org/10.1016/S0140-6736(03)12119-8.

Patel, Vikram, Helen A. Weiss, Neerja Chowdhary, Smita Naik, Sulochana Pednekar, Sudipto Chatterjee, Bhargav Bhat, et al. 2011. Lay health worker led intervention for depressive and anxiety disorders in India: Impact on clinical and disability outcomes over 12 months. *British Journal of Psychiatry* 199 (6). ISSN: 00071250. https://doi.org/10.1192/bjp.bp.111.092155.

Patel, Vikram, Helen A. Weiss, Neerja Chowdhary, Smita Naik, Sulochana Pednekar, Sudipto Chatterjee, Mary J. De Silva, et al. 2010. Effectiveness of an intervention led by lay health counsellors for depressive and anxiety disorders in primary care in Goa, India (MANAS): A cluster randomised controlled trial. *The Lancet* 376 (9758). ISSN: 01406736. https://doi.org/10.1016/S0140-6736(10)61508-5.

Pons, Pascal, and Matthieu Latapy. 2006. Computing communities in large networks using random walks. *Journal of Graph Algorithms and Applications* 10 (2). ISSN: 15261719. https://doi.org/10.7155/jgaa.00124.

Reddy, K. Srinath, Vikram Patel, Prabhat Jha, Vinod K. Paul, A. K.Shiva Kumar, and Lalit Dandona. 2011. *Towards achievement of universal health care in India by 2020: A call to action,* 9767. https://doi.org/10.1016/S0140-6736(10)61960-5.

Schweren, Lizanne, Claudia D. Van Borkulo, Eiko Fried, and Ian M. Goodyer. 2018. *Assessment of symptom network density as a prognostic marker of treatment response in adolescent depression,* 1. https://doi.org/10.1001/jamapsychiatry.2017.3561.

Sen, B. 1987. Psychiatric phenomena in primary health care their extent and nature. *Indian journal of psychiatry* 29 (1). ISSN: 0019-5545.

Sullivan, Patrick F., Mark J. Daly, Stephan Ripke, Cathryn M. Lewis, Dan Yu Lin, Naomi R. Wray, Benjamin Neale, et al. 2013. A mega-Analysis of genome-wide association studies for major depressive disorder. *Molecular Psychiatry* 18 (4). ISSN: 14765578. https://doi.org/10.1038/mp.2012.21.

Tibshirani, Robert. 2011. Regression shrinkage and selection via the lasso: A retrospective. *Journal of the Royal Statistical Society. Series B: Statistical Methodology* 73 (3). ISSN: 13697412. https://doi.org/10.1111/j.1467-9868.2011.00771.x.

Van Borkulo, Claudia, Lynn Boschloo, Denny Borsboom, Brenda W.J.H. Penninx, J. Waldorp Lourens, and Robert A. Schoevers. 2015. Association of symptom network structure with the course of depression. *JAMA Psychiatry* 72 (12). ISSN: 2168622X. https://doi.org/10.1001/jamapsychiatry.2015.2079.

Van den Bergh, Nathan, Igor Marchetti, and Ernst H.W. Koster. 2021. Bridges over Troubled Waters: Mapping the Interplay Between Anxiety, Depression and Stress Through Network Analysis of the DASS-21. *Cognitive Therapy and Research* 45 (1): 46–60. ISSN: 15732819. https://doi.org/10.1007/s10608-020-10153-w. https://doi.org/10.1007/s10608-020-10153-w.

Wasil, Akash R., Katherine E. Venturo-Conerly, Sachin Shinde, Vikram Patel, and Payton J. Jones. 2020. Applying network analysis to understand depression and substance use in Indian adolescents. *Journal of Affective Disorders* 265. ISSN: 15732517. https://doi.org/10.1016/j.jad.2020.01.025.

Weaver, Lesley Jo. 2017. Tension Among Women in North India: An Idiom of Distress and a Cultural Syndrome. *Culture, Medicine and Psychiatry* 41 (1). ISSN: 1573076X. https://doi.org/10.1007/s11013-016-9516-5.

World Health Organization. 2004. ICD-10 : international statistical classification of diseases and related health problems : tenth revision, 2nd ed. World Health Organization. *Radiology management* 33 (3). ISSN: 01987097.

Zhao, Tuo, Han Liu, Kathryn Roeder, John Lafferty, and Larry Wasserman. 2012. The huge package for high-dimensional undirected graph estimation in R. *Journal of Machine Learning Research* 13. ISSN: 15324435.