Symptom Networks of Common Mental Disorders in an Adult Primary Care Sample in India

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Abstract

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The common mental disorders (CMDs) which include non-psychotic depression and anxiety-related disorders aggregate mental illnesses commonly seen together without assuming clear diagnostic boundaries. Thus, it provides an excellent platform for a symptom-level investigation of common suffering in regions where the current Western-based diagnostic categories may not apply. This current study investigates the symptom networks of CMDs among adult primary care patients in India, using data from a clinical trial testing the effectiveness of a collaborative stepped-care intervention led by lay health counselors. Network modeling was used to investigate a) symptom centralities, b) boundaries between depression and anxiety-related disorders, and c) baseline differences in network configurations across gender, public versus private health care settings, and treatment response over one-year of follow-up. Intense anxiety/panic and fatigue were the most central symptoms overall. While panic and depressed mood were the most central in public health care settings, fatigue and depressed mood were most central in private settings. Overall, findings indicate central symptoms might differ across cultures and socioeconomic groups. To the knowledge of this current author, this is the first study investigating the symptom networks of CMDs among primary care patients in India.

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Dedication

To my parents, Şule and Abidin…

Introduction

The concept of "common mental disorders" (CMDs) captures a large array of commonly seen and highly comorbid depressive and anxiety-related disorders and has gained popularity in community settings. The Revised Clinical Interview Schedule (CIS-R), specifically developed to assess and diagnose CMDs in primary care settings has been extensively used in the non-Western world. The primary advantage of using the CMD conceptualization is to simplify the diagnostic categorization in community settings and to ease case identification. However, in the absence of a locally developed gold standard for mental illness in the non-western world, the CMD case categorization may not be applicable universally. An alternative and novel approach to psychopathology is the network model approach, where symptom correlations are mapped into a visual graph and their strengths of association are evaluated using various metrics.

The overall aim of this current study is to examine the symptom network structure of common mental disorders (CMDs) among adult primary care patients in India who screened positive for depression or anxiety. The study utilizes cross-sectional and prospective data from the MANAS trial, where the effectiveness of a collaborative stepped-care intervention led by lay health counselors was tested in primary care settings in India to reduce the prevalence of the CMDs (Patel et al., 2011). The MANAS trial followed a stratified cluster randomized design with health facility as unit of randomization and included all primary care patients aged over 17 years who screened positive on the 12-item General Health Questionnaire (GHQ-12). The Revised Clinical Interview Schedule (CIS-R) was administered to all participants to detect CMDs and to assess severity of illness. In this current study, the 14 subscale scores of CIS-R capturing all depression and anxiety-related symptom clusters and functional impairment (i.e.,

appetite and weight, somatic symptoms, fatigue, concentration problems, sleep problems, irritability, worry about health, depressed mood, depressive ideas, worry, anxiety, panic, phobias, functional impairment) were included in the network models.

More specifically, this study has three aims: 1) to explore the network configuration of CMD symptoms, 2) to examine diagnostic boundaries between depression and anxiety-related symptoms, 3) to examine differences in network configurations of CMD symptoms across patients of differing sociodemographic groups and treatment status.

To the current author's knowledge this is the first study investigating the network structure of CMDs among adult primary care patients in a low-and-middle-income country (LMIC). Furthermore, the use of the CIS-R, a structured clinical interview, allowing a comprehensive but parsimonious assessment of all symptoms of CMDs is novel. A symptom-level examination of the CMDs, using a network model approach, among all screen-positive primary care patients, sheds light on the cardinal symptoms among a high-risk primary care population.

Chapter 1: Background

"What brings patients to doctors is discomfort and dysfunction, not the pathology which may underlie them". Eisenberg (1986)

Common mental disorders

Patients who seek services in psychiatric facilities are a highly skewed sub-set of everyone who might suffer from a mental disorder (Goldberg & Huxley, 1980). Mental illnesses encountered in community settings are less severe than those seen in psychiatric hospitals (Goldberg & Huxley, 1992), yet they cause enormous suffering and financial burden (Mathers & Loncar, 2006). In an effort to reduce the number of diagnostic categories and to ease the detection and management of commonly seen and less severe forms of mental illness, Goldberg and Huxley (1992) introduced the notion of common mental disorders (CMDs) as a distinct category of mental illnesses, to include all depression and anxiety-related and somatoform disorders listed in the World Health Organization (WHO)'s International Classification of Disease, 10th Edition (ICD-10; WHO, 1992), and American Psychiatric Association (APA)'s Diagnostic and Statistical Manual (DSM-IIIR; APA, 1987). CMDs are the leading neuropsychiatric cause of disability worldwide (Mathers, Lopez, & Murray, 2006) and are projected to be among the three leading causes of the burden of disease by 2020 (Mathers & Loncar, 2006; World Health Organization, 2009). In developing regions, unipolar major depression is projected to be the leading cause of disability-adjusted life years DALYs in 2020 (Murray & Lopez, 1997).

In a comprehensive meta-analysis of 174 population surveys conducted between 1980 and 2013, and across 63 countries, the overall lifetime prevalence of CMDs was 29.2% and the period prevalence was 17.6% (Steel et al., 2014). Highest lifetime rates were found among

English-speaking, high-income countries (39.7%), and lowest in East Asia and Pacific countries (8.6%). The overall period and lifetime prevalence rates of CMDs in low-income countries were reported as 17.2% and 22.7%, respectively. The lifetime rate of CMDs was lower in low-income countries than those found among high-income countries (29.2%), while the point prevalence was similar in both. The cultural validity of the instruments used to assess CMDs is in question and might be the reason for the under-enumeration of CMDs in low-income countries.

CMDs in Primary care. The notion of common mental disorders has been proposed as a way to mitigate the complexities of the DSM and ICD categorizations and allow easier identification of more common and less severe disorders in community settings (Goldberg & Huxley, 1980). This argument is even more valid in a primary care setting, which is the commonest route of referral to mental health services (Gater et al., 1991).

The prevalence rates of CMDs in primary care settings vary dramatically from 9% to 53% across cultures (Puschner, Kösters, & Bouché, 2017; Ormel et al., 1994; Harding et al., 1980), with depression and anxiety being the most common and most frequently related with increased disability (Ormel et al., 1994). In a benchmarking cross-national study by the World Health Organization (WHO; Üstün & Sartorius, 1995), the point prevalence of CMDs among primary care patients across 14 countries was 21%, with major depressive disorder (MDD) and generalized anxiety disorder (GAD) most frequently diagnosed, having point prevalence rates of 10% and 8% respectively. This study also reported that the rates of CMDs did not differ across levels of development of the country or various socioeconomic factors. Furthermore, across cultures, CMDs were similarly related with increased disability among primary care patients, even after controlling for physical disease, highlighting the severe personal and socioeconomic impact of these illnesses (Ormel et al., 1994).

Nevertheless, rates of CMDs in primary care appear to be elevated in individual studies, for some LMICs. For example, in Chile, the prevalence rate of psychiatric morbidity in a primary care clinic was 53% (Araya, Wynn, Leonard, & Lewis, 1994). In Zimbabwe, 25% of primary care attendees and a third of those attending traditional healers had depression (Patel, Abas, Broadhead, Todd, & Reeler, 2001). In India, the prevalence rates of CMDs in primary care settings range from 19% to 50% (Patel et al., 2010; Shamasundar, Murthy, Prakash, Prabhakar, & Subbakrishna, 1986; Patel, et al., 1998; Sen, 1987).

Many patients with psychiatric disorders seek care for somatic symptoms in primary care settings (Goldberg & Bridges, 1988), which complicates the clinical picture and is a reason for misdiagnoses. A somatization disorder is typically diagnosed when there are 6 to 13 medically unexplained, impairing symptoms with at least two years of duration. In a meta-analysis including 32 studies from 24 countries, Haller, Cramer, Lauche, and Dobos (2015) found 41% lifetime and 34.8% period prevalence (over the past year) of at least one somatoform disorder based on DSM or ICD among primary care patients. Furthermore, in 40-49% of all primary care patients, there was at least one medically unexplained symptom.

Somatization is highly comorbid with depression and anxiety disorders and is linked with increased medical cost independent of psychiatric comorbidity. In the United States, 57.7% of the primary care patients who received a provisional diagnosis of somatization also had a depression or anxiety disorder. Somatization was linked with high increased hospital visits, admissions, and inpatient and outpatient costs even after adjusting for psychiatric and medical morbidity and sociodemographic characteristics (Barsky, Orav, & Bates, 2005).

Cross-cultural studies investigating rates of somatization reveal no clear differences across the level of development or geographic location (Simon, VonKorff, Piccinelli, Fullerton,

& Ormel, 1999). The proportion of psychological symptoms to physiological symptoms of depression is similar across cultures, and the association between somatic and CMD symptoms does not differ across different levels of economic development (Simon, Gater, Kisely, & Piccinelli, 1996). In one study, somatization of depression (i.e., reporting only physical complaints as reasons for visit but endorsing symptoms of depression when elicited) was higher in walk-in health care settings, where the patients had no prior relationship with the doctor, compared to settings where the visits were scheduled and privacy is emphasized (Simon et al., 1999).

Almost all primary care patients with mental suffering first report somatic problems across cultures. This is even more prominent in LMICs where spontaneous expressions of distress that bring patients to the primary care almost always involve somatic complaints such as aches, weakness, and fatigue (Patel, 2011). While psychological problems are brought up more frequently in the Western world (Ustun & Sartorious, 1995), these complaints are also reported when elicited in non-Western developing world (Patel, 2011). Overall, it appears that context-dependent variables such as stigma or awareness of CMDs may influence spontaneous reporting of psychological symptoms in health care settings, perhaps more so than the experience of psychological symptoms.

Factor analytic models and CMDs. In 1970, in order to facilitate psychiatric diagnosis for illnesses that are commonly seen in the community, Goldberg and colleagues developed the Clinical Interview Schedule (CIS), as a reliable and acceptable interview even for those who may not see themselves as psychiatrically disturbed. In 1992, the CIS was revised for use by lay interviewers where clinical diagnosis is standardized (CIS-R; Lewis, Pelosi, Araya, & Dunn, 1992). The following 14 symptoms were included in CIS-R; somatic symptoms, fatigue,

concentration and forgetfulness, sleep problems, irritability, worry about physical health, depression, depressive ideas, worry, anxiety, phobias, panic, compulsions, obsessions. Various studies investigated the factor structure of the CMDs, utilizing the CIS-R across cultures, primarily aiming to understand the comorbidities between depression and anxiety (For more details on the CIS-R, see the Methods section).

In a nationally representative sample of 7403 adult participants in England (McBride et al., 2013), the authors carried four confirmatory factor analyses testing the one-factor and two-factors models on both continuous and dichotomized 14 CIS-R symptom scores. The authors found both one-factor and two-factor models fitted the data well, and concluded that the **dichotomized one-factor model** gave the most parsimonious account of the CIS-R. In the two-factor "anxiety-depression" model, somatic, fatigue, concentration, irritability, depression, depressive ideas, and sleep loaded on the "depression" factor, while worry about physical health, worry, anxiety, phobia, panic, compulsions and obsessions loaded on the "anxiety" factor.

In 2013, McCrea conducted a factor analytic study on 13 CIS-R symptoms (excluding depressive ideas) using pooled data on 22,574 adults from three cross-sectional surveys of psychiatric morbidity in Great Britain. This study revealed that one-factor, two-factor, and three-factor solutions exceeded recommended cut-offs for the fit indices, with improved fit for the two-factor and three-factor models, however, the two-and three-factor models had high factor correlations, ranging between 0.61 and 0.82.

In the two-factor model, fatigue and concentration loaded onto the first factor; irritability, depressed mood, worry, anxiety, phobias, panic, compulsions, and obsessions loaded onto the second factor, while somatic, sleep, and worry about health loaded on both factors.

In the three factor model, somatic, fatigue, concentration, sleep, worry about health, and depression loaded onto the first factor, worry, anxiety, and obsessions loaded onto the second, phobias, panic, compulsions loaded onto the third factor, and irritability loaded onto both first and second factors.

While the author concluded that **the most parsimonious and well-fitting model was the one-factor model** which largely supported the assumption of unidimensionality, the better fit indices of the two- and three-factor models could indicate some violation of this assumption. Furthermore, the authors suggested that there were variations in factor loadings for different symptoms, for example, the factor loading of the panic symptom from the singe-factor model was very high (0.82), meaning that this symptom provided more information about the severity of an individual's distress than other symptoms such as, compulsions that had a low factor loading (0.55).

In a cross-sectional study in Greece with 2431 adolescents (16-18 years old), Skapinakis and colleagues (2010) found that a one-factor model fit the data poorly, while a two factor, a two first-order and one second-order factor (internalizing) models fit the data well. The authors concluded that a revised version of **the three-factor model had the best goodness-of-fit, supporting a tripartite model of mental illness, while factor correlations were high (ranging from 0.73 to 0.89)**. The first factor "anxiety" consisted of panic, phobia, anxiety, worry (cross-loading), compulsions and obsessions, the second factor "depression" consisted of depressed mood depressive ideas, and worry (cross-loading), the third factor called "distress" consisted of irritability, concentration problems, fatigue, and sleep problems. The somatic symptoms and worry about health were not included in these analyses.

Cross-cultural factor analytic studies were also conducted using the CIS-R. In 1998, Jacob, Everitt, Patel, Weich, Araya, and Lewis compared the factor structures of four CIS-R data sets from adult health care center patients in Chile, Zimbabwe, and United Kingdom (one from White and one from ethnically Indian patients). Both one factor and two-factor models fit data well, while the three-factor model did not. **Given the very high correlations between anxiety and depression factors (0.9) in the two-factor models, the authors concluded that the one-factor models is the most parsimonious even across cultures**. The authors also noted that for both models, the fit indices improved when the constraints for the loadings of worry, anxiety, and concentration were released, indicating cross-cultural differences in these symptoms and perhaps suggesting that while the depression-related symptoms are similar across cultures, the anxiety-related symptoms might show differences.

In another validation study of the CIS-R, Das-Munshi and colleagues (2014), used a nationally representative data from England consisting of White British (n = 837), Irish (n = 733), Black Caribbean (n = 694), Bangladeshi (n=650), Indian (n=643) and Pakistani (n = 724) respondents. **Exploratory analyses based on data collected from the White British sample indicated a three-factor solution, while two-factor and one-factor solutions were equally well fitting**: 1) "depression-anxiety" factor including concentration problems, sleep problems, irritability, depressed mood, worry, anxiety, obsessive thoughts and depressive ideas, 2) "somatic" factor, somatic symptoms, fatigue, physical health worries, panic, and 3) "phobic compulsions" factor consisting of phobias and compulsive behaviors. The two-factor solution was similar to three factor solution, phobias and compulsive behaviors loaded under the first "depression-anxiety" factor, and anxiety loaded under "somatic symptoms" factor. Confirmatory analyses with the full ethnic minority sample, revealed all three models were fitting well, with

the three-factor model showing marginally better fit. When the "somatic symptoms" were allowed to vary across minority groups, while holding the depression-anxiety construct invariant, all models improved, suggesting variability in reporting somatic symptoms across groups.

Summary of factor analytic studies on CIS-R. Overall, these results provide some evidence for the hypothesis of unidimensionality of CMDs, since in all but one study, one-factor models showed adequate goodness-of-fit. In two large nationalistic studies conducted in the UK and one cross-cultural study of health care patients, the authors chose a single-factor model over two- or three-factor models based on their parsimony, and also because of the high correlations between factors. In a study conducted with adolescents in Greece, and in a cross-ethnic minority study conducted in the UK, authors reported a better fit of a three-factor model. In another cross-cultural study where all 14 symptoms of the CIS-R were included, the three factors were, depression-anxiety, somatic, and panic-compulsions. Cross-cultural studies concluded that there appears to be evidence for universality of the CMDs, as the same factor structure holds across groups (particularly depression-related symptoms), though, these studies also indicate that certain symptoms (anxiety and somatization-related) might be expressed differently across cultures.

India. The CMD framework has been widely used for decades in India, one of the world's most populous low-and-middle-income country, in an attempt to move beyond the myriad of categorizations offered by today's predominant diagnostic systems developed in the Western world. Symptom-level investigations were conducted and local idioms of distress were also explored by many researchers, pointing out the similarities and differences of the clinical picture in India compared to the rest of the world. Below, a review of rates of CMD prevalence and research on the psychiatric phenomena in India is provided, followed by a section summary.

Prevalence of CMDs in India. In India, health system is heavily privatized and health-care expenditures are a leading cause of poverty (Reddy et al., 2016). High rates of CMDs are reported in India across public and private primary care clinics. An early study by Sen (1978) reported a 46% of CMD prevalence rate among 114 consecutive adult patients from three primary health care clinics in Calcutta, India. In another study, 303 adult primary care patients in two health facilities in Goa, India, 46.5% were identified as CMD cases using the total score of the CIS-R (Patel, Pereira, Coutinho, Fernandes, Fernandes, & Mann, 1998). Lower rates of CMD prevalence were reported as part of the MANAS trial, where a large number of primary care patients were screened (Patel et al., 2010; 2011). Of 20,352 patients screened across 24 public and private health care facilities in Goa, India, 3816 (18.8%) screened positive for CMDs. Among these, 46% received mixed anxiety-depressive disorder.

Symptoms of CMDs and local idioms of distress in India. Symptom-level analyses of CMDs were conducted in India, in an effort to investigate the nature of the psychiatric phenomena as it is observed locally (Sen, 1987). In a multiple linear regression analysis, only four items of the 20-item Self Reporting Questionnaire (SRQ) contributed significantly to the total CIS score. One of these items was the core symptom of depression "unhappy", and the remaining three were non-DSM, "can't think clearly", "daily work suffering", and "always tired", jointly explaining 38% of the variance. Further, the principal component analysis on the SRQ revealed seven factors, with the first factor capturing the two core symptoms of depression "unhappy", "unable to enjoy", plus one anxiety symptom "anxious/tense/worried". This factor explaining more than 20% of the total variance was labeled as the "depression anxiety" component by the authors. The remaining six factors each explained between 5% and 8% of the

variance, and the depression, anxiety and somatic phenomena were not clearly separated in most of these factors (Sen, 1987).

The clinical presentation of CMDs in India has been studied qualitatively among low-income women (Pereira et al., 2007) and postpartum mothers (Rodrigues, Patel, Jaswal, & de Souza, 2003). Building on these studies, Andrew, Cohen, Salgaonkar, and Patel (2012) conducted a qualitative study among 117 primary care patients with CMD, participating in an effectiveness trial in Goa (MANAS, Patel et al., 2010). The commonest reasons for consulting the primary care physician were aches and pains and lack of sleep (89%, for each category), followed by autonomic symptoms (82%), and weakness/tiredness (79%). While psychological complaints were very rarely reported as the reason for consultation, 90% of the patients reported emotional phenomena and over 80% reported cognitive phenomena when probed. The emotional phenomena included anger/irritability (75%), lack of interest (50%), sadness (48%), feeling fed up of ongoing problems (45%), nervous/scared (26%), hopelessness (12%). The most frequently reported cognitive phenomena included thinking too much/worrying (79%) followed by forgetfulness (21%).

When asked to name their problems, 50% stated “tension and worry” while 15% labeled their illness as “weakness”. Fourteen percent attributed their problems as physical illness (e.g., diabetes and hypertension), while none referred to it as “mental illness”. Based on these results, the authors proposed a conceptual model of the causal pathways of CMD, where life events and social difficulties lead to “tension” or “worry”, which in turn lead to somatic and emotional symptoms (Andrew et al., 2012). Similarly, Weaver (2017) proposed that “tension” is a central feature of psychological distress in India and used free-lists, unstructured and semi-structured interviews to develop a locally derived scale of tension. The master list of tension included five

anger-related items; feeling angry, upset, irritable, feeling like hitting something, and blaming others. Feeling bad, not feeling like doing anything, thinking too much or worrying, inability to sleep, somatic pain, gas, or digestion problems, feeling restless, feeling weak or tired out were among other items in the tension scale.

Gender and socioeconomic risk factors for CMDs in India. Socioeconomic status and gender are two demographic factors that are related with CMDs in low and middle-income countries (e.g., Lund et al., 2010). In a community survey, Patel et al. (2006) reported among 2494 women, gender-related factors such as sexual violence, being widowed or separated, having low autonomy in making decisions, low levels of support from family, and gynecological factors were independently associated with the risk for CMD.

Financial status is another correlate of CMDs. In their cross-sectional survey study, Patel and colleagues (1998) interviewed the participants on five proxy economic status indicators and found that in addition to being female, all economic status indicators were significantly related with CMD caseness; being in debt, unemployed, unable to buy food due to lack of money in the past month, unable to meet daily needs with the money they had were significantly related, and higher index for crowd (the number of persons in the household divided by the number of rooms in the house).

A major finding from the MANAS trial (Patel et al., 2011) was about the differential effect of the collaborative stepped-care model across private versus public clinics. While the intervention was more effective than the enhanced care in public setting for all primary outcomes, such difference was not found in private clinics, which was explained by the already "client-centered" and personalized care provided by the private setting. This differential effect could be due to various other confounding factors pertaining to the types of patients who can

afford private care. Nevertheless, the type of clinic appears to be an important factor in India's health care system.

Summary of research in India. Several conclusions could be drawn based on the body of research investigating the CMDs (based on ICD-10) in India. First, CMDs as defined in the Western world could be found among more than a quarter of primary care patients in India. Second, being female and belonging to lower socioeconomic class appears to be among the most important risk factors in this population.

Third, somatic symptoms such as **aches and pains, autonomic symptoms,** along with more physical symptoms **such as lack of sleep and weakness/tiredness** appear to be among the primary concerns bringing these patients to the primary care clinics.

Fourth, primary care patients with CMDs almost always report somatic concerns when inquired about reason for visit, and almost all patients report psychological symptoms that capture both depression and anxiety-related constructs when inquired. The CMD cases often exhibited mixed depression and anxiety symptoms along with somatic complaints and factor analyses failed to distinguish depression and anxiety symptoms. In fact, a local idiom of distress, "tension", seems to capture some depression and anxiety symptoms as conceptualized in the Western world: **anger/irritability**, and **lack of interest** are among the most commonly cited emotional symptoms, and **thinking too much (conceptualized as worry)** emerges as the most prominent cognitive symptoms. These findings beg the question whether clear diagnostic boundaries, as defined in the Western world, exist in this population.

The qualitatively identified local idioms of distress seem to overlap with the following six symptom clusters measured by the CIS-R: somatic symptoms, sleep problems, fatigue, irritability, depressed mood, and worry. The way in which these symptoms are connected with

each other and the rest of the symptom clusters (e.g., concentration and forgetfulness, appetite and weight change, anxiety, worry about physical health, hopelessness and suicidal ideation, phobias, and panic) and the functional impairment is unknown. Further, in some studies, the participants were already diagnosed with a CMD. Therefore, it is unknown whether these six symptom clusters would also be reported by those who did not meet the criteria for a CMD.

An exploration of these symptoms using a network modeling approach, including all primary care patients who screened positive for a CMD could shed light on the symptoms that might have clinical value. A close examination of the symptom networks across different demographic backgrounds (i.e., gender and private versus public settings) may help examine whether the relationships between symptoms can explain why certain subgroups are more at-risk than others. Understanding whether the baseline symptom networks change across different groups of patients with different response to treatment can alert primary care physicians to certain central symptoms and intervene accordingly. For example, if irritability is a central symptom among those who responded to treatment, however, sleep problems appear to be more central among those who did not respond, a recommendation for an intervention on the sleep problems could be made to primary care physicians, hoping to change the course of treatment.

In the following sections, the existing literature and findings on the network model approach is introduced. First, several limitations of the current diagnostic approach are discussed including those that pertain to cross-cultural validity, conceptual and psychometric issues, and clinical practice. Second, the network models are described and defining characteristics of a network are outlined. Third, clinical applications of network analysis are reviewed.

Limitations of the diagnostic approach

Cross-cultural validity. Local idioms of distress across cultures have been investigated in various cultures, revealing some overlap with each other and Western concepts of depression and anxiety. Locally developed or culturally adapted versions of western-based measures appear to be mostly similar in their item composition and could be used in the assessment of CMDs (Patel, 2011). For instance, thinking too much or rumination was found in Zimbabwe (*kufungisisa*; Patel, Simunyu, & Gwanzura, 1995) and Haiti (*reflechi twop*; Kaiser et al., 2014); constant worry, sadness or sorrow, and hopelessness were found in Rwanda (*guhangayika, agahinda kenshi*, *kwiheba*, respectively; Betancourt et al., 2011); no interest in things, sadness, and irritability were reported in Uganda as symptoms of the local depression-like syndromes "self-hatred" and "self-pity" (*Yo'kwekyawa* and *Okwekubaziga*; Wilk & Bolton, 2012). However, even if phenomena like low mood, anhedonia, or hopelessness are part of a universal syndrome, it is unknown whether its diagnostic criteria would have to follow the Western gold standard in non-Western settings.

Conceptual limitations. In our current schema of mental illness, the first assumption is the distinct disease category (Fried, 2015). As proposed by Kendler and colleagues, a DSM diagnosis should consist of a psychological or behavioral syndrome related to an underlying psychobiological disturbance, also called the common cause model. Yet, depression and anxiety-related disorders often appear together (Kessler, Chiu, Demler, & Walters, 2005), and seem to have similar epidemiological profiles and treatment responsiveness. The comorbidity rates for anxiety and depressive disorders ranges from 40%-80% in epidemiological studies (Lamers et al., 2011; Kessler et al., 2005) and research on the biomarkers has been inconclusive, likely due to the remarkable heterogeneity of these disorders (Drysdale et al., 2017), potentially small effect

sizes (Ripke et al., 2013) and shared neurobiological substrates across diagnoses (Goodkind et al., 2015).

There are psychometric limitations attached to this conceptualization. The common cause model refers to the assumption that a latent underlying factor causes the disease's symptoms (e.g., measles infection causes measles symptoms; Fried, 2015). Factor analytic models are the ones that best capture this conceptualization. In factor analysis, symptoms are often viewed as equally central to the disorder, and locally independent, as in, their correlations are considered to be "spurious" beyond their shared origin (Holland and Rosenbaum, 1986). However, there is compelling evidence that symptoms often influence each other (insomnia causing fatigue, or hopelessness causing suicidal ideation), forming vicious circles, maintaining each other and the disorder.

Clinical limitations. In our current conceptualization of mental illness, the emphasis is on two outcome measures: 1) the "caseness", whether a patient meets a predetermined criteria of a certain mental illness, and 2) the "sum/total scores" of diagnostic measures (Fried, 2015). The diagnostic categorization and sum scores, often crucial in clinical research and treatment, may obscure the unique symptom presentation of mental illnesses within each individual and across different populations. Changes in sum scores are often used as a measure of improvement in treatment, without assessing the symptoms that change versus remain the same over time, or the symptoms that are closely linked with functional impairment. Furthermore, sub-threshold patients may not receive clinical care that they might actually need.

An alternative conceptualization: Network models

Cramer and colleagues (2010) proposed an alternative model to the latent factor models of a disorder, where the disorder is conceptualized as an interactive and mutually reinforcing network of symptoms, rather than being a latent construct. This alternative framework posits that the symptoms do not cluster together because of a shared origin, but because they tend to trigger, influence, and maintain each other. Growing evidence supports the usefulness of using network modeling. Recent studies shed further light on the issue of comorbidity, revealing the importance of overlapping symptoms across diagnoses that contribute to comorbid conditions (Cramer et al., 2010). Using network models, symptoms were found to be differentially related with functional impairment (Fried & Nesse, 2014), the onset (Boschloo et al., 2016) and the course of illness (van Borkulo, et al., 2015). Furthermore, Cramer and colleagues (2012) tested the network models of depressive episode against the traditional common cause model. The results indicated that the model based on the common cause framework fit the data significantly worse than the model based on the network framework. Similar findings were reported in another study looking at persistent complex bereavement disorder (or complicated grief, CG), where the network modeling fit the data better than the common cause approach when the loss of a spouse was included in the model (Fried et al., 2015).

Network estimation. For data that is assumed to be multivariate normal, the most common method is to estimate a network of partial correlation coefficients, either by inverting the sample variance–covariance matrix or by multiple regressions and standardizing the obtained coefficients (Epskamp, Borsboom & Fried, 2018). Since, only applying this method would lead to many very weak but non-zero edges, it has become popular to apply the least absolute shrinkage and selection operator (lasso; Tibshirani, 1996), which in essence, “shrinks” all

estimates by limiting the sum of absolute partial correlation coefficients, thus some coefficients become zero. This method generates a collection of networks ranging from fully connected to fully disconnected, and a network is selected by optimizing the fit between the network and the data, using the Minimizing the Extended Bayesian Information Criterion (EBIC; Chen & Chen, 2008).

When using lasso with EBIC, the researcher has to make an important decision on whether they would like to err on the side of discovery (dense network with potentially more spurious edges, hardly any true connections are missed) or caution (parsimonious network with fewer edges, hardly any false positives but true connections are missed). Based on that decision, the hyperparameter γ (gamma) is set between 0 (for discovery) and 0.5 (for caution). While setting $\gamma = 0.5$ has been previously recommended (Foygel & Drton, 2010), Ebskamp and Fried (2016) showed that this was fairly conservative and suggested the selection of this parameter was somewhat arbitrary and up to the researcher. For exploratory, hypothesis-generating research, where the researcher would like to err on the side of discovery, a value of 0.25 was proposed as a useful compromise (Hevey, 2018).

Network characteristics. A symptom network is a graphical model with two components: nodes and edges. Each symptom included in the analysis is a *node*. Nodes are connected with each other through an *edge*, representing the zero-order correlation between the two connected symptoms. The number of edges that connect to a node is called the *degree* of a node, and the magnitude of the correlation between two nodes is called *weight*.

Symptom centrality. Three indices of centrality are typically used in network modeling: strength, closeness, and betweenness. The *strength* of a node refers to the sum of the weights of edges that are connected to this symptom (i.e., total correlation magnitudes). The *closeness* refers

to the average distance from that node to all other nodes. The *betweenness* is defined as the number of times that node lies on the shortest path between two other nodes.

Network connectivity and density. The network connectivity is defined as the number of connections that were estimated to be non-zero (Boschloo et al., 2016; Costantini et al., 2015), while the network density (or global strength) is defined as the average edge strength.

Comorbidity networks. Diagnostic comorbidities have been evaluated using two different approaches. Some studies simply organized the network graphics based on pre-established criteria (i.e., DSM, ICD-10) and either visually investigated the sub-groups, or looked at the symptom correlations within and across diagnostic groups (e.g., Cramer, 2012, Boshchloo et al., 2015). Other studies (e.g., Choi et al., 2017) used a special network property called *community structure*. In this method, the network nodes are divided into groups, where symptom connections are denser within sub-groups compared to across sub-groups (Newman & Girvan, 2004).

Applications of network models

The network modeling of psychopathology had numerous applications in a variety of populations and diagnostic categories. Symptom networks of PTSD (McNally et al., 2015; Armour, Fried, Deserno, Tsai, & Pietrzak, 2017), eating disorders (Forbush, Siew, Vitevitch, 2016), and psychotic symptoms in relation with childhood trauma (Isvoranu et al., 2016) were previously investigated. Symptoms of depression have been investigated together with generalized anxiety disorder (Cramer et al., 2010), in relation with the loss of spouse (Fried et al., 2015), as predicted by stressful life events (Cramer, Borsboom, Aggen, & Kendler, 2012), and in relation with the course of depression (Van Borkulo et al., 2015). The dynamic nature of the symptom network of depression has been explored in several studies through frequent

assessment of symptoms over time, using ecological momentary assessments (Van Leemput et al., 2013; Bringmann, Lemmens, Huibers, Borsboom, & Tuerlinkx, 2015; Snippe et al., 2017).

Symptom networks of depression and anxiety. The first empirical paper investigating symptom networks of psychopathology came from Cramer and colleagues (2010). In this study, authors used data from the National Comorbidity Survey Replication (NCSR; Kessler et al., 2005) and investigated the symptom network of MDD and GAD. The symptoms were assessed using the World Mental Health (WMH) version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMH-CIDI), a structured interview generating diagnoses based on the International Classification of Diseases, 10th (ICD-10) and DSM-IV diagnoses. In this study, **depressed mood and loss of interest** were the most central symptoms among all. Furthermore, authors found that the GAD symptoms were more frequently endorsed than the MDD symptoms, a finding that is surprising given the higher prevalence of MDD diagnosis in this sample. The authors argued that the diagnostic criteria for GAD (e.g., duration, symptoms occurring outside of MDD) might overshadow the prevalence of GAD symptoms.

The authors found evidence for high comorbidity rates attributable to overlapping symptoms that exist in both conditions (e.g., sleep disturbances, restlessness, fatigue). Nevertheless, some symptoms specific to depression (e.g., loss of interest) had high co-occurrence with some symptoms specific to anxiety (e.g., worry about more than one event) indicating true comorbidity. The overlapping symptoms appear to be a true challenge in the interpretation of the results, since, removing these symptoms would not give the complete picture, and there was not enough statistical evidence that the same symptoms could be collapsed either. It appeared that, for example, the answers for sleep problems in depression section were

not the same as the answers for the anxiety section, since that question might have been skipped for someone who did not endorse the gauging questions and that section was skipped entirely.

Using cross sectional data from 34,653 adults participating the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Boschloo and colleagues (2015) included 120 symptoms of twelve psychiatric diagnoses established by the structured Alcohol Use Disorder and Associated Disabilities Interview Schedule DSM-IV Version (AUDADIS-IV) in a network model. This study was the first to apply a network model to a range of DSM-IV symptoms, in a large community sample. The results revealed more connections between symptoms that are within the same diagnosis (i.e., 64.7%-100%) than those across diagnoses (i.e., 1.1%-6.9%), supporting the global framework of the DSM. In addition, symptoms of a given diagnosis were connected to at least three symptoms from other diagnoses, potentially accounting for comorbidity. For instance, similar to the findings by Cramer and colleagues (2010), the authors found **depressed mood symptom** of major depressive episode to be strongly connected to worry of **generalized anxiety disorder**. Among the symptoms of depression **depressed mood** and **fatigue** were the most central.

One limitation of this study was the skip-logic inherent to the structured interview, which resulted with missing data for some participants who did not endorse the gauging question for a diagnosis. The authors encouraged future researchers to apply the network techniques to diagnostic information assessed by instruments that don't follow the skip-structure of the DSM.

In a follow up study, Boschloo, van Borkulo, Borsboom, and Schovers (2016) tested whether symptom centrality was related with the risk of developing MDD. 501 adults with no lifetime DSM-IV depressive or anxiety disorder were selected from the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA) and the specific items of the

Inventory of Depressive Symptomatology were entered into a symptom network. The authors found **fatigue, concentration problems, loss of interest/pleasure, and depressed mood** had the highest strength, while hypersomnia, suicidal thoughts and a decrease in weight/appetite had the lowest symptom strength. Furthermore, the authors reported that these symptoms more strongly predicted the onset of MDD compared to those that were less central.

In a study including 3,463 depressed outpatients from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the 28 symptoms of depression were investigated using network modeling (Fried, Epskamp, Nesse, Tuerlinckx, & Borsboom, 2016). The results revealed that among the 28 symptoms of depression included in the network, **energy loss and sadness** were the two most central symptoms. Overall, the symptoms that are listed in the DSM under the criteria for the major depressive disorder were not more central than symptoms that are not in the DSM. For instance, **anxiety**, a non-DSM symptom for depression, was more central than many DSM symptoms of depression such as self-blame, insomnia, hypersomnia, weight problems and agitation. Somatic complaints and irritability were among the least central, though still more central than weight problems, agitation, hypersomnia, sexual disinterest. One limitation was that the participants had to fulfill DSM-IV criteria for single or recurrent nonpsychotic MD, which makes it hard to generalize the findings to all persons who experience distress. Another limitation was the lack of parsimony among symptoms. There were three insomnia items (early, late and mid), highly inter-correlated, which might have changed their centrality.

Symptom networks of depression and anxiety in non-Western world. Recently, the role of daily stressors in explaining the link between trauma exposure (e.g., war, displacement) and distress; particularly PTSD, anxiety, and depression symptoms (Miller & Rasmussen, 2010) were

further explored using network analysis in non-Western regions. These studies included youth in Northern Uganda (De Schryver, Vindevogel, Rasmussen, and Cramer, 2015), adult war survivors in Sri Lanka (Jayawickreme et al., 2017), and Darfur refugees in Chad (Mootoo, Fountain, & Rasmussen, 2019).

Jayawickreme et al. (2017) conducted a study among 337 survivors of war in Sri Lanka, who sought psychosocial assistance at a local clinic. Researchers included items from a locally developed questionnaire as nodes in a network. The questionnaire included three sections; 1) trauma exposure (torture and other war trauma), 2) stressful life problems (family problems, economic problems, social problems, lack of basic needs, and physical problems) and 3) symptoms of psychopathology (anxiety and depression). The authors found symptoms of psychopathology, problems pertaining to lack of basic needs, and social problems to be central, in contrast to traumatic events and other types of stressful life problems, highlighting the importance of daily stressors and the need for holistic approaches in mental health. In terms of psychopathology symptoms, researchers found avoidance due to fear and not visiting nearby relatives (PTSD/anxiety sub-scale); lack of happiness, feeling unable to live even one day, and carelessness/impatience (depression sub-scale) as key symptoms in this sample.

In a more recent study, Mootoo, Fountain, and Rasmussen (2019) used the network approach to model relationships between traumatic events, displacement stressors, impairment, and distress among 863 Darfur refugees residing in two refugee camps in Eastern Chad. In this study, authors used a locally developed distress measure, *hozun* (meaning "deep sadness") which had many overlapping symptoms of depression and PTSD as defined in DSM. In terms of symptoms of distress, nodes with highest strength were melancholy, flashbacks, recurring thoughts, recurrent nightmares, and being physiologically reactive.

Most recently, network analysis was applied to a sample from India. Wasil and colleagues (2020) found among 13,035 ninth grade adolescents that "sad mood" and "feeling like a failure" symptoms of the PHQ-9 were central. Authors pointed out that the latter might be a potentially culture-specific non-Western central symptom. This study only focused on symptoms of depression (not anxiety) using the PHQ-9 questionnaire.

Comorbidity networks. To the current author's knowledge, the only study where the comorbidity between depression and anxiety disorders was investigated using the community network included depression and PTSD symptoms among a community sample of adults in a multisite RCT in the United States (Choi et al., 2017). The symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) and Davidson Trauma Scale (DTS). The authors found evidence for distinct depression and PTSD symptom subclusters. The number of connections was greater between symptoms of the same disorder than across disorders. Furthermore, the substantial modularity measure revealed that depressive symptoms tended to group separately from PTSD symptoms.

External factors. Multimodal data could be used in network models. Within the network perspective, it is possible to extend the symptom space to include certain external factors (e.g., stressful life event) or consequences (e.g., suicide attempt). Daily stressors and war exposure questionnaire items were included in several studies (De Schryver, Vindevogel, Rasmussen, & Cramer, 2015; Jayawickreme, 2017) symptoms. Demographic variables, self-reported IQ, level of daily activity were previously included in a well-being network among patients with autism spectrum disorder (Deserno, Borsboom, Beeger, & Geurts, 2016). Other examples of variables successfully included in networks include, personality structures (Constantini et al., 2015), behavioral problems in a preadolescent sample (Boschloo, Schoevers, van Borkulo, Borsboom,

& Oldehinkel, 2016), and components of attention measured in a laboratory experiment (Hareen and McNally, 2016).

Network comparisons across groups. Choi et al. (2017) qualitatively compared the network structure of depression and PTSD across patients who reported high-sexual risk versus low-sexual risk behavior. The networks appeared to have similar densities in both groups. However, in the higher-risk group, the connectivity of symptoms within the avoidance and intrusions clusters of the PTSD appeared to be denser.

Course of depression. The course of depression was prospectively investigated using network modeling, revealing differences in symptom networks of those whose depression remitted at 2-years follow-up compared to those whose depression persisted. Using the NESDA dataset, Van Borkulo and colleagues (2016) found that among 515 participants with a past-year MDD diagnosis, 253 had persistent MDD at 2-years follow-up. The symptom network of those who persisted was denser than the network of those who remitted. Furthermore, **fatigue/loss of energy** and **feeling guilty** had larger node strength in the persisters' network compared to the remitters' network.

Summary of results and gaps in the literature. The results were mixed in terms of the DSM categorization, largely indicating no clear boundaries between anxiety and depression. While in some studies, there was evidence supporting the global framework of DSM, findings from other studies indicated that some non-DSM symptoms are more central than DSM symptoms. Energy loss emerged as a central symptom in addition to the two other core symptoms of depression. In terms of the DSM categorization of depression, the results largely supported the centrality of the two core depression symptoms, depressed mood and lack of

interest. Yet, the diagnostic boundaries between depression and anxiety did not seem to hold. Core symptoms of depression appeared be strongly connected core symptoms of anxiety.

Overall, Western and non-Western network model findings seem to be in line with the symptom-level investigations of the CMD symptoms in India in two ways: 1) the potential importance of fatigue/energy loss in addition to loss of interest among those with CMD, 2) the strong association between the core anxiety and depression symptoms. In India, however, irritability appear to be an important symptom as indicated by both qualitative and quantitative research, which is included as a variable in this current study.

A large body of research focused on depression and anxiety related disorders together but these studies did not entirely adopt the CMD approach, as the symptoms were often assessed either using self-report questionnaires or structured interviews (other than CIS-R) and entered into the network as nodes. As a result, overlapping symptoms between depression and anxiety, which were captured twice and entered in the network separately caused a common problem in previous studies. These nodes showed strong correlations with each other as expected and might have influenced the network connections (Cramer et al., 2010).

Most studies were conducted with Western samples. A body of research in war and conflict affected regions did investigate the depression and anxiety in non-Western world (e.g., Sri Lanka, Darfur refugees in Chad). A major strength of these studies was that they used locally developed questionnaires capturing local idioms of distress. These studies were different than the current study in that they primarily focused on trauma response, PTSD, and a specific population exposed to severe adversity, thus it would be difficult to generalize the results to broader population. There was one study where the symptom network of depression was investigated among a large sample of adolescents in India, where sadness and failure to be more central than

the other seven symptoms of the PHQ-9 (e.g., sleep, suicidal ideation, appetite). This study used a brief self-report questionnaire, primarily focused on depression and did not include adults.

Overall, the results reveal that the network modeling can be a conceptually and statistically valid way of investigating the symptom-level data, with potentially clinical importance. The symptoms that appear to be central in the network analysis may actually play a critical role in predicting the onset and the course of depression, in the absence of treatment. It would be important to understand the differences between baseline symptom network of treatment responders with non-responders.

Rationale and Significance

The network models of CMDs might offer new ways of understanding most frequently encountered mental illnesses in the non-western world. The research on global mental health starts with the investigation of idioms of distress in non-western cultures to see whether depression and anxiety exist in these cultures. Years of evidence suggest the maladaptive response to stress presents itself similarly around the world and even if the exact constructs are not frequently used for various reasons, proxies are. However, the presence of individual symptoms in one culture does not warrant the presence of that illness as conceptualized in another culture. The present study fills the gap in the literature in several ways.

First, to the current author's knowledge, symptom networks of CMDs have not been investigated among distressed primary care patients in a non-Western, developing country. Second, the participants are those who were screened positive using a culturally valid screening questionnaire. Therefore, this study includes both threshold and sub-threshold CMD cases allowing for a more complete picture of a high-risk population. Third, this study offers a prospective exploration of the networks across different levels of treatment response.

Fourth, the use of a clinical interview, CIS-R, in network modeling is novel and presents several advantages. The CIS-R, a structured interview asking about 14 distinct symptom clusters, captures the presence, frequency, and duration of all symptoms necessary to know in order to give a CMD diagnosis. The use of the CIS-R symptoms as nodes in a network model contributes to the body of research in four ways: 1) even though it is a diagnostic tool, the interviewer does not follow a skip-algorithm in CIS-R, different than other diagnostic interviews. All relevant symptoms are assessed for everyone, allowing for a wider range of symptom constellations, even for those who are not given a diagnosis. 2) The use of CIS-R allows for the generation of one composite score for each symptom clusters instead of generating multiple ones for each diagnostic criteria, leading to a more parsimonious network. 3) In terms of the item content, The CIS-R appears to be culturally appropriate for India. Even though the CIS-R was developed to mirror all the symptoms captured by the common mental illnesses as defined by ICD-10, most symptom clusters (or individual items) captured by the CIS-R well overlap with the idioms of distress in India, including irritability, lack of interest, worry, somatic pains, lack of sleep, autonomic symptoms, and fatigue (Andrew et al., 2012; Weaver, 2017). 4) The CIS-R includes a three-item functional impairment sub-scale, allowing for an examination of symptoms that are most related with functional impairment, within a network model.

Significance. Understanding the presentation of symptoms from a CMD approach in a group of primary care patients has significant public health implications in terms of prevention, case identification, and intervention. First, the centrality of a symptom in the network indicates that this symptom is well connected with other symptoms. Changes in this symptom may influence the rest of the symptoms, making this symptom a prime candidate for intervention (Epskamp et al., 2018, pp. 420). Second, knowing the central symptoms would also help with the

identification of at-risk patients. Let's take two patients who endorse symptoms of depression but don't meet the criteria for a mental illness. One presents with two symptoms that are central as established through network analysis in their particular context (e.g., lack of interest and fatigue), the other presents with two symptoms that are not central in that setting (e.g., somatic pain and irritability). The first patient would be more likely to develop a full-fledged disorder compared to another patient who presents with two non-central symptoms and a clinician who has this knowledge can prioritize interventions geared towards the central symptoms. Third, knowing the central symptoms of those who did not respond to treatment in a similar setting could help develop interventions for other similar patients. Fifth, knowing which symptoms are more central in various risk groups (e.g., females and those receiving care from a public health care setting) might be a useful first step to understand the mechanisms in which these demographic factors might trigger mental illness.

From a conceptual standpoint, identifying whether symptoms cluster under distinct groups, and examining whether these groups overlap with our current diagnostic categorization would be important especially in non-Western settings. The existing categorizations have evolved over time as a result of years of observation and scientific research, largely coming from Western cultures. If the depression and anxiety symptoms cluster, as we would expect in the Western cultures, this would support the universality of the DMS framework. If not, it would be interesting to start thinking about alternative ways of understanding mental illness as it presents itself in primary care settings in India and develop new diagnostic criteria that might best capture psychological suffering. Furthermore, if irritability or anger, sleep problems, fatigue and worry appear to be central and closely tight with functional impairment, it may not be necessary that

the patient meets one of the two core symptoms of depression to be categorized as suffering from mental illness and receive treatment.

Study Aims

Aim 1. To examine the network configuration of symptoms in common mental disorders (CMDs) among primary care patients at baseline assessments.

Aim 1.1. To descriptively examine the centrality (closeness, strength, betweenness) of CMD symptoms and functional impairment.

Aim 1.2. To examine the comorbidity networks of CMDs, particularly to see the extent to which depression and anxiety form distinct sub-groups.

Aim 2. To examine changes in CMD symptom network configurations across patients of differing sociodemographic groups at baseline.

Aim 2.1. To examine the CMD symptom network structures across males and females.

Aim 2.2. To examine the CMD symptom network structures across private versus public healthcare settings.

Aim 3. Among the participants meeting case-level criteria for the diagnosis of a CMD at baseline, examine if symptom centralities and comorbidity at baseline changes across levels of treatment status at follow-up.

Hypothesis 3.1. The network density will be lower for those who had sustained remission, when compared to those who were non-responders across 12-months.

Hypothesis 3.2. The network density will be lower for those who had sustained remission, when compared to all the other groups, across 12-months.

Chapter 2: Method

Setting and participants

The data come from a stratified cluster randomized controlled trial testing the effectiveness of an intervention led by lay health counselors to improve CMDs among primary care patients who screened positive for CMDs (MANAS trial; Patel, et al., 2010). A total of 24 (12 public and 12 private) health facilities in Goa, a state in West India, were randomly selected among all eligible facilities and randomly allocated to either the intervention or control arm. The intervention arm involved collaborative stepped care involving psychoeducation, medication management and/or individual interpersonal psychotherapy delivered by lay counselors (8-12 sessions). All primary care patients older than 17 were screened for CMDs using the 12-item General Health Questionnaire (GHQ; previously validated cutoff score of >5; Patel et al., 2008). Those who screened positive were included in the study if they were a resident in Goa for the subsequent 12 months, were speaking Konkani, Marathi, Hindi or English, did not require urgent medical attention, did not have difficulty with hearing, speaking or cognition that makes interviewing difficult, and gave consent to participate. Those who were eligible were then administered the Revised Clinical Interview Schedule (CIS-R; Lewis, Pelosi, Araya, & Dunn, 1992). A total of 2796 participants were included in the study and assessed at 2, 6, and 12 months for symptom severity, presence of CMDs based on the ICD-10 criteria, and disability levels, between 2007 and 2009.

The current study draws data collected at baseline, 6 months, and 12 months timepoints, from the entire sample (n=2796, screen-positive and eligible), which was predominantly female (82%), with a mean age of 46.3 years (SD = 13.3). Among these, a total of 2242 (81%) received an ICD-10 diagnosis at baseline (ICD-10 diagnosis group). 1032 (46% of all those with CMD)

received mixed anxiety-depressive disorder, 774 (35%) had depression, including comorbid anxiety disorders, and the remaining 436 (19%) had a 'pure' anxiety disorder. Overall, 2181 (78%) of all screen-positive participants were seen at all three follow-up visits.

Measures

Demographic variables. This study includes the two demographic variables listed below and one variable identifying whether they are in the control versus intervention arm.

- **Gender**, male versus female
- **Clinic type**, public versus private
- **Arm,** collaborative stepped care versus treatment as usual

These three variables were included in the symptom networks when applicable. Further, to conduct network comparisons across groups, data were split into two based on these three variables.

CIS-R. The Revised Clinical Interview Schedule (CIS-R; Lewis, Pelosi, Araya, & Dunn, 1992) is the revised version of the Clinical Interview Schedule (CIS; Goldberg et al., 1970), which was the first standardized interview designed specifically to assess CMDs by lay interviewers and has been extensively used globally (Patel et al., 2011). The CIS-R showed adequate internal consistency ($\alpha = 0.82$; Lewis et al., 1992). The CIS-R, previously adapted and extensively used in Goa, India (Patel et al., 1998; Patel et al., 2003) assesses the presence and severity (duration, intensity, and frequency in the past week or month depending on the diagnostic criteria) of twelve non-psychotic psychiatric symptoms, each captured through multiple item questions, plus one question about the weight and appetite, and an additional question on the overall effects of the complaints.

When administering the CIS-R, no skip logic is followed based on any diagnostic

categorization. Items or sections could be skipped only when questions are not applicable because of a previous answer. All symptoms are covered with each participant with the exception of the depressive ideas and panic symptoms, which are skipped if the respondent did not endorse any items on the preceding depressed mood and anxiety or phobia symptoms, respectively. Not always all individual items within a symptom subscale are asked. For instance, if a patient did not endorse any sleep problems established by the first two items in the sleep problems subscale, the rest of the items are not administered, and the interviewer is directed to the next section. The individual item scores for each of these symptoms range from 0 to 4 (except for depressive ideas, ranging from 0 to 5) resulting in a total score ranging from 0 to 57 (CIS-R total score).

Based on the answers, the CIS-R generates two kinds of outcome variables: 1) A continuous psychiatric severity measure, which is the total score of CIS-R and a 2) binary CMD case status variable (CMD case versus non-case). A computer algorithm (Programmable Questionnaire System [PROQSY] program) generates ICD-10 diagnoses for each participant based on individual item responses.

Distinct ICD-10 categories could also be derived from responses to the CIS-R. These include the following depression and anxiety related disorders: mild depressive episode with and without somatic symptoms (F32.0), moderate depressive episode with and without somatic symptoms (F32.1), severe depressive disorder (F32.2), agoraphobia with and without panic disorder (F40.0), social phobias (F40.1), specific phobias (F40.2), panic disorder (F41.0), generalized anxiety disorder (GAD) (F41.1), mixed anxiety and depressive disorder (MADD) (F41.2), and obsessive compulsive disorder (F42).

The obsessions and compulsions subscales of the CIS-R have not been part of the interview used in Goa, India, as part of the MANAS trial. Therefore, in this study, below twelve subscale scores were used as assessed by the CIS-R in the network analysis. The symptom subscale scores range from 0 to 4, except for fatigue and the depressive ideas, which ranges from 0 to 5. When binarized, scores that are equal to or higher than 2 were coded as "1" as in the original CIS, these scores were thought to indicate clinical severity of a symptom, while scores that are less than 2 are thought to indicate absence of symptom, habitual traits, or borderline subclinical levels (Goldberg et al., 1970). This type of dichotomization was also utilized in a factor analytic study on the CIS-R symptoms (McBride, Bebbington, Cooper, 2013).

- **Somatic symptoms**, consisting of items relating to the respondent's experience of any ache, pain or discomfort (e.g., "*Have you had any sort of ache or pain in the last month*"?).
- **Fatigue**, including items related to feeling tired or lacking in energy (e.g., *"Have you felt tired/lacking energy for more than 3 hours in total on any day or most of the day in the past seven days?").*
- **Concentration and forgetfulness***,* consisting of items relating to experience of problems with memory and/or concentration (e.g., "*Have you noticed any problem with forgetting things in the past month*?").
- **Sleep problems**, assessing problems with trying to get to sleep, waking up too early, or sleeping more than is usual (e.g., "In the past seven days, on how many nights did you spend three or more hours trying to get to sleep?")
- **Irritability**, relates to feelings of irritability, being short-tempered or angry (e.g., "Many people become irritable or short tempered at times, though they may not

show it. Have you felt irritable or short tempered with those around you in the past month?")

- **Worry about physical health**, includes items asking about the extent of health-related worries (e.g., "*In your opinion, have you been worrying too much in view of your actual health?*").
- **Depressed mood,** relating to respondents' feelings of sadness, misery or depressed or unable to enjoy or take an interest in things as much as usual (e.g., "*Almost everyone becomes sad, miserable, or depressed at times. Have you had a spell of feeling sad, miserable or depressed in the past month?*").
- **Depressive ideas**, captures diurnal variation, restlessness, psychomotor agitation, feeling guilty, blaming him/herself when things went wrong, worthlessness, hopelessness, and suicidal ideas (e.g., "*In the past seven days, have you thought of a way in which you might kill yourself?*").
- **Worry,** captures worries about things and circumstances, other than the physical health (e.g., "*On how many of the past seven days have you been worrying about things other than your physical health?*").
- **Anxiety,** includes items asking about anxious feelings, nervousness or tension (e.g., "*When anxious, nervous or tense, had one or more of following symptoms: heart racing or pounding, hands sweating or shaking, feeling dizzy, difficulty getting breath, butterflies in stomach, dry mouth, nausea or feeling as though he/she wanted to vomit?"*).
- **Phobias,** assesses experience of phobia or avoidance related to specific situations (e.g., "*Can you tell me which of the situations or things made you the most*

anxious/nervous in the past month: crowds or public places, enclosed spaces, social situations, sight or blood or injury, specific single cause, others?").

- **Panic,** includes items asking about feelings of panic, or of collapsing and losing control (e.g., *"Thinking about the last 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?"*).

Two additional variables were computed manually and included in the network analysis. The appetite and weight change had three levels, (1 = "no change", 2 = "appetite increase/decrease", 3 = "change in appetite and weight"). When treated binary, any change in appetite was coded as "1". The overall effects variable had four levels (1= "no change in functioning", 2 = "feelings made it difficult even though got everything done, 3 = "impacted functioning once", 4 = "impacted functioning more than once"). When treated binary, impacted functioning once and impacted functioning more than once were coded as "1".

- **Appetite and weight change,** capturing any marked loss or gain of weight and increased or decreased appetite (e.g., "Have you noticed a marked increase in your appetite in the past month?").
- **Overall effects (i.e., functional impairment),** assesses whether or not and the extent to which the symptoms have affected the participant (e.g., *"Has the way you have been feeling ever actually stopped you from getting on with things you used to do or would like to do?"*).

Three other binary variables were computed to be used in this study:

- **CMD case at baseline,** computed from the algorithm generating ICD-10 diagnoses from the CIS-R responses (case at baseline versus non-case at baseline)

- **CMD case at 6 months,** computed from the algorithm generating ICD-10 diagnoses from the CIS-R responses (case at 6 months versus non-case 6 months)
- **CMD case at 12 months,** computed from the algorithm generating ICD-10 diagnoses from the CIS-R responses (case at 12 months versus non-case 12 months)

For those who met diagnostic criteria for a CMD at baseline, the variable "treatment status" with four mutually exclusive levels were computed based on the CMD case status at 6 and 12 months:

- **Sustained remission,** refers to those who were non-case across at both 6 and 12 months.
- **Relapse at 12 months,** refers to those who were non-case at 6 months but were cases at 12 months.
- **Delayed remission,** refers to those who were cases at 6 months but were no longer cases at 12 months
- **Non-remission,** refers to those who were cases at both 6 months and 12 months

Data Analysis

Data distribution, transformation, and recoding. The composite subscale scores for the 12 CIS-R symptoms were already computed by the primary research team following a particular algorithm and were available in the dataset. A composite score for weight and appetite changes and functional impairment were manually computed based on the 3-4 individual item scores for each.

The 12 CIS-R subscale scores are sum of 4-5 binary variables. Based on the central limit theorem positing that the sum of independent random variables tends toward a gaussian distribution, these 12 subscale scores were assumed to be continuous and coming from a normal

distribution. When their distribution is examined at baseline, nine of these variables appeared to be non-normally distributed. As recommended, a non-parametric transformation was applied to these variables given that they were assumed to be continuous (Ebskamp & Fried, 2007). The huge package in R was used for the transformation (Zhao et al., 2015). Three other variables, anxiety, panic, and phobia appeared to be highly skewed (with approximately 70% of the data being "zero", and the rest evenly distributed between 1-4). Thus, a decision was taken to binarize these variables before entering in the analyses. The remaining variables; appetite change and functional impairment were also treated as binary for the analyses as these were manually computed based on three to four individual items. For appetite change, anxiety, panic, and phobia, any endorsement of symptom (i.e., scores ranging from 1 to 4) were coded as one, while zero scores were kept as zero. For functional impairment, any endorsement of impairment (i.e., feelings stopped from doing things once or more than once in the past week) were coded as one, while "feelings did not stop from doing things " or "feelings made it difficult but did not stop from doing things" were coded as zero.

Correlation network (Aim 1.1). Given the mixed nature of the data (continuous and binary), the correlation network at baseline was modeled using the undirected mixed graphical methods (MGM), allowing for variables with different distributions to be entered appropriately. The *mgm* package in R was used (Haslbeck & Waldorp, 2016). Regularized partial correlation networks via the graphical LASSO were used based on the Extended Bayesian Information Criterion (EBIC, Foygel and Drton, 2010). This method is considered to generate a relatively parsimonious network where spurious correlations are reduced. As previously discussed in the background section, the hyperparameter γ (gamma) could be set between 0 (for discovery) and 0.5 (for caution). Given the exploratory nature of this study, 0.25 was selected as a reasonable

compromise, as previously suggested by Hevey (2018). Edge weights below the Low and Wainwright (2013) threshold were put to zero. The R package *qgraph* (Ebskamp, Cramer, Waldorp, Schimittmann, & Borsboom, 2011) was used to visualize data and compute node centrality measures. In *qgraph*, the edge lengths are visualized such that they correspond directly to the actual edge weights using a modified force-embedded algorithm proposed by Fruchterman and Reingold (1991).

The network configuration of CMD symptoms at baseline was descriptively examined and evaluated in terms of the 1) network stability and accuracy (described in more detail below) 2) centrality of each symptom, as established by symptom strength, closeness, and betweenness, and when applicable, 3) network connectivity in terms of the number of existing edges given the number of all possible edges, 4) global strength of the network when comparing groups. Strength centrality is the sum of the weights of all edges connected to one node. Closeness centrality is the inverse of the sum of the distances of the node from all the other nodes, where the distance between two connected nodes are calculated by taking the inverse of the absolute value of the edge-weight. Betweenness is calculated based on the shortest path between any two nodes that pass through the focal node.

The 6 months and 12 months timepoint evaluations, originally part of the study aims, were removed from the aims for two reasons. First, given that this is a clinical trial and the sample is heterogeneous in terms of the treatment received at different timepoints, networks would need to be evaluated separately for the treatment and control groups, which would make the comparison with baseline network challenging. Second, given that many patients improved, the data distribution was much more skewed at 6 month and 12 months for all variables.

Network Accuracy and Stability. The accuracy and stability of the network structures were evaluated in three steps as previously recommended: 1) stability of centrality indicating whether the order of the centrality indices remain the same after re-estimating the network with subsets of the data, 2) accuracy and stability of the edge-weights, and 3) difference tests between edge-weights and difference tests between centrality indices (Ebskamp, Borsboom, & Fried, 2017; Fried, 2018).

Centrality stability. The stability of the centrality indices were evaluated through the correlation between the original centrality indices and the bootstrapped indices. The correlation stability coefficient, CS (cor = 0.7) was proposed as a measure of centrality stability, indicating the maximum proportion of cases that can be dropped to maintain the correlation between the original centrality indices and the indices obtained through the subset is 0.7 or higher (Epskamp, Borsboom, & Fried, 2017). Based on a simulation study, the CS-coefficient is recommended to be above 0.5, and not below 0.25 (Epskamp, Borsboom, & Fried, 2018).

Edge-weight accuracy. The accuracy of edge-weights were assessed through the bootstrapped Confidence Intervals (CIs) for each edge using the *bootnet* R package (Ebskamp, Borsboom, & Fried, 2018). Generally, large CIs indicate less accurate edge-weights.

Edge-weight stability. Because the network estimation uses a process called regularization, where edges that are non-zero are included in the network, the bootstrapped CIs might be misleading when they overlap with zero. Therefore, as recently recommended by Fried (2018), the stability of the edge-weights were evaluated by looking at the number of times an edge was estimated to be non-zero.

Significant differences. In *bootnet*, the difference tests are done by taking the differences between bootstrap values of edge-weights (or centrality indices), constructing a bootstrapped CI

around the difference scores, and checking whether the CIs overlap with zero (Epskamp, Borsboom, & Fried, 2018).

Comorbidity networks (Aim 1.2.). The community structure was assessed using community detection analyses within the *igraph* package (Csardi & Nepusz, 2006). These analyses were computed with the *walktrap* random walk algorithm (Pons & Latapy, 2006). In community analyses, positive modularity was proposed to indicate a potential community structure, with higher values of modularity indicating better partitioning. Zero modularity means that the subgraph has no more links than expected by chance, and negative modularity indicates that there is no community. While no clear cut-off value for modularity has yet been established, our results were compared to other networks with strong community structures, which were previously shown to have modularity indices that ranged between 0.3-0.7 (Newman & Girvan, 2004).

Group comparisons (Aim 2 & 3). The second and third aims involved subgroup comparisons using the Network Comparison Test (NCT; van Barkulo, 2015). The NCT, implemented in the R package NCT, is a 2-tailed permutation test where the differences between groups are calculated repeatedly (1,000 times) for random groups of individuals. The NCT is currently only suitable for gaussian or binary data distributions, therefore, these analyses were repeated following two different methods: 1) treating all variables as continuous and 2) binarizing all variables so that any symptom score that represents clinical levels (i.e., composite score equal to or more than 2) would be considered "1" (For more details, see Methods section).

As a first step, the network of the 12 CIS-R symptoms plus the two manually coded appetite and functional impairment, was estimated 1) with the gaussian graphical model (GGM, with graphical LASSO, EBIC and a hyperparameter set at 0.25, and 2) with the Ising model

using the R package IsingFit that uses the eLasso method and EBIC for model selection, with a hyperparameter set at 0.25 (van Borkulo, Epskamp & van Borkulo, 2016). Then, the network structures were estimated separately for males and females, private versus public clinics, and sustained responders versus non-responders. The NCT was conducted to compare 1) the global strength 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 edges weight. These NCT was repeated twice, first, treating all variables as continuous, and all variables as binary.

It should be noted that the EBIC is a function of sample size; lower sample sizes would result in more parsimonious networks (Epskamp, & Fried, 2017). This leads to two conclusions: First, visually or descriptively comparing network density and edge-weights across groups with unequal sample sizes could be misleading. Second, it was previously shown that when the two samples are unequal in terms of size, depending on the degree of this difference and the underlying network density, the NCT may lose power (for a simulation study, see VanBorkulo, 2017).

The sample size problem was addressed for the Aim 3, as part of the follow-up analyses. The sustained responders group (n = 903) was compared to the other three groups combined (i.e., those who did not respond, those who only responded at 12 months follow-up, and those who responded at 6 months but had relapse at 12 months; n = 954) leading to two similarly sized groups. A second hypothesis which was not originally listed was added under Aim 3 (Hypothesis 3.2.), stating that the symptom network of those who are sustained responders would be less densely connected compared to all other three groups combined. 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.

Chapter 3: Results

At baseline, 2796 participants screened positive using the GHQ-12 were included in the trial. Mean age was 46.29 (SD = 13.12) and the mean years of education was 3.67 (SD = 4.14). The majority of participants were female, unemployed, and reported financial difficulties at timepoint 2. A demographic breakdown and rates of CMD and MDD diagnoses along with the rates of four different treatment response categories are shown in Table 3.1. The means and standard deviations of the twelve CIS-R sub-section scores and the frequencies of the overall functional impairment and appetite change for the three timepoints are shown in Table 3.2, bivariate correlations are shown in Table 3.3. When coded as binary, at baseline, the most frequently endorsed symptom was fatigue, where 82.3% endorsed at least 2 out of the 5 fatigue symptoms. Phobias were the least endorsed, with 19.2% scoring equal or higher than 2 on the composite score.

Table 3. 1. Demographic breakdown and rates of CMD, MDD and treatment status (n = 2796)

Age	Frequency	Percentage
18-31	434	15.5
32-44	825	29.5
45-57	808	28.9
58-70	677	24.2
> 71	52	1.9
Sex		
Male	491	17.6
Female	2305	82.4
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
Total	2506	89.6
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
Clinic type		
Public	1648	58.9
Private	1148	41.1
CMD diagnosis at baseline		
Yes	2242	80.2
No	554	19.8
MDD diagnosis at baseline		
Yes	774	27.7
No	2022	72.3
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

Table 3. 2. Mean scores of CIS-R section scores and frequencies at baseline (n = 2796)

12 CIS-R subscale scores plus two additional symptoms	When treated continuous for the *GGM*				Dichotomized[b] for the *Ising* model	
	Min	Max	Mean	SD	Frequency	Percentage
Somatic	0	4	1.88	1.625	1587	56.8
Fatigue	0	5	3.27	1.658	2300	82.3
Concentration	0	4	1.81	1.297	1689	60.4
Irritability	0	4	0.93	1.174	820	29.3
Sleep	0	4	2.00	1.304	1913	68.4
Worry about health	0	4	1.60	1.47	1460	52.2
Depression	0	4	1.62	1.213	1482	53
Worry	0	4	2.14	1.59	1777	63.6
Depressive thoughts	0	5	2.24	1.555	1887	67.5
Anxiety[a]	0	4	0.66	1.135	601	21.5
Panic[a]	0	4	0.86	1.495	709	25.4
Phobias[a]	0	4	0.63	1.111	536	19.2
Appetite[a]	0	2	0.96	0.76	1923	68.8
Functioning[a]	0	3	2.15	0.95	1889	67.6

[a]*Dichotomized values of these variables were used for the MGM.*
[b]*The 12 CIS-R variables were dichotomized based on their clinical significance (scores of 2 or more were coded as "1"), with the exception of "appetite" and "functioning", which are not part of the standardized CIS-R where clinical levels were ascertained by "any changes" in appetite (scores 1 or more) and "any changes" in functioning (scores 2 or more).*

Table 3. 3. Pearson bivariate correlations among 12 CIS-R subscale scores, appetite/weight change, and functional impairment

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Functional impairment	1	.216**	.255**	.293**	.184**	.141**	.170**	.273**	.198**	0.003	.073**	.134**	.116**	.181**
2. Somatic	.216**	1	.414**	.290**	.235**	.172**	.233**	.267**	.198**	0.022	.175**	.202**	.160**	.236**
3. Fatigue	.255**	.414**	1	.377**	.278**	.147**	.256**	.325**	.188**	0.004	.179**	.193**	.166**	.210**
4. Concentration	.293**	.290**	.377**	1	.258**	.208**	.198**	.355**	.185**	0.026	.156**	.149**	.175**	.233**
5. Sleep	.184**	.235**	.278**	.258**	1	.116**	.222**	.276**	.209**	0.009	.169**	.176**	.123**	.186**
6. Irritability	.141**	.172**	.147**	.208**	.116**	1	.106**	.231**	.192**	0.01	.079**	.111**	.140**	.139**
7. Worry health	.170**	.233**	.256**	.198**	.222**	.106**	1	.239**	.133**	.066**	.119**	.180**	.182**	.209**
8. Dep. mood	.273**	.267**	.325**	.355**	.276**	.231**	.239**	1	.332**	0.018	.127**	.201**	.187**	.219**
9. Worry	.198**	.198**	.188**	.185**	.209**	.192**	.133**	.332**	1	-0.007	.075**	.210**	.114**	.163**
10. Dep. ideas	0.003	0.022	0.004	0.026	0.009	0.01	.066**	0.018	-0.007	1	0.023	0.016	0.019	-0.001
11. Appetite	.073**	.175**	.179**	.156**	.169**	.079**	.119**	.127**	.075**	0.023	1	.100**	.080**	.106**
12. Anxiety	.134**	.202**	.193**	.149**	.176**	.111**	.180**	.201**	.210**	0.016	.100**	1	.106**	.379**
13. Phobias	.116**	.160**	.166**	.175**	.123**	.140**	.182**	.187**	.114**	0.019	.080**	.106**	1	.431**
14. Panic	.181**	.236**	.210**	.233**	.186**	.139**	.209**	.219**	.163**	-0.001	.106**	.379**	.431**	1

** *Correlation is significant at the 0.01 level (2-tailed).*

CMD Symptom Networks (Aim 1.1.)

The CMD symptom network at baseline estimated using MGM and the results are presented below. Since the network comparison test (NCT) could only be done either with continuous or dichotomized data, in preparation for the NCT, the CMD symptom network analyses for the entire sample were repeated using two additional methods, GGM and ising model (for more details, see the Methods section).

Mixed graphical method (MGM). The MGM network is presented in Figure 1. The centrality indices, including the strength, closeness, and betweenness values of each node are presented in Figure 2.

Centrality stability. The case-dropping bootstrap revealed that the order of node strength is interpretable, with a CS-coefficient of 0.75, higher than the recommended threshold. The CS-coefficient of betweenness was 0.206, lower than the recommended threshold of 0.25, while the CS-coefficient of closeness could not be calculated, which appears to be a flaw in the R package and is being fixed in the newest version. Visual inspection of the average correlations reveals higher stability for both strength and closeness (Figure 3), where the average correlation between the original and bootstrapped indices remains higher than 0.75 even when more than 30% of the cases are dropped. These results indicate that the order of node strength and closeness are interpretable, while the order of node betweenness is not interpretable.

Node centrality differences. Figure 4 shows the bootstrapped differences between the node strengths. *Panic's* strength was significantly greater than all the rest of the symptoms. Panic was followed by *phobia, anxiety, depressed mood,* all similarly central to the network. Depressed mood's centrality index was similar to, and followed by those of *somatic complaints*, *concentration*, *functional impairment* and *fatigue*. Fatigue and functional impairment were not

significantly different than, and followed by, *sleep problems, worry about health and worry* followed, in decreasing order of node strengths. *Irritability and appetite* were significantly smaller than all the above. The node strength of *depressive ideas* was significantly lower than all other symptoms.

Edge-weight accuracy and stability. In terms of edge accuracy, Figure 5 shows that most edges were positive and some edges had sizable bootstrapped CIs around the estimated edge-weights, indicating that many edges were not significantly different than each other. In terms of edge stability, Figure 6 shows variability; out of 91 possible edges ($n! = n * (n-1) / 2$, where n is the number of nodes = 14), 53 were estimated non-zero, and 21 were never estimated as zero (e.g., the edge between somatic and fatigue).

***Edge-weight differences*.** Taking Figure 5 and Figure 6 together, it appears that *edges phobia-panic, anxiety-panic* are reliably the two strongest, since their bootstrapped CIs did not overlap with the bootstrapped CIs of the other edges. These two were followed by *somatic-fatigue*, since its CI did not overlap with most of the other edges. In terms of edge-weight differences, Figure 7 reveals that the three edges listed above are also significantly stronger than all the other edges. The *phobia-anxiety* edge seems to be significantly stronger than *anxiety-panic* edge, which is stronger than *somatic-fatigue* edge. Visual inspection of Figure 6 and 7 reveals that the following six edges have CIs that little overlap with the rest and highly stable since these were estimated non-zero in 100% of the bootstraps: *worry-anxiety, depressed mood-worry, functional impairment-concentration, fatigue-concentration, and concentration-depressed mood, somatic-panic.*

The edge *somatic-panic* is noteworthy in terms of its smaller CI and stability; while it is not significantly stronger than most of the other edges, it appeared to be significantly stronger

than any other edges that are connecting to the symptom "somatic", after the edge fatigue-somatic.

One negative edge is observed between *anxiety and phobias*, significantly smaller than the rest, however, this edge was only estimated non-zero in 62% of the bootstraps, meaning that it was not highly stable.

Gaussian graphical model (GGM). The GGM was run with 14 variables, treating all variables continuous. The resulting network is presented in Figure 8. The case-dropping bootstrap revealed that the order of node strength is interpretable, with a CS-coefficient of 0.75, higher than the recommended threshold. The CS-coefficient of betweenness was 0.283, also higher than the threshold of 0.25. The CS-coefficient of closeness could not be calculated. Visual inspection of the average correlations reveals higher stability for both strength and closeness (Figure 9), where the average correlation between the original and bootstrapped indices remains higher than 0.75 even when more than 30% of the cases are dropped. These results indicate that the order of node strength and closeness are interpretable, while the order of node betweenness is not interpretable.

When all variables are treated as continuous, the ordering of the centrality scores were different compared to the mixed gaussian model. The GGM model revealed that the highest centrality score belonged to *depressed mood,* which was not significantly different than the centrality scores of *panic, fatigue, concentration problems* (Figure 10). Next, somatic symptoms' centrality index was smaller than depressed mood, but similar to panic, fatigue, and concentration problems. *Sleep problems* had the next highest centrality score, followed by *anxiety, worry about health, phobias, worry, and functional impairment*. *Irritability's* centrality score was next, followed by the *appetite*, and *suicidal ideas*.

In terms of the edges, similar to the MGM model, the following three edges *phobia-panic, anxiety-panic, and somatic-fatigue* were reliably the three strongest, since their bootstrapped CIs did not overlap with the bootstrapped CIs of the other edges (Figure 11 and Figure 12). The edge phobia-panic was stronger than the other two who had CIs that overlapped entirely. Visual inspection of the edge differences (Figure 13) revealed several other edges that are significantly different than most of the rest. The edges that were also found strong with the MGM model included *depressed mood-worry, fatigue-concentration, concentration-depressed mood*, and *functional impairment-concentration, worry-anxiety.* An additional edge for GGM appeared to be stronger than the rest; *fatigue-depressed mood.*

The edge *anxiety and phobias* was significantly smaller than the rest, however, this edge was only estimated non-zero in 61% of the bootstraps, meaning that it was not highly stable.

Ising Model. The Ising model network is presented in Figure 14. The case-dropping bootstrap (Figure 15) revealed that the order of node strength is interpretable, with a CS-coefficient of 0.75, higher than the recommended threshold. The CS-coefficient of betweenness was 0.517, also higher than the threshold of 0.25. The CS-coefficient of closeness could not be calculated. These results indicate that the order of node strength and betweenness are interpretable.

When all variables are treated as dichotomous, the ordering of the centrality scores (Figure 16) were different than what was found using the MGM and GGM. The Ising model revealed that *fatigue* and *panic* had the two highest centrality indices, and while panic was significantly higher than all the remaining indices, fatigue's centrality index was not significantly higher than those of concentration and depressed mood (Figure 17). *Depressed mood* was followed by *somatic*, and *concentration*, all three not significantly different than each other.

Concentration problems were followed by and not significantly different than *anxiety* and *phobia*. *Functional impairment* had the next highest centrality score, followed by and not statistically different than *worry about health*, *worry*, *and sleep problems, and irritability*. The next was *appetite change*, which was only similar to irritability. The smallest index belonged to *depressive ideas*, significantly smaller than the rest.

In terms of the edges, similar to the MGM and GGM model, the following three edges *phobia-panic, anxiety-panic, and somatic-fatigue* were reliably the three strongest, since their bootstrapped CIs did not overlap with the bootstrapped CIs of the other edges (Figure 18). Visual inspection of the edge differences revealed several other edges that are significantly different than most of the rest, which overlapped with the MGM and GGM: *functional impairment-concentration*, *fatigue-concentration, depressed mood-worry, concentration-depressed mood. The edge somatic symptoms-panic was also notable, similar to the MGM model.*

The edge *anxiety and phobias*, significantly smaller than the rest, however, this edge was only estimated non-zero in 74% of the bootstraps, meaning that it was not highly stable.

Summary of CMD Network Findings (Aim 1.1.) All centrality indices found using these three different models, MGM, GGM, and Ising, are plotted in one graph (Figure 19). Across three models, certain findings overlapped: 1) Panic had either the highest or the second highest strength centrality index, and in no model was there another symptom with a significantly higher strength index compared to panic. Appetite change, irritability, and depressive ideas had the smallest centrality indices across models. 2) Depressed mood, somatic symptoms, and concentration problems were either among the most central, or among the second most central group. 3) Three strongest edges were panic-anxiety, panic-phobia, and somatic-fatigue across all models. 4) There was a negative edge between anxiety and panic, although not

very stable. Across models, the percentage of times this edge was estimated non-zero ranged between 61% and 74%.

The centrality of anxiety and phobia showed differences across models; in MGM they were third and second, while in Ising model they were sixth and seventh, and in GGM seventh and ninth, respectively, in terms of their ranking. The centrality of fatigue also showed differences across models, in the Ising model it had the highest centrality, though in GGM it was the third, and in MGM it was the eight.

Comorbidity Networks (Aim 1.2.)

The community detection using the *walktrap* random walk algorithm did not reveal strong evidence for a community structure; the modularity was 0.019 (smaller than the 0.4 threshold previously suggested). When the algorithm was applied on the GGM model the results were similar, with a modularity index of 0.043. When the Ising model was followed and the walktrap algorithm was applied, there was more evidence, although weak, for a community structure suggesting three communities, with a modularity index of 0.17: 1) panic, anxiety and phobia, 2) fatigue, concentration, depressed mood, somatic, worry, functional impairment, sleep, appetite, and irritability, worry about health, and 3) depressive ideas (Figure 20).

Network comparisons across demographic variables (Aim 2)

Network comparisons across gender. The GGM was run for males (n = 491) and females (n = 2305). The density of the network among males was 4.44, while it was slightly higher, 4.72 for females. The NCT revealed no significant differences ($p = 0.722$) in terms of the global strength of male and female network structures. No significant differences were found in the permutation test concerning the maximum difference in edge-weights ($p = 0.225$).

The visual and descriptive comparison of the observed data is presented in Figure 21, however, as explained above, the interpretation of the network structure of the observed dataset may be misleading particularly when the sample sizes are different, since the edge estimates are heavily affected by the sample size (Epskamp, & Fried, 2017). In addition, the network accuracy analyses revealed that unstable centrality parameters for males, where the average correlation between bootstrapped indices and the original sample indices showed a drastic decline after dropping 40% of the sample. On the other hand, the network of females appeared to be highly stable, with a CS-coefficient of the strength index (CS = 0.75).

When the NCT was repeated treating the data binary, the results remained the same (differences in strength = 10.39756, p = 0.437), and no edges were found significantly different across groups.

Network comparisons across clinic types. The GGM was run for public (n = 1648) and private clinics (n = 1148). The CIS-R total scores, GHQ total scores, and the 12 CIS-R subscale scores across public and private settings are shown in Table 3.4.

Table 3. 4. CIS-R Total Score, GHQ score, and the 12 CIS-R Subscale scores across PHC and GP

	PHC				**GP**			
	(n = 1648)				(n = 1148)			
	Mean	SD	F	%	Mean	SD	F	%
CIS-R Score	19.39	9.22	n/a	n/a	19.98	8.91	n/a	n/a
GHQ Score	7.72	1.57	n/a	n/a	7.54	1.36	n/a	n/a
Somatic	1.82	1.65	905	55	1.97	1.58	**682***	**59**
Fatigue	3.21	1.65	1354	82	3.34	1.66	946	82
Concentration	1.87	1.27	**1038****	**63**	1.71	1.34	651	57
Sleep	1.95	1.33	1103	67	2.07	1.27	**810***	**71**
Irritability	0.97	1.21	**516***	**31**	0.86	1.11	304	26
Worry health	1.34	1.5	725	44	1.96	1.35	**735****	**64**
Dep. mood	1.63	1.21	893	54	1.62	1.22	589	51
Worry	2.22	1.62	**1080***	**66**	2.02	1.54	697	61
Dep. ideas	2.17	1.56	1082	66	2.34	1.54	**805***	**70**
Anxiety	0.69	1.2	**387***	**23**	0.62	1.04	214	19
Phobias	0.52	1.02	259	16	0.79	1.21	**277****	**24**
Panic	0.92	1.58	430	26	0.78	1.35	279	24
Appetite	0.94	0.74	400	24	0.99	0.8	**361****	**31**
Functioning	2.21	0.91	**1170****	**71**	2.07	1	719	63
CMD Case	n/a	n/a	1307	79	n/a	n/a	935	81

PHC = Public Health Care

GP = General Practitioner (Private Health Care)

**p<0.001

*p<0.05

The network graphs for public and private settings are presented in Figure 22. The overall CIS-R was not significantly different across settings and the rates of CMD case at baseline were not related with the setting (Table 4). The density of the network, however, among public health care attendees was 4.73, while it was lower for the private health care attendees, 4.34. The NCT revealed that this difference was not significant ($p = 0.157$). Two edge weights were found to be significantly different across groups: In public health care clinics, the edges between *anxiety-panic*, *depression-worry* were significantly stronger compared to the weights of these edges in the private health care clinics ($p < 0.001$), while the edge between *somatic-fatigue* appeared to be stronger in the private clinics compared to the public health care clinics ($p < 0.001$).

Separate network accuracy analyses for these subgroups revealed stable strength centrality indices for both public and private settings (CS-coefficient = 0.75 for both groups), the CS-coefficient of betweenness was 0.21 for the public health care setting, and it was 0.28 for the private health care setting.

While the visual network comparison across groups should be done with care given the differences in the sample size, the differences across groups in edge-weights were found to be significant and the centrality indices across both groups were found to be stable. Therefore, a close examination of the strength centrality ranking across groups could be meaningful. For public settings, the strength score of the *panic and depressed mood* symptoms were similar to each other. While the strength centrality of panic was significantly greater than all the remaining symptoms, the strength centrality of depressed mood was similar to that of anxiety. For private settings, *fatigue, depressed mood, and somatic* had the highest centrality indices, and these were not significantly different than each other.

In terms of edge-weights, for the public settings, the highest ranked six edge-weights that had confidence intervals that had little overlap with the rest of the edges and were estimated non-zero in all bootstraps were *phobia-panic, anxiety-panic, depressed mood-worry, somatic-fatigue, and fatigue-concentration* (Figure 25). In private settings, only two of the highest ranked edges appeared to have CIs that did not overlap with the rest: *phobia-panic and somatic-fatigue* (Figure 26).

When the NCT was repeated treating the variables as binary, the density for the public health care patients appeared higher than the network for the private health care patients, 18.73 16.61, respectively. However, this difference was not significant (differences in strength = 2.127892, p = 0.523) and no edge-weights were found to be significantly different.

Network comparisons across treatment status (Aim 3)

The GGM was run for the sustained remission (n = 903) and the non-remission group (n = 443). The global strength of the network for the sustained remission group was 1.08, higher than the non-remission group 0.37. The permutation test revealed no significant differences (p = 0.702) in global strength across groups. Thus, Hypothesis 3.1. was not supported. No significant differences were found in the permutation test concerning the maximum difference in edge-weights (p = 0.413). The network graphs for sustained and non-remission groups are presented in Figure 27. No significant differences were found between the network densities when the analyses were repeated based on binarized data. No significant differences were found in the permutation test concerning the maximum difference in edge-weights.

As explained in the previous section, one reason for this finding could be the loss of power due to the large differences in the sample size. To reduce the sample size difference between the groups, the non-remission group was combined with those who showed delayed

remission and those who relapsed at 12 months. This new group was called "not sustained" responder group. The GHQ total scores, the CIS-R total scores, and subscale scores across these two groups are presented in Table 3.5.

Table 3. 5. CIS-R Total Score, GHQ score, and the 12 CIS-R Subscale scores across sustained versus not sustained

	Original data			
	Sustained (n=903)		Other (n = 954)	
	Mean	SD	Mean	SD
CIS-R Total Score	**21.48***	**6.80**	**23.87***	**7.38**
GHQ Total Score	7.84	1.50	7.90	1.55
Subscale scores**				
Somatic	2.08	1.57	2.30	1.59
Fatigue	3.59	1.37	3.82	1.30
Concentration	1.98	1.22	2.16	1.24
Sleep	2.15	1.20	2.34	1.21
Irritability	1.01	1.17	1.07	1.23
Worry health	1.78	1.40	1.93	1.50
Dep mood	1.77	1.11	1.99	1.16
Worry	2.32	1.51	2.56	1.53
Dep ideas	2.20	1.53	2.28	1.53
Anxiety	0.72	1.13	0.88	1.26
Phobias	0.70	1.16	0.83	1.22
Panic	0.94	1.51	1.20	1.68

$p < 0.001$
***Subscale scores represent actual values,*
none of these values were normally distributed, t-test statistics are not conducted

Sustained remitters versus not sustained remitters. When the GGM network of the sustained group was compared to the network of the remaining groups combined (i.e., not sustained; n = 954), the global strength of the sustained group was found to be 2.203 while the global strength of the not-sustained group was higher, 2.556. The NCT revealed that the permutation test concerning global strength was not statistically significant (p = 0.688), not

supporting the Hypothesis 3.2., meaning the network for those who showed sustained remission was *not different* at baseline, compared to those who either showed delayed remission, relapse, or no-remission at 6 months or 12 months follow-up. No significant differences were found in the permutation test concerning the maximum difference in edge-weights ($p = 0.202$). The network graphs for sustained and not sustained groups are presented in Figure 28.

The results were the same when the comparison was conducted separately for the intervention arm and control arm. For the intervention arm (stepped care) the network density of the sustained responders ($n = 481$) was 1.072, while the non-sustained responders ($n = 412$) was 1.13. Although the latter was slightly higher, this difference was not statistically significant ($p = 0.913$), no edges were significantly different ($p = 0.566$). For the control arm (enhanced care) the network density of the sustained responders ($n = 422$) was 1.156, while the non-sustained responders ($n = 542$) was 1.381. Although the latter was slightly higher, this difference was not statistically significant ($p = 0.852$), no edges were significantly different ($p = 0.989$).

No significant differences were found between the network densities when the analyses were repeated based on binarized data. No significant differences were found in the permutation test concerning the maximum difference in edge-weights.

Chapter 4: Discussion

Sample Characteristics

The sample consisted of primary care patients in India, Goa, screened positive for a CMD. This sample was mostly female, married, Hindu, without education, unemployed, and with financial difficulties. Eighty percent of the sample received a CMD diagnosis, which is high given previously reported statistics among primary care patients, though makes sense since the current sample has already been screened positive for a CMD. Symptom prevalence rates also appeared to be higher compared to other primary care patients, for example in Santiago, Chile; and Harare, Zimbabwe; and compared to an Indian sample who lived in Ealing, United Kingdom (Jacob et al., 1998). In Ealing, fatigue symptoms had the highest rate endorsement (38%), which was similar to this current sample where fatigue had the highest rate of endorsement (82.3%). In Ealing, panic was not endorsed, phobia was endorsed by 2% and anxiety was endorsed by 1%. In the current sample, we saw a similar ranking in terms of the rates where phobias, anxiety, and panic, were the least endorsed, though with much higher rates compared to Ealing, 19.2%, 21.5%, 25.4%. Since patients in this current sample have already been screened positive for CMDs, higher rates of endorsement for all symptoms were expected. However, these high rates for anxiety, panic, and phobia are still noteworthy.

The CMD Network (Aim 1.1.)

The CMD network analyses were conducted using three different models, MGM, GGM, and Ising model. All three models resulted in acceptable stability indices, and the edge-weight accuracy and stability appeared to be acceptable.

Given the discrepancy across the findings from three models, findings for Aim 1.1. are summarized as follows, based on agreement between two out of three models: 1) Panic and

fatigue were among the nodes with *highest* strength centrality index scores in two models (MGM and Ising), 2) depressed mood and somatic symptoms were *among* the second most central symptoms across two models (GGM and Ising), 3) concentration problems, anxiety and phobia were at least among the third central across all models, 4) suicidal thoughts were the least central across models, 5) after suicidal thoughts, appetite and irritability were the least central across models, 6) suicidal thoughts were only connected to the rest of the network worry about health symptoms (except for the Ising model where these were not connected to the rest of the network), 6) the edges between phobia-panic, anxiety-panic, and somatic-fatigue appeared to be the strongest across all three models, 7) the following four edges appeared to be the next strongest edges in at least two models: worry-anxiety, depressed mood-worry, fatigue-concentration, concentration-depressed mood, and functional impairment-concentration, somatic-panic.

Fatigue, depressed mood and concentration problems. In line with findings of previous studies conducted in the Western world (Boschloo et al., 2015, 2016; Fried et al., 2016) fatigue was among the highest centrality index group across two out of three models in this sample. In other words, in India, similar to Western cultures, endorsing fatigue might result in, and/or, might be the result of, an active CMD symptom network overall. In clinical terms, this means that when a primary care patient in India complains of fatigue, an assessment of CMDs might be useful. Since fatigue is a central symptom, its presence would make it likely that other symptoms that are closely linked to fatigue, such as, concentration problems or depressed mood, might already be activated or could be activated soon.

Interestingly, depressed mood which had the highest index score in Western studies (Cramer et al., 2000; Boschloo et al., 2015, 2016; Fried et al., 2016) and in one study done in

India (Wasil, 2020) only belonged to the second highest strength category in this sample. Concentration problems belonged to the third category, while it appeared to be among the most central previously (Boschloo et al., 2016). Depressed mood and concentration problems appear to be important but likely less than what it would be expected based on previous studies. Either way, these symptoms, since relatively more central to the CMD network than some others (e.g., sleep problems, worry, irritability), could contribute to the onset or maintenance of a CMD. An implication is to potentially assess and monitor these symptoms even when the patient does not meet full criteria for a CMD and consider targeting these in clinical interventions.

Somatic problems. Different than one study where somatic symptoms were not found as central (Fried et al., 2016), somatic symptoms were among the second most central symptoms in two out of the three models in this study. An interesting finding was about the strong edge between somatic and fatigue. Across models, it appeared that the somatic symptoms and fatigue are strongly connected, potentially one triggering the other or connected via a feedback loop. In other words, when a patient has somatic pain, they will be more likely to have fatigue even when other symptoms are held constant. One hypothesis can be that this relationship between somatic pain and fatigue might be responsible for an overall activation of the CMD network, causing a healthy state to turn into unhealthy, or maintaining an unhealthy state. While such connection was not emphasized in one study where somatic symptoms were entered in the network (Fried et al., 2019), the network structure reported by the authors exhibited a significant link between somatic symptoms and energy loss. Given that the current study consists of a primary care sample, it does make sense that somatic complaints and their link with fatigue would play a role in the activation of the CMD network.

Another link with somatic symptoms was between somatic and panic, which is in line with the "tripartite" model of depression and anxiety, suggesting that somatic arousal is uniquely associated with anxiety while low level of positive affectivity is uniquely associated with depression (Ask, Waaktar, Seglem, & Torgersen, 2016). Overall, one possible hypothesis is that somatic symptoms might play a role in the activation the entire CMD network and if unaddressed may potentially trigger two other key/central symptoms; fatigue and panic, and subsequently other CMD symptoms. It is difficult to know whether this is the case in India only or in primary care patients in general.

Panic. Different than previous studies where anxiety/panic symptoms were of considerable importance but not necessarily of high centrality among those who were diagnosed with depression (Fried et al., 2016), in this current study, panic symptoms appeared to be either the most central or among the most central symptoms across models. This finding might be unique to this sample, primary care patients screened positive for CMD and not only depression.

In the current study, anxiety and phobia followed panic in one model yet were not among the most central group in other models. Noteworthy, the edges anxiety-panic and phobia-panic were the strongest across all models. The gauge question for panic in CIS-R might help explain such a tight relationship among these three variables: "*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*?" While there are other questions inquiring about the severity, duration, as well as other criteria to establish a panic disorder diagnosis, the panic symptom composite score will go up whenever someone endorses this item, which is essentially assessing an extreme version of anxiety or tension.

In previous qualitative studies in India, “tension”, conceptually similar to an anxious state, was the most commonly reported name for the illness (Andrew, Cohen, Salgaonkar, & Patel, 2012). In fact, in the CIS-R, the word “tension” was directly used when assessing panic, phobia, and anxiety symptoms. Thus, the fact that “extreme levels of anxiety, nervousness, and tension” is an important symptom of CMDs in India would make sense given previous qualitative studies in the region. Although the sample characteristics were largely different, it is noteworthy that the study conducted among war survivors in Sri Lanka (Jayawickreme et al., 2017) also highlighted the centrality of avoidance and emotional numbness (anxiety-related symptoms) in that population.

If panic, or in other words, extreme anxiety/tension/nervousness is truly central in India, their presence might have an impact on the rest of the network in that they might play a role in switching the system from an unhealthy state to a healthy state. Alternatively, it might be that if there were a few activations in the symptoms, panic symptom would be activated, leading to a feedback loop among symptoms maintaining an unhealthy state. In fact, in the current sample, out of 709 who endorsed any symptom of panic, only 6 patients did not have a CMD diagnosis.

Panic/extreme anxiety could also be differentiated from other symptoms (such as worry, worry about health) through its ties with sympathetic activation, potentially indicating that a threat/stress response is activated. The fact that panic symptoms appeared to be central across models, might highlight the importance of hyperarousal. If this is true, this might have broad implications on the clinical interventions for common mental disorders in India, where one might want to focus on incorporating more mindfulness or deep breathing (e.g., longer exhales) activities aiming at the activation of the parasympathetic system.

As an alternative to a possible true finding about the importance of intense anxiety, there might also be a validity concern if the three variables panic, anxiety, and phobia are assessing the varying severities of the very same construct. In other words, perhaps it is not that the panic (intense anxiety) symptoms are very central to the network, but it is that they measure the same construct as phobia and anxiety (either due to errors in translation or a cultural bias) and the edge weights connecting them to each other are responsible for driving panic centrality scores high. The problem about certain nodes capturing the same phenomenon has been discussed previously as an important factor increasing the centrality of these nodes (Fried & Cramer, 2017), and it was recommended that the researchers consider each variable carefully before deciding to enter them in the network. To some extent, the use of CIS-R had helped to overcome this problem in the current study, since two separate scales with same symptoms were not included in the same network. Furthermore, panic and phobia are assumed to be distinct enough than anxiety, conceptually. However, it might be that either due to an error in translation, or a cultural bias where distinctions among these concepts are not readily available to the population in India, these three constructs might be capturing the same phenomenon.

Noteworthy, a particular relationship among these three variables might have been uncovered. In all models, a negative edge between phobia and anxiety was found, although this edge was non-zero in only about 70% of the bootstraps. Such result, when not grounded in a particular theory or hypothesis (e.g., there is no reason to think that anxiety and phobias would be negatively related when other symptoms are controlled for), might indicate a possible "collider" effect, where two arrows along a path both point directly into the same variable (Elwert & Winship; 2014). This has two implications 1) the negative link is in fact spurious, in other terms, only because we controlled on panic, which was a collider, that such negative

correlation was induced and 2) anxiety and phobia are both causing panic, since, no other combination (e.g., panic → anxiety and panic → phobia; or anxiety → panic → phobia; or phobia → panic → anxiety) would be plausible.

Functional Impairment. An important gap in the literature was that functional impairment was often missed as a node in the symptom networks. This study highlighted that the link between functional impairment and concentration might be important. In fact, the strongest and most stable edge that connected functional impairment to the rest of the network, was with concentration problems. Clinically, it makes sense that concentration problems would cause impairments in functioning, rather than vice versa. One problem with this finding is that one item of the concentration subscale asked "*In the past seven days have these problems with your concentration actually stopped you from getting on with things you used to do or would like to do?*" which conceptually overlapped with the functioning questions. No other symptom subscale had a similar question. Among other edges with functioning, the edges with *somatic, depressed mood, and worry* were estimated non-zero in 95% of the bootstraps across three models. The edges with *panic* and *fatigue* were estimated non-zero in 95% of the bootstraps across one or two models only. This is in line with a study where depressed mood, concentration problems, and fatigue were found to explain a large proportion of variance in impairment whereas appetite and sleep-related symptoms explained much less (Fried & Nesse, 2014).

Irritability and worry. Contrary to what was expected based on a qualitative study (Andrew, Cohen, Salgaonkar, & Patel, 2012) where anger/irritability was the most commonly reported emotional symptom and thinking too much (conceptualized as worry) was the most commonly endorsed cognitive symptom, worry and irritability did not appear to be central. It might be that, perhaps, these are culturally more unacceptable or concerning symptoms that are

more frequently noticed, reported, sought help for. Yet, it might be that their presence or absence is not necessarily indicative of a mental disorder to emerge.

Unidimensionality of CMD (Aim 1.2.)

The community analyses did not reveal substantial evidence for a distinction between anxiety and depressive-related symptoms. When symptoms were treated as binary, there was some evidence for such separation, where anxiety, panic, and phobias appeared to be clustered in one community, while the rest were separated, except for the depressive ideas symptom, which formed a separate community. While the modularity index was lower than the threshold followed in previous studies, any non-zero modularity might indicate that there might be, although weak, community structure, separating anxiety-related symptoms from depression-related symptoms.

Assuming that there is in fact a separation between these two clusters, **worry** belonging to the depression-like symptoms, could be a bridge symptom, since the worry-anxiety edge appeared to be a strong edge across models and bootstraps. In previous studies, a strong connection between depressed mood and worry was also reported (Cramer et al., 2000; Boschloo et al., 2015) and it was concluded that "worry" could be a bridge symptom between depression and anxiety-related disorders. This is particularly interesting since worry did not appear to be a central symptom necessarily, however, it might have a critical role in that if the depression-related symptoms are activated, then the activation of worry might serve as a bridge to activate the anxiety-related symptoms (or vice-versa).

The lack of a *strong* community structure with two or three communities might be in line with several previous factor analytic studies where authors concluded the most parsimonious structure was the one-factor structure, where they also noted that there might be some unexplained variance since two- or three-factor structures marginally improved fit. While both

methodologies can complement each other, the conceptualizations of the latent factor and network models are quite different. In one, the existence of one (or more) latent variable(s) is assumed and symptoms are thought to be locally independent (unless certain relationships are allowed), and joint variations of symptoms are searched to determine the optimum number of factors. In network analyses, the variations in each symptom are modeled in terms of the variations of the other symptoms and a community structure is assumed based on the probability of one symptom activating the other versus the rest of the network. Thus, a community is simply a constellation of symptoms that tend to get activated together, and there doesn't have to be a common cause that underlies this pattern. While the existence of a community structure does not have an implication on the existence of a latent factor (since the reason for a partitioning is rather conceptual question), the non-existence of a community structure might imply a unifactorial structure. As such, the findings of this study give some (although *weak*) support to the idea that anxiety-related variables activate each other more than they activate depression-related variables (and vice versa), such pattern does not necessarily support the common cause theory.

CMD networks across different demographic characteristics (Aim 2)

When the baseline CMD networks of males and females were compared, the two networks did not differ significantly both when the variables were treated continuous and when they were treated as binary, although this might have been due to the large difference in sample sizes across gender. When the networks were compared across private and public sector settings, no differences in terms of the network density was found across the two methods, however, differences existed in terms of the edge-weight strengths, only when variables were treated as continuous. The edges between **panic and anxiety, and depression and worry** were stronger in the public health care setting compared to the private setting. The edge between **fatigue and**

somatic was significantly stronger in the private health care setting compared to the public health care setting. Descriptively, in public health care settings, **panic and depressed mood** appeared to be the two most central symptoms, followed by concentration, fatigue, sleep, anxiety, and somatic symptoms. On the other hand, in private health care settings, **fatigue and depressed mood** appeared to be most central, followed by somatic symptoms, concentration problems and panic symptoms.

Somatic symptoms are often considered to be linked with somatic awareness or oversensitivity to bodily sensations (Barsky, Goodson, Lane, & Cleary, 1988). This finding could be due to heightened sensitivity to physical sensations and fears about finances among those who have better resources and perhaps working conditions, such as non-farm salaried employment (Das, 2008), compared to those who work in the farms who might be less sensitive to somatic complaints and more vulnerable to feelings of panic and/or worry. It should be pointed out that while there are some differences in terms of the rates of endorsement across settings, the network results don't refer to the rates, but explain a certain vulnerability to developing a CMD, if and when a symptom is endorsed.

As such, attention should be paid to somatic and fatigue-related symptoms in private health care settings when assessing and monitoring for CMD, while panic might be more important to track in public health care settings, not because these symptoms are more commonly endorsed in these settings, but if endorsed, the system might switch to an unhealthy state quicker than if another symptom was endorsed.

It should be noted that the distinction between public and private health care settings is not just one that relates to financial resources, but two more factors might be important to consider. First, in India, those who consider themselves to be more ill (either based on signs or

subjective symptoms) tend to choose private health care and they often sell a land or an asset in order to afford better care. Yet, to some extent, patients who attend private health care settings could be those who are more concerned about their health, thus they made sure to receive better care. In fact, even though the overall symptom severity and rates of CMD were similar across settings, those who are in the private health care appeared to have significantly higher rates of somatic symptoms and were significantly more worried about their health compared to public health care setting. Those in the public health care were more anxious and worried in general and exhibited more functional impairment (Table 4). Second, it might be that the private health care patients either are more "resourceful", perhaps they have larger and better-connected family and social networks, or they have better problem solving skills when concerned about their health. As such, the public versus private setting distinction should not just be taken solely as a financial proxy.

CMD networks across different treatment response statuses (Aim 3)

No significant differences were found, when the baseline network of those who showed sustained remission was compared to a) those who did not respond or b) who did not show sustained remission. These results were the same when the analyses were conducted with a different method, treating all variables as binary, and also when conducted separately for the intervention arm and for the control arm. This result was different than a naturalistic study where the network density of those who recovered in subsequent years were found to be less dense at baseline compared to those who continued to be depressed (vanBorkulo et al., 2015). The authors concluded that a loosely connected network would eventually find its healthy state when the stressor is removed. However, in a letter published in 2018, Schweren and colleagues reported null findings regarding the network density differences across adolescents who

responded to depression treatment versus those who did not. Taken together, it might be that the network density is not a prognostic marker when symptoms or networks are actively challenged. In other words, when the network is densely connected, an appropriate treatment targeting some of the strong edges might result in a quicker resolution than a weakly connected network. Let's say, a person with diabetes, both feels depressed and have poor sleep because they wake up frequently during the night with hunger. In this scenario, depressed mood and sleep problems may not be linked and intervening on the sleep problems may not alter the rest of the network.

Implications

To the knowledge of the current author, this is the first study investigating the network structure of CMDs among primary care patients in a non-western and low-income sample, using the CIS-R. The use of CIS-R addressed several important problems in the literature. First, depression and anxiety-related symptoms were entered together in the same network without including the overlapping symptoms twice. Second, the problem of "skip questions" were avoided since all symptom clusters are administered with CIS-R.

The results shed light on the CMD symptom structure in India. First, it highlighted the similarities with the western structure where depressed mood, fatigue, concentration, and somatic symptoms were found to be central. Second it revealed a potentially important symptom, panic, as a form of severe anxiety and tension, unique to this sample. Third, it presented little evidence supporting anxiety and depression being distinct conditions in India (weak separation and only when the items are binarized) and more evidence for the unidimensionality of the CMDs as measured by the CIS-R. Fourth, it allowed researchers to generate hypotheses about the mechanisms of CMDs, through significant edges between symptoms. Fifth, it shed light on potentially different mechanisms across private and public health care settings.

While centrality implies that a symptom is highly connected to the network, the interpretation of this finding remains limited, as it is often difficult to develop a treatment where one symptom could be isolated and intervened upon (Bringmann et al, 2018). Furthermore, caution is needed when interpreting centrality. A central symptom may also be the "causal endpoint" of a pathway, or part of a feedback loop, in which cases, intervening on that symptom may not lead to changes in the system (Fried et al, 2018).

Another parameter that offers perhaps more useful, though one that requires unpacking, is the edge weights. While the presented graphs don't indicate any temporal connections, they do indicate *potentially* causal relationships and offer rich information (Ebskamp, 2018). Based on the finding where panic was the most central, important edge-weights could be utilized to better understand how the network switches from a healthy state to an unhealthy state. One plausible hypothesis about how a CMD network could be activated is as follows (Figure 29): somatic pains (Phase 1) might increase patient's level of panic (Phase 2, somatic-panic edge), and simultaneously worsen fatigue (Phase 2, somatic-fatigue edge). The increase in cognitive load caused by panic and fatigue may lead to worsening in concentration and memory (Phase 3, concentration-panic edge). The worsening in memory and fatigue might together cause depressed mood (Phase 3, concentration-depressed mood edge), activating the network and causing to switch to an unhealthy state. Subsequently, depressed mood might worsen the worry (depressed mood-worry edge), which might then cause further anxiety (anxiety-worry edge), leading to further panic (anxiety-panic edge), maintaining the entire network in this fashion.

The differences in edge strengths across public versus private setting might imply that the mechanisms of CMDs (either in terms of the onset or maintenance) is different for private health care patients versus public health care patients. This might have important public health

implications. For instance, private health care patients more frequently endorsed somatic pain, but more importantly, **they appeared to be more vulnerable to feeling tired when they have somatic pain (and vice versa),** potentially resulting in an activation of both symptoms and causing an onset/maintenance of CMD. If this statement is true, an idea for intervention might be to target this link, through pain management, mindfulness activities, and breathing techniques. For public setting on the other hand, it might be that anxiety is more easily turning into panic (given the collider effect and also because panic is interpreted as an intense version of anxiety) and also, **they might be more vulnerable to get depressed mood when they are worried (or vice versa)**. For these patients, it might be possible to further unpack the link between worry and depressed mood; while they might be given hope that their depressed mood might be treated, they might also be offered treatments where their worrisome thoughts could be challenged, and problem-solving techniques could be offered.

Limitations

Skewed nature of the data. There were several limitations. First, the skewed data distribution and lack of clarity regarding the most appropriate way to treat the CIS-R symptom composite scores presented some problems. In fact, the findings highlighted the importance of making careful decisions about the appropriate method of analysis, as there were differences across models.

An important implication of the skewed nature of the data is that it might affect the symptom's centrality scores. Certain symptoms that are crucial in terms of morbidity or mortality, such as suicidal ideation/behavior or functional impairment, might have low centrality scores because they are rarely encountered (with low frequency) or have low differential variability. Relatedly, another point that is worth noting here is that, inherent to the network

modeling approach, symptoms are treated equal in terms of their significance or public health implications. As such, caution should be applied when interpreting the results, since a symptom that does not appear to be central (e.g., suicidality) might still need to receive utmost attention in terms of assessment and treatment.

Model selection. As previously discussed, the selected model that best captures the data is network is done by optimizing the fit between the network and the data through minimizing the EBIC, which depends on two important factors; sample size and the hyperparameter γ (gamma). Depending on these two factors, the estimated network might miss some of the true edges (low sample sizes, N<100, tend to result in lower sensitivity; Ebskamp & Fried, 2017) or might have too many spurious edges.

In order to see the influence of different hyperparameters on the network selected, a dataset of 100 people was simulated based on a known network of a chain graph of 8 variables (Ebskamp & Fried, 2017). For varying values of γ, a network was selected through EBIC minimization. For $\gamma = 0$, the network that was selected featured three weak spurious edges compared to the pre-determined true network; meaning that it failed to exclude three edges that were not there in true network structure. Perhaps the most important and obvious implication of this study is that, a much denser network could be selected for a lower value of γ, and without having an idea of the "true" network it would not be possible to know which parameter would lead to the most accurate network.

Symptom selection and construct validity. A second limitation involved concerns around symptoms that might be measuring similar constructs; anxiety and phobia appeared highly linked with panic scores, which might not be distinct concepts, and might have led to biased centrality indices. Another similar finding was with functional impairment and concentration problems

presenting a strong edge, which might have been because they shared a common item assessing how much the functioning was affected. In a future study, the CIS-R symptom variables could perhaps be collapsed (e.g., anxiety and panic), and the results could be reevaluated.

A third concern was potential heterogeneity of some of the symptom composite scores, particularly the symptom "depressive ideas", which is a composite of five items that included diurinal variations, psychomotor retardation, guilt, self-blame, and suicidal ideas. This variable was only linked with worry about health and overall had the least strong centrality, which might not be because what it captures is not central, but it might be because it captures more than one symptom. Thus, some variables (e.g., depressive ideas) could be unpacked in a future study, and rather than using the subscale composite scores, certain individual items could be selected based on their diagnostic relevance in order to then be entered into an Ising model. For example, self-blame and guilt items of the "depressive ideas" sub-scale, could be important to capture individually, since the item "feeling like a failure" was found to be central in a previous study among adolescents in India by Wasil and colleagues (2020).

Cross-sectional study design. A fourth and important limitation is one that is inherent in the methodology and study design. Given the cross-sectional nature of the data, it is hard to know whether the results could be generalized to intra-individual networks (Cramer et al., 2016). In other words, while public health recommendations could be possible in terms of screening and case identification (i.e., recommend further assessment on CMD if a patient endorses severe anxiety/panic or fatigue), treatment recommendations would require further evidence on causal relationships between symptoms. Even though cross-sectional and undirected networks do offer rich information about potentially causal effects, it is difficult to infer any particular "flow" across symptoms without using methods involving repeated measures or experimental studies.

Therefore, dynamic networks are needed to better understand the causal relationships among symptoms.

Future directions

While the notion of centrality seems intuitive and easy to understand, a major criticism of the examination of centrality measures was about the lack of evidence on their predictive value (Borsboom et al., 2019). Furthermore, the assumption that symptoms are "distinct" and "interchangeable" was questioned in the field, which makes the centrality indices more difficult to interpret. First, it is very difficult to distinguish, for instance, somatic pain from fatigue, especially when it comes to designing an intervention. Second, some symptoms, for instance, suicidal ideation is considered more severe than say, concentration problems and require immediate attention in terms of intervention.

To address this, one suggestion has been to leave the whole idea of centrality behind and focus on the "network as a whole" (Borsboom et al., 2019). This is in line with recent studies where the "network connectivity/density" has been proposed to have prognostic value; a tight network could mean that the person is more vulnerable to stressors since activation on one symptom could lead to the activation of other symptoms more quickly (Cramer et al., 2016). If it is agreed upon that the network density might be an important and promising index for future studies (e.g., researching the predictive value of network density or its correlates), the issue of hyperparameter selection might become even more important. As discussed previously, different levels of the hyperparameter can lead to higher or lower density. Therefore, in future studies, repeating the analyses for varying levels of the hyperparameter and commenting on how the densities would be different for different levels might be a necessity, rather than a choice.

One important area of research in CMDs involves “residual symptoms”, as these have been reported as one of the important predictors of relapse (Wojnarowski et al, 2016). Using more advanced network modeling approaches accounting for zero-inflated data, in a future study, the residual symptom networks of those who responded/remitted at both 6-month and 12-month follow-up could be investigated in comparison to those who relapsed at the 12-month follow-up.

An important future direction would be one that is aiming to further explain the links between symptoms, including certain important external factors in the network. Focusing exclusively on the connections between symptoms might not be informative without understanding the factors (i.e., third variables). The links between two symptoms might be loaded with information about important factors like psychosocial ones such as weakened social support, psychological, such as adaptive coping skills, genetic predisposition, or neural correlates. Let’s take the example of somatic symptoms and functional impairment and imagine an unemployed woman with two small children who experiences back pain. Finding that there was a strong link between the pain and functional impairment would be informative, though without further investigation, it would be difficult to make treatment recommendations. Could it be that the patient is lacking interpersonal skills causing her to be more vulnerable to develop CMD when having back pain? If so, then it might be possible to think that they might benefit from mobilizing resources and finding someone who can help take care of the children since they experience pain.

The current study sheds light to the network structure of CMDs in a non-Western, developing country, and highlights the importance of intense anxiety/panic in this sample, particularly among public health care patients. While these findings have important implications

in terms of the etiology of CMDs, future studies are required before any strong public health recommendations could be made.

As an alternative to the traditional factor analytic models, network modeling allows for a graphical representation of a complex and dynamic system of symptoms. When applied to cross-sectional data, findings are used not to confirm but generate testable hypotheses about any potentially causal relationship. Even when causality could be inferred with sound methodology, the clinical implications are not always clear since the symptoms are often intertwined and hard to isolate to target. Rather than exclusively focusing on the "centrality" of individual symptoms, examining the dynamics of the complex system overall is recommended, through indices like network connectivity, or identifications of clusters of symptoms with strong reciprocal relationships.

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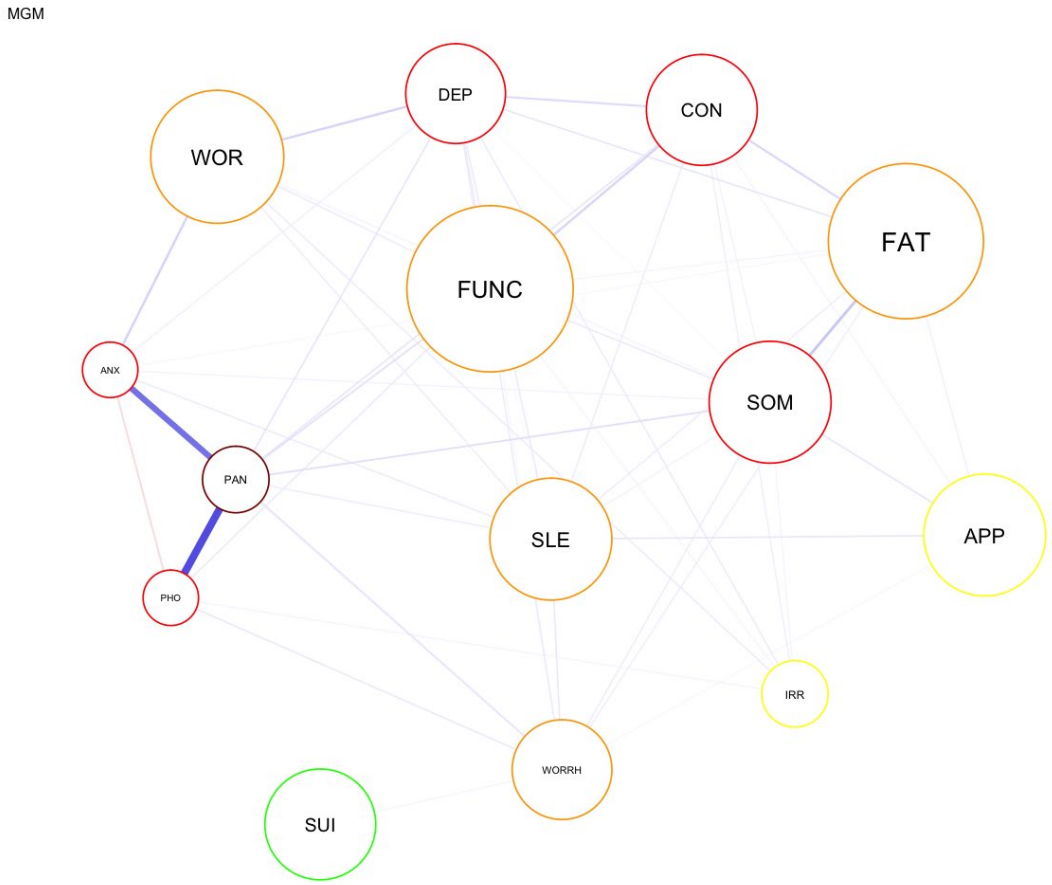
Figure 1: Mixed graph model network of the 14 CMD symptoms at baseline



Note 1: The size of the nodes represents their mean value. 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.

Figure 2: The centrality indices of the CMD symptoms at baseline

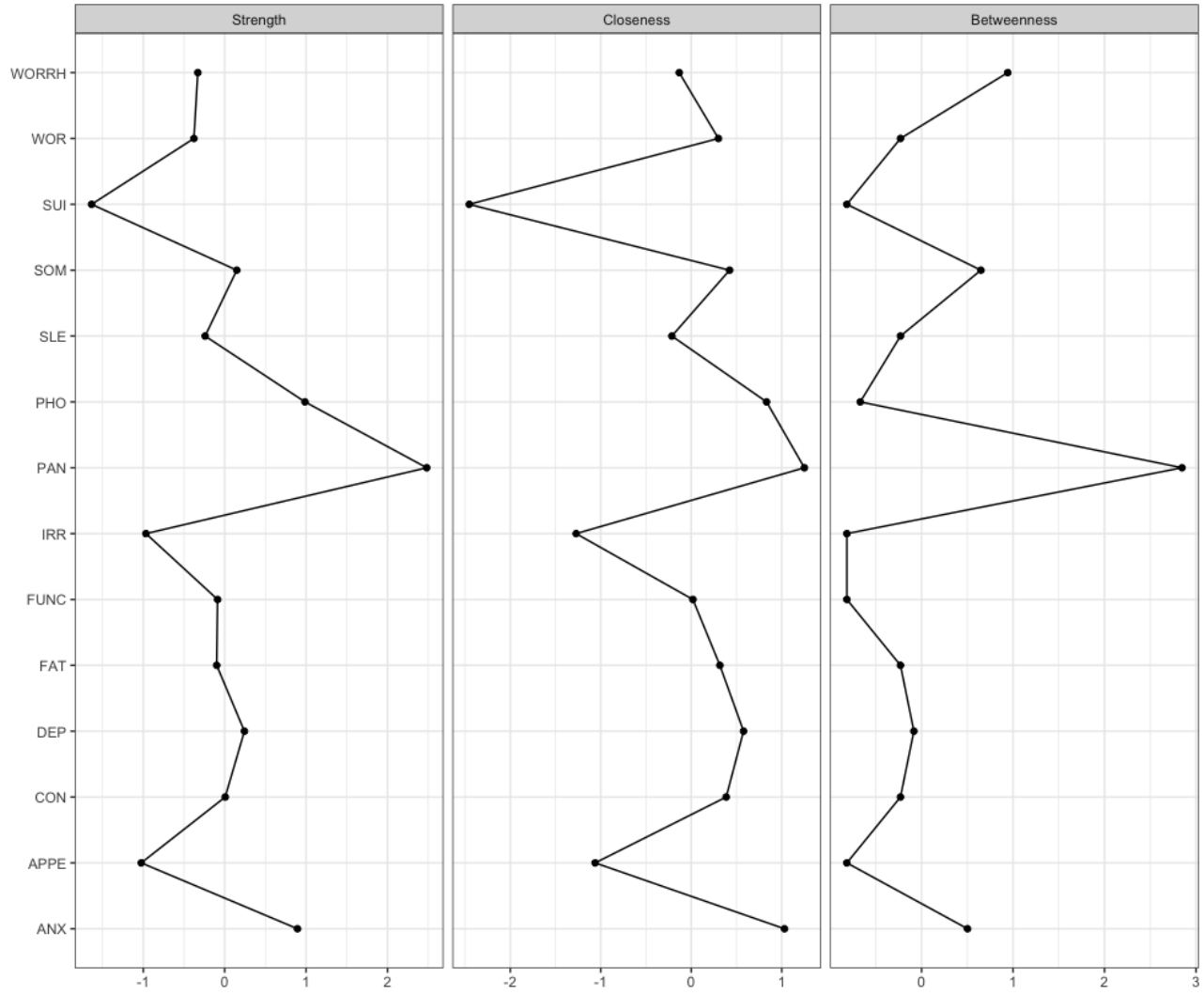


Figure 3: The average correlation of the bootstrapped indices with the original sample (network stability)

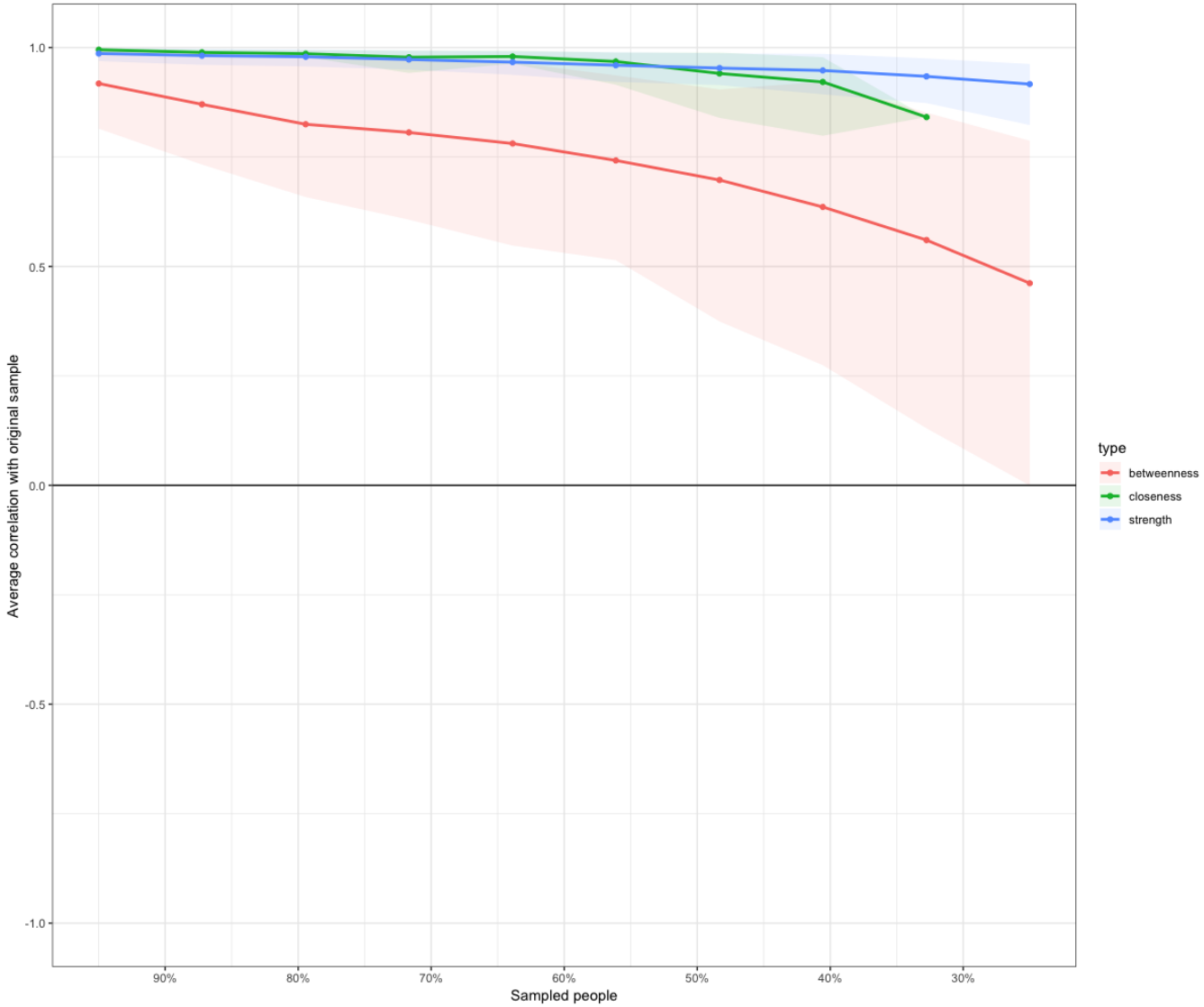


Figure 4: The bootstrapped differences of the centrality indices at baseline (black boxes indicate significant difference)

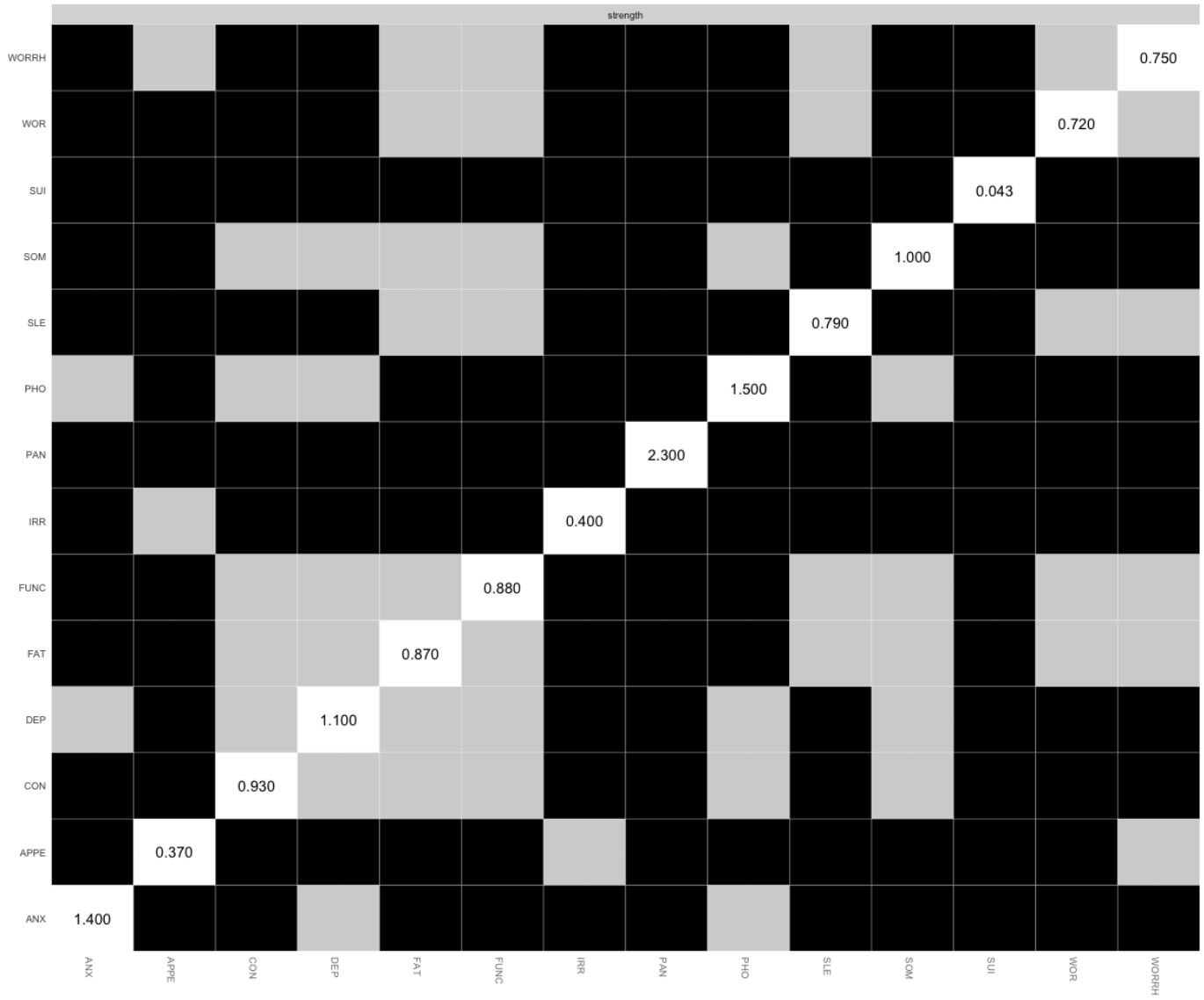


Figure 5: The bootstrapped edge-weights and the CIs (edge-weight accuracy)

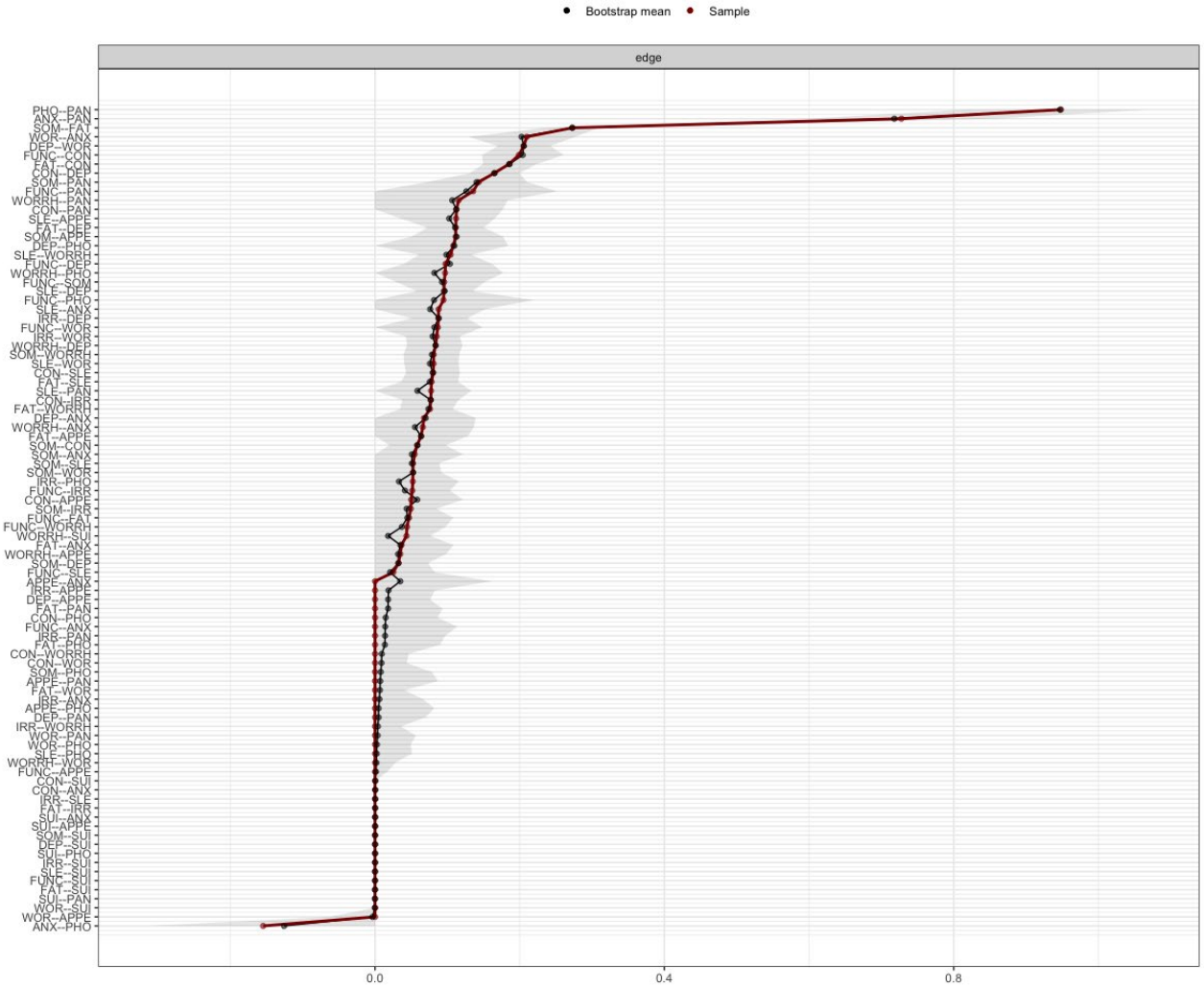


Figure 6: The bootstrapped edge-weights, the CIs, and the percentage of times an edge was estimated as zero (edge-weight stability)

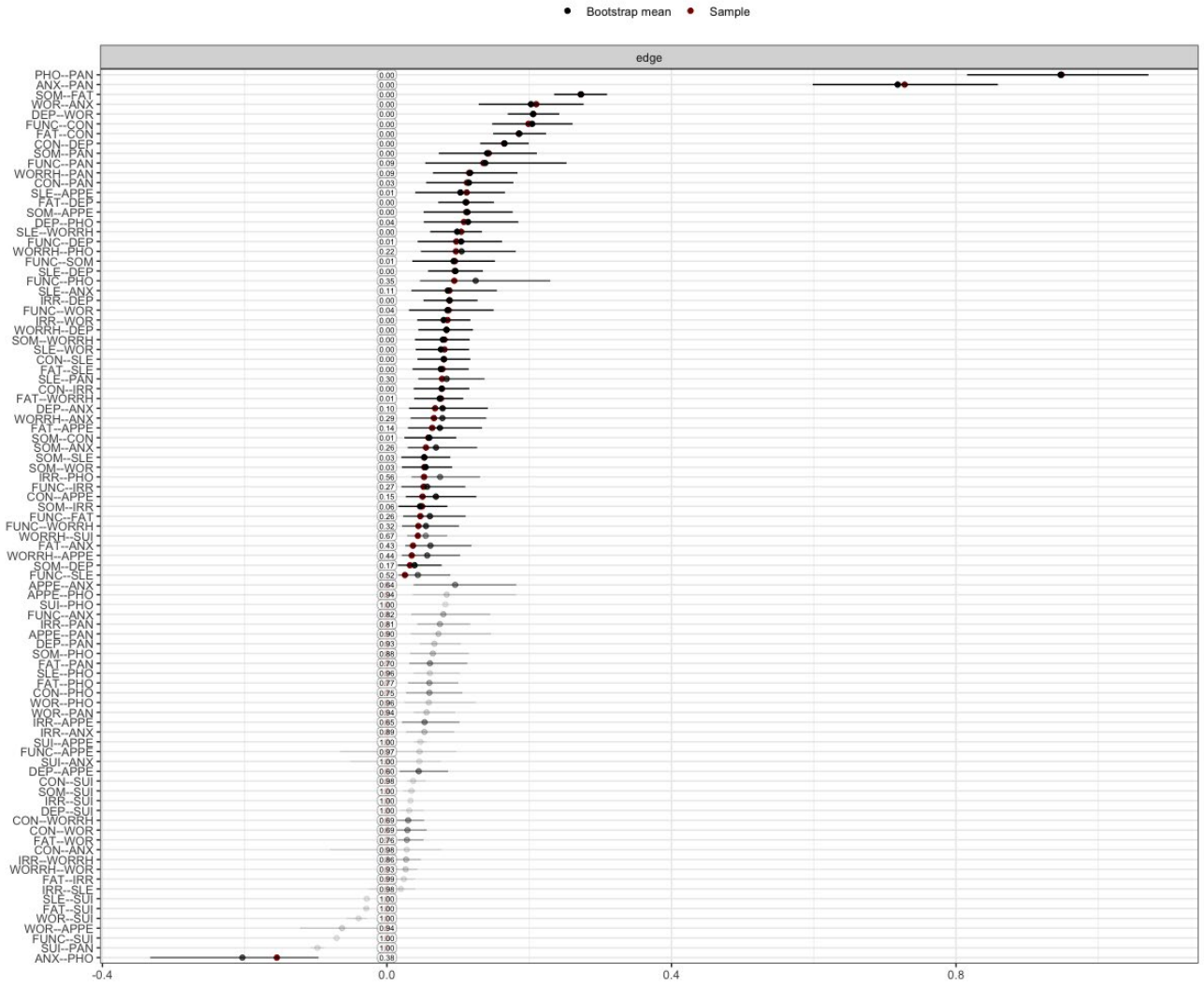


Figure 7: The bootstrapped differences of the edge-weights at baseline (black boxes indicate significant difference)

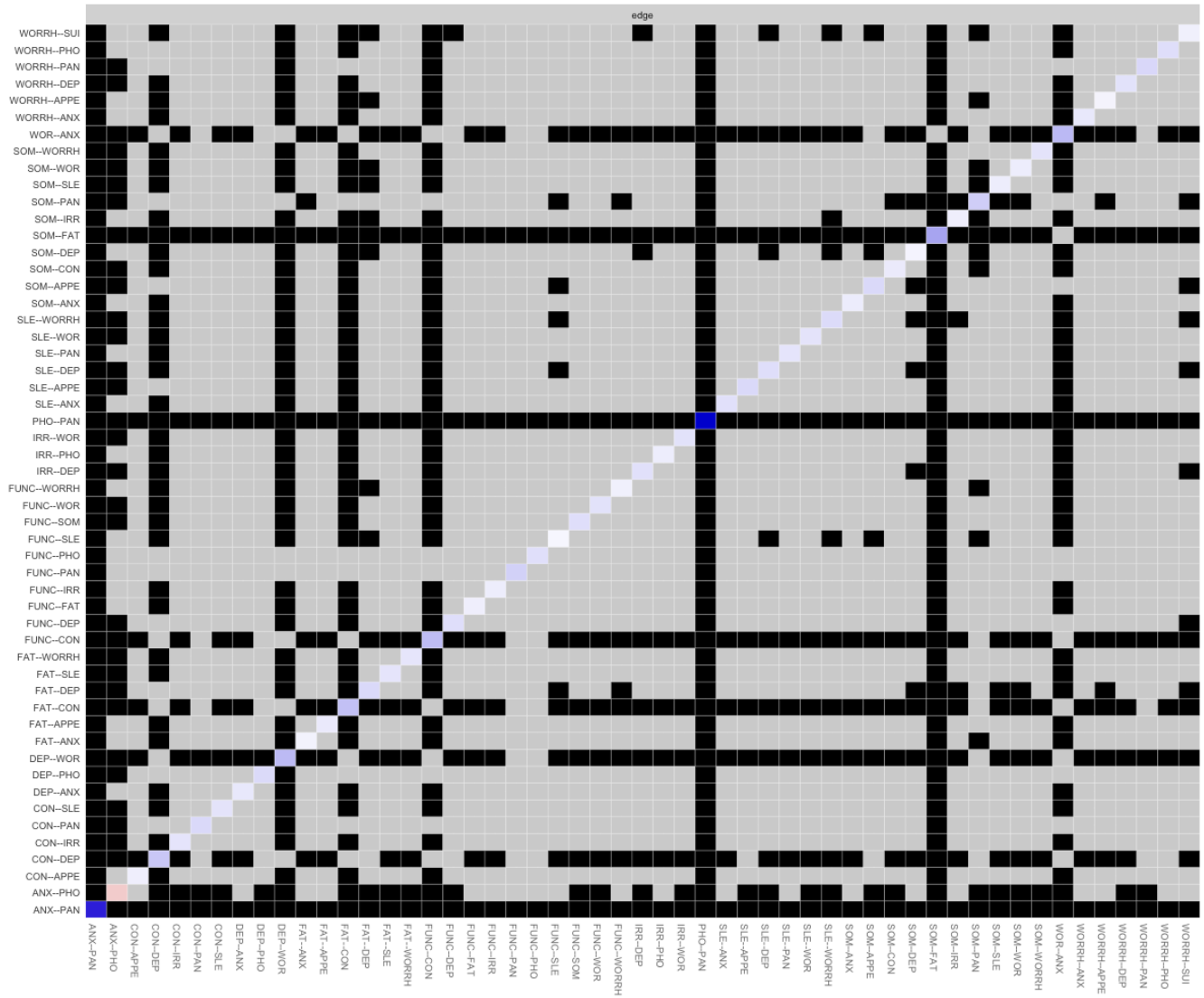
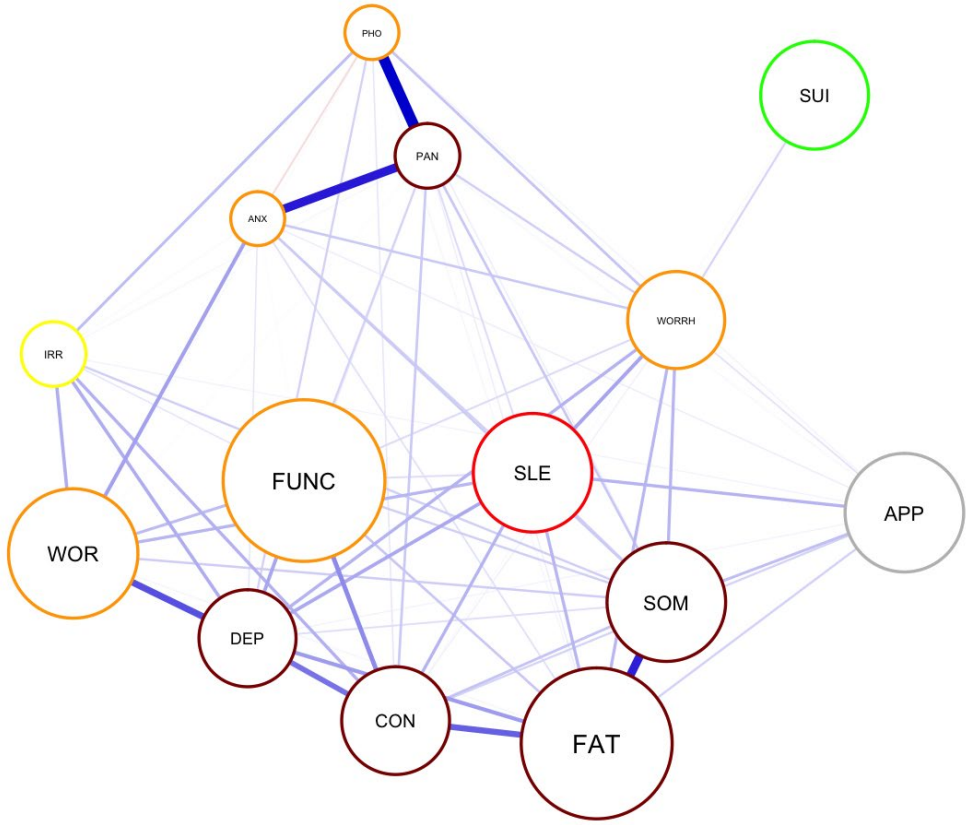


Figure 8: The Gaussian graph model (GGM) network of the 14 CMD symptoms at baseline



Note 1: The size of the nodes represent the mean value of the node and . 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.

Figure 9: The GGM network, average correlation of the bootstrapped indices with the original sample (network stability)

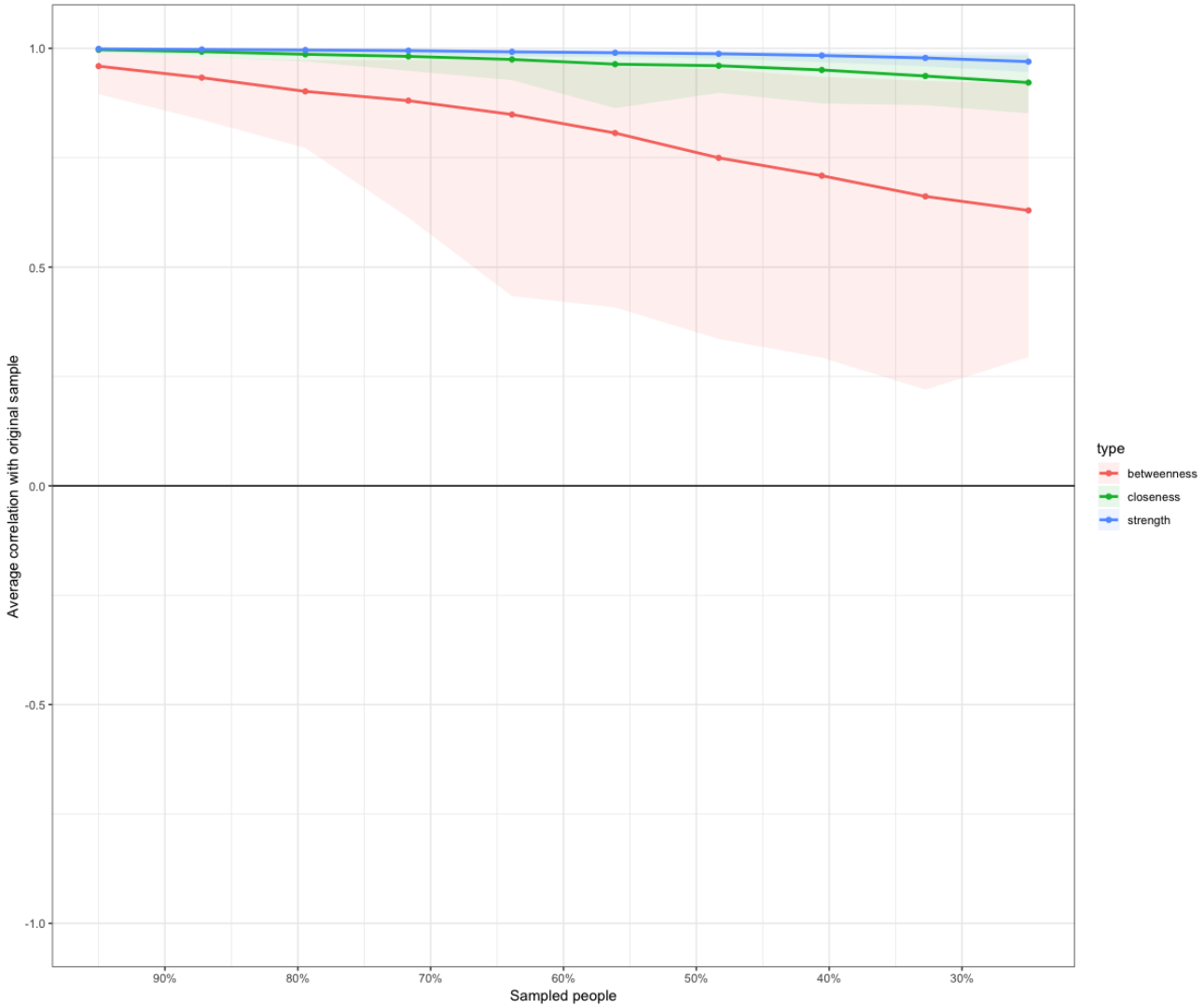


Figure 10: The centrality indices of the GGM network at baseline

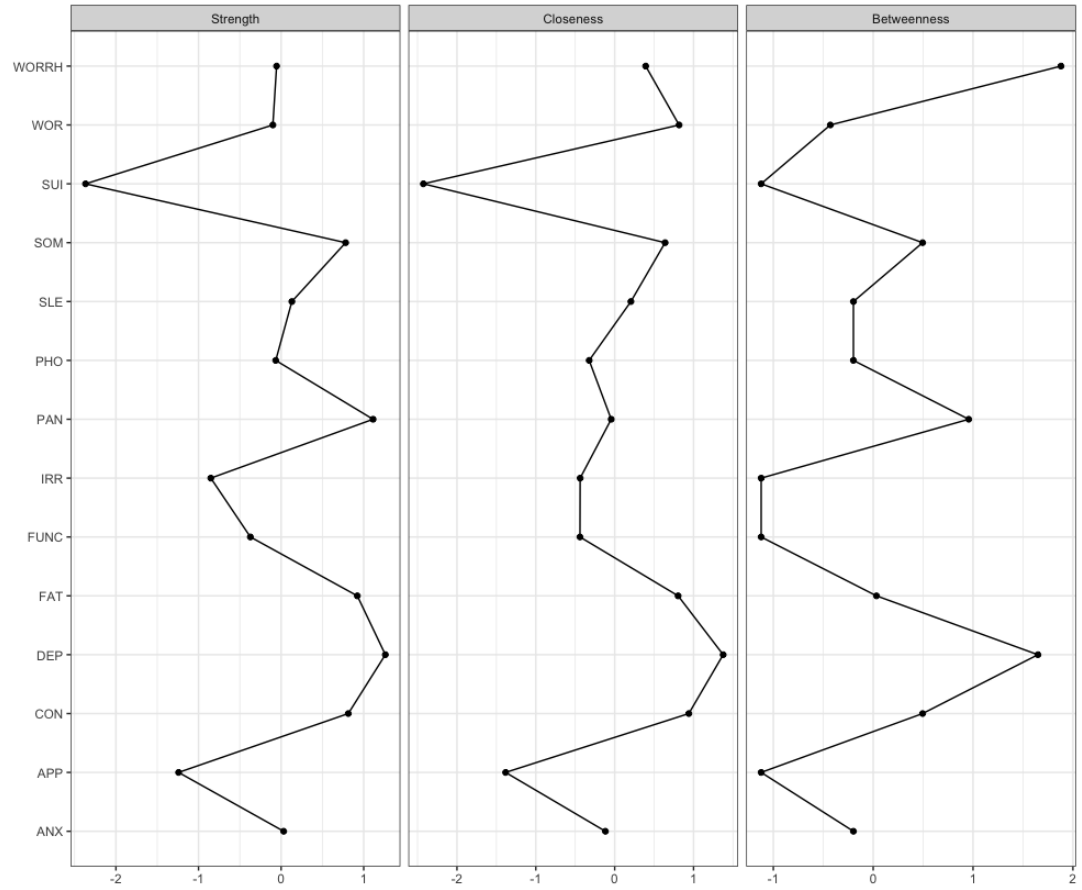


Figure 11: The GGM network, bootstrapped edge-weights and the confidence intervals (edge-weight accuracy)

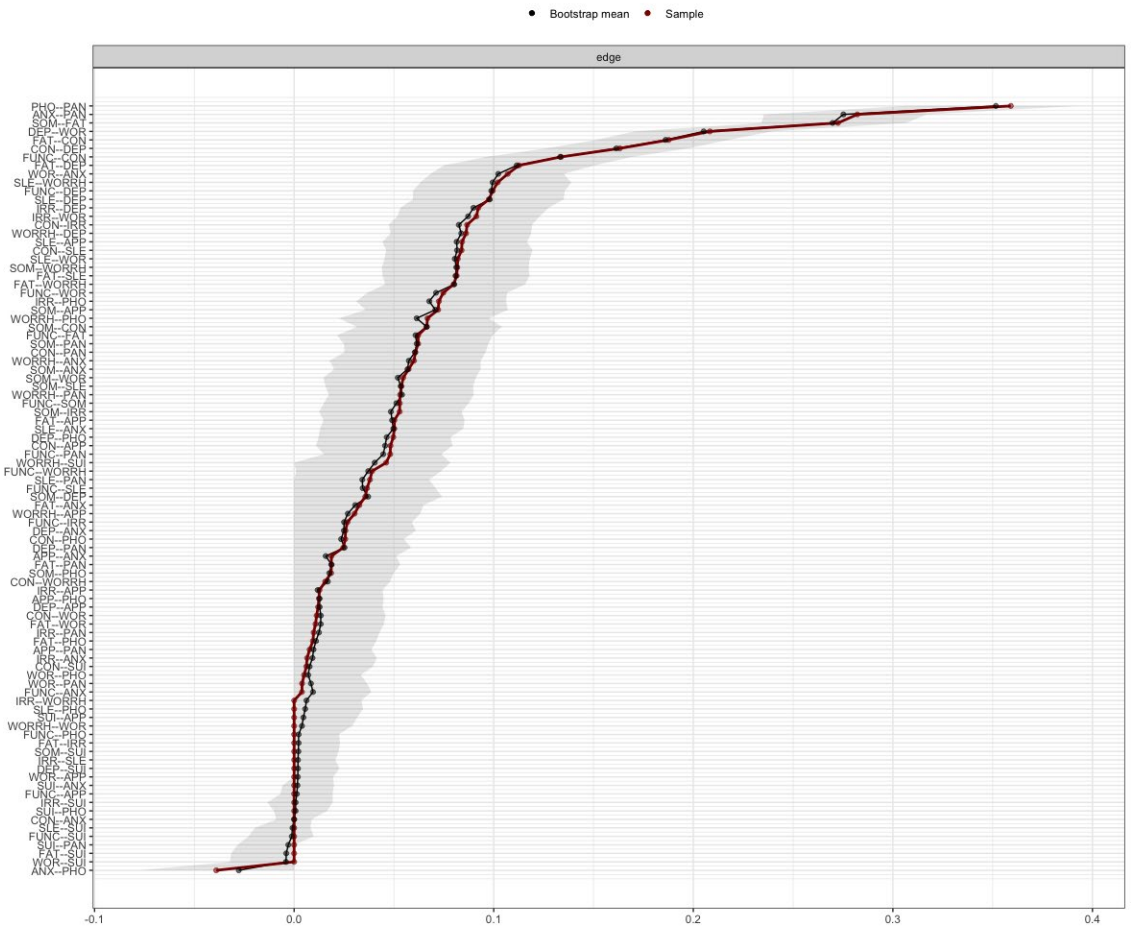


Figure 12: The GGM network, bootstrapped edge-weights and the % of times an edge was estimated as zero (edge-weight stability)

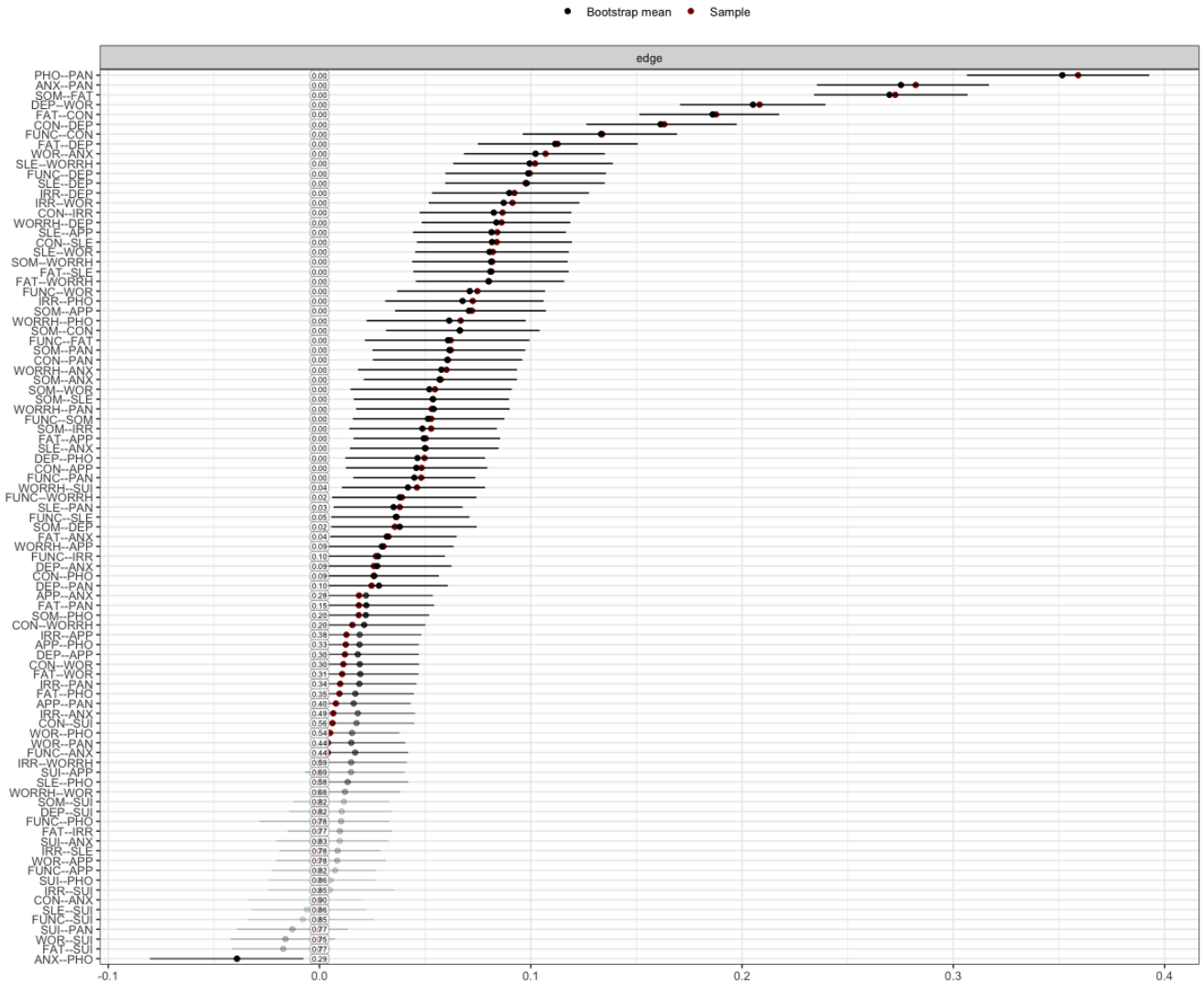


Figure 13: The bootstrapped differences of the edge-weights at baseline (black boxes indicate significant difference)

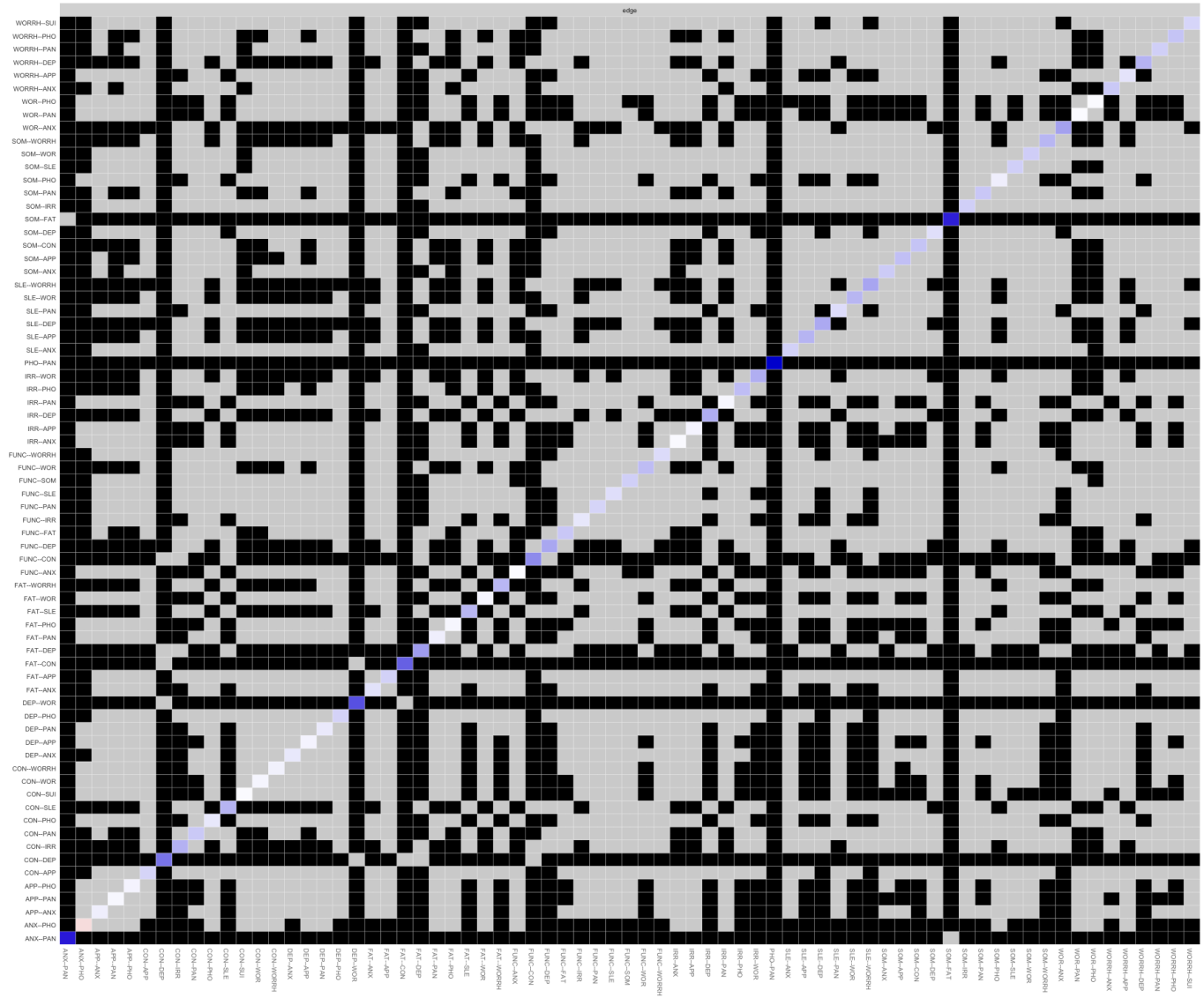


Figure 14: Ising Model

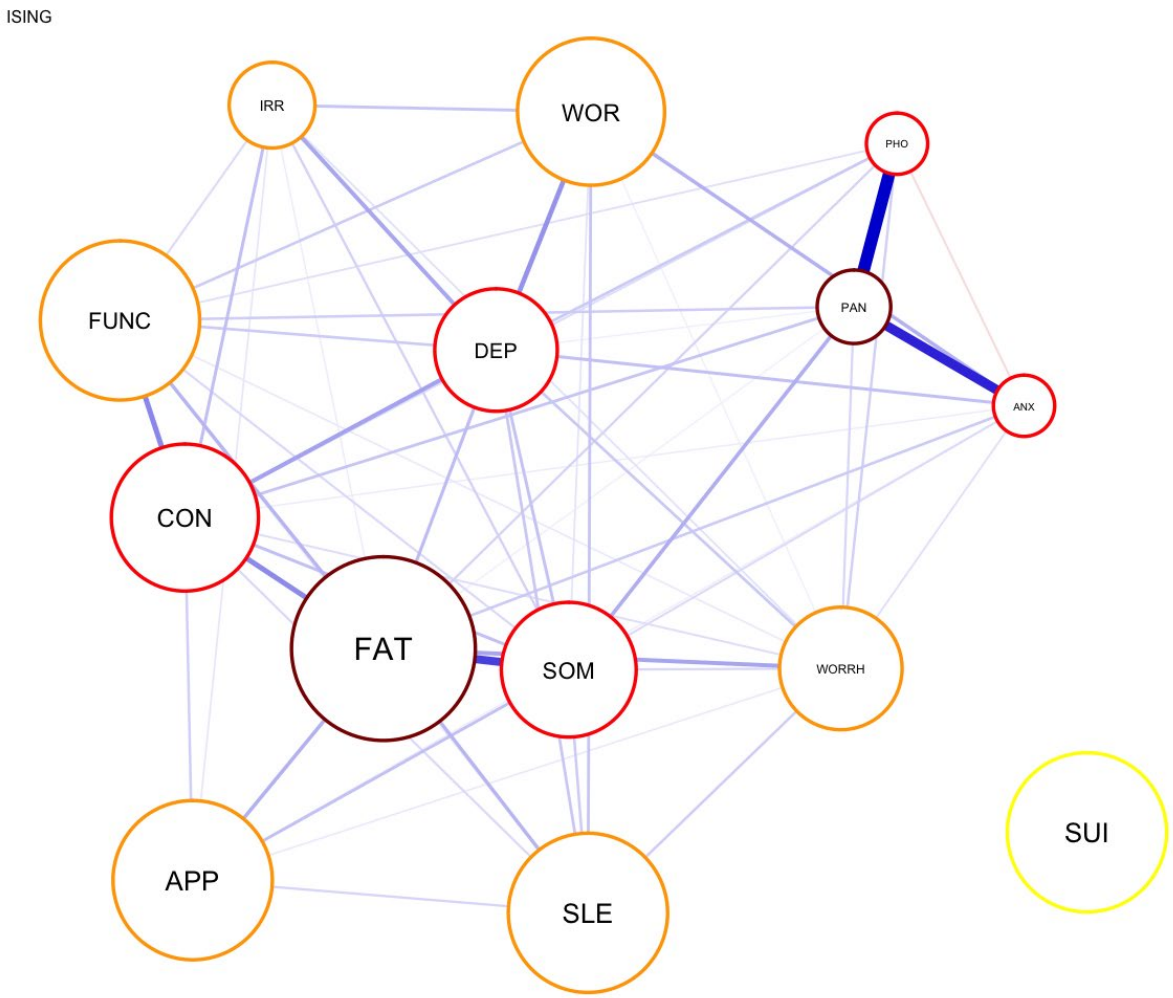


Figure 15: Ising Model, average correlation of the bootstrapped indices with the original sample (network stability)

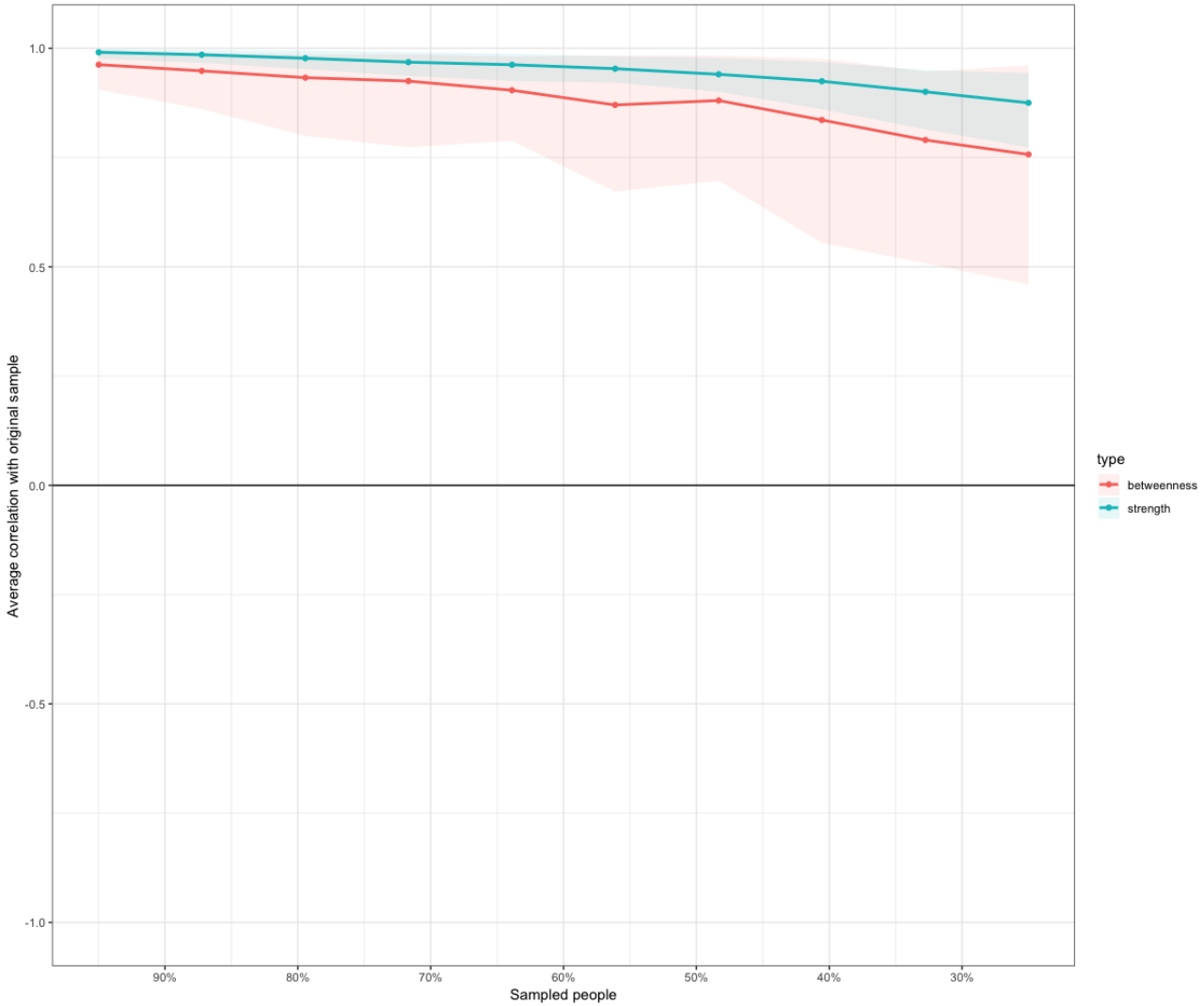


Figure 16: Ising Model, centrality indices

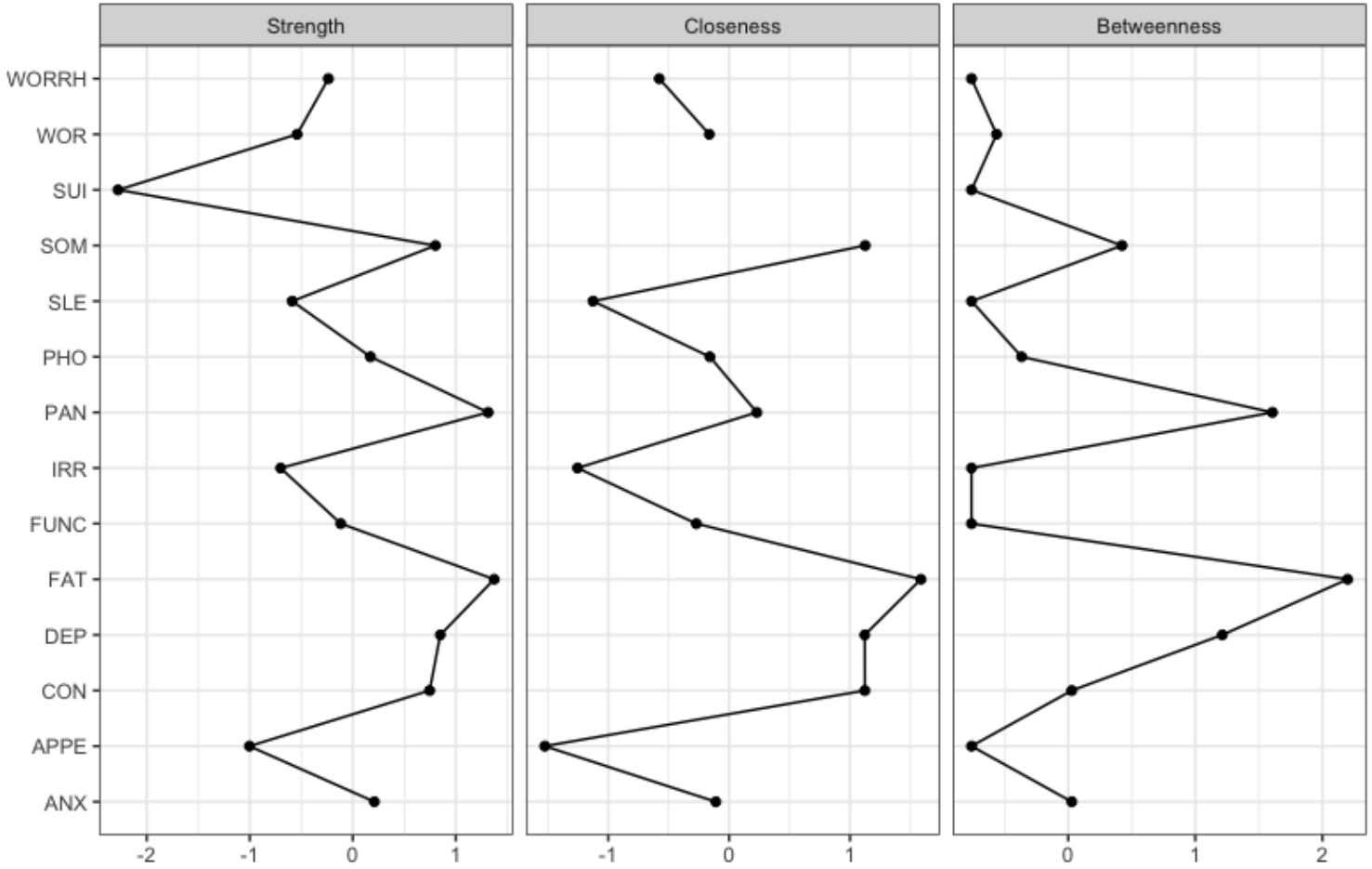


Figure 17: Ising Model, bootstrapped differences of the centrality indices (black boxes indicate significant difference)

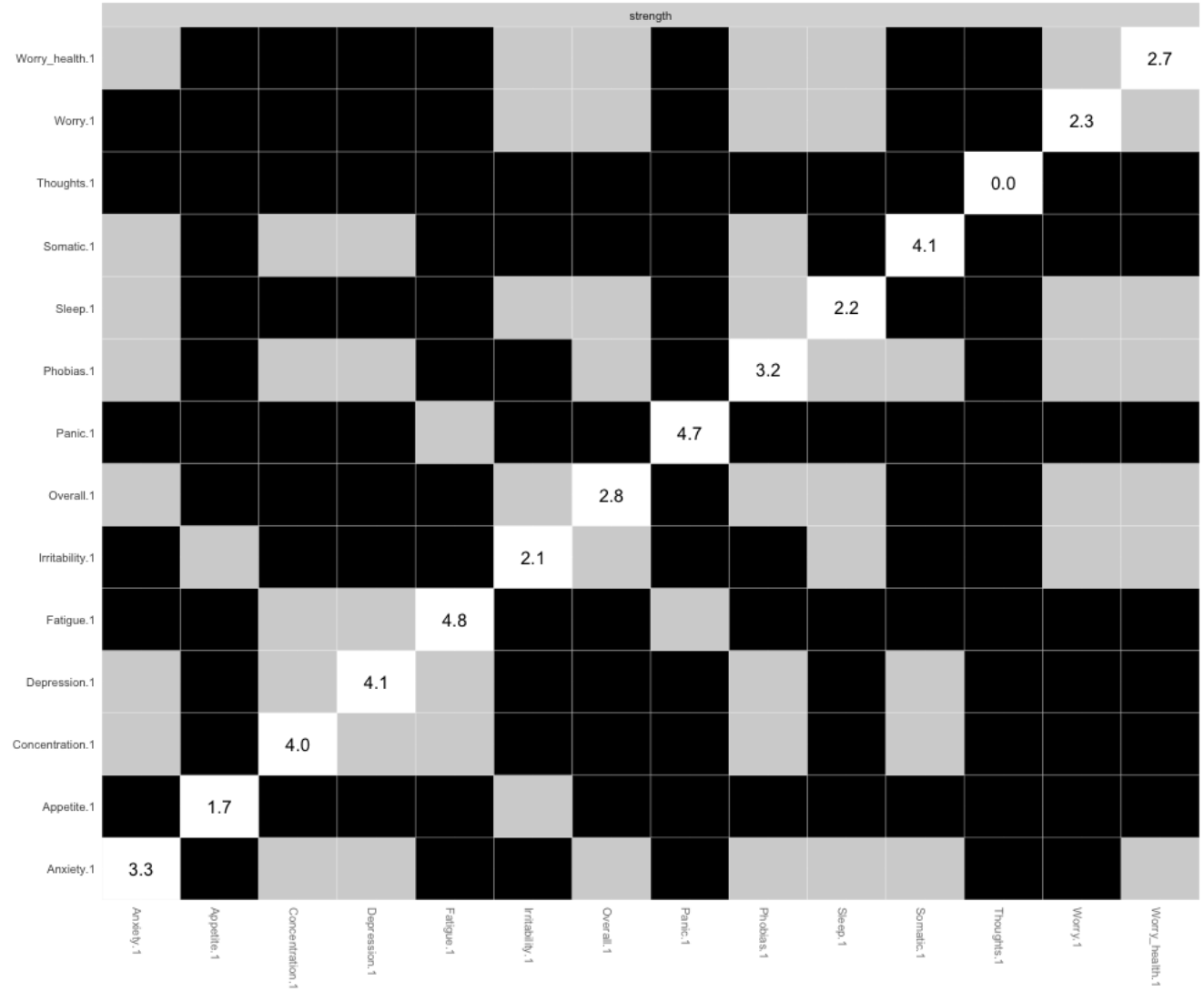


Figure 18: Ising Model, bootstrapped edge-weights, the CIs, and % of times the edges were estimated as zero (edge-weight stability)

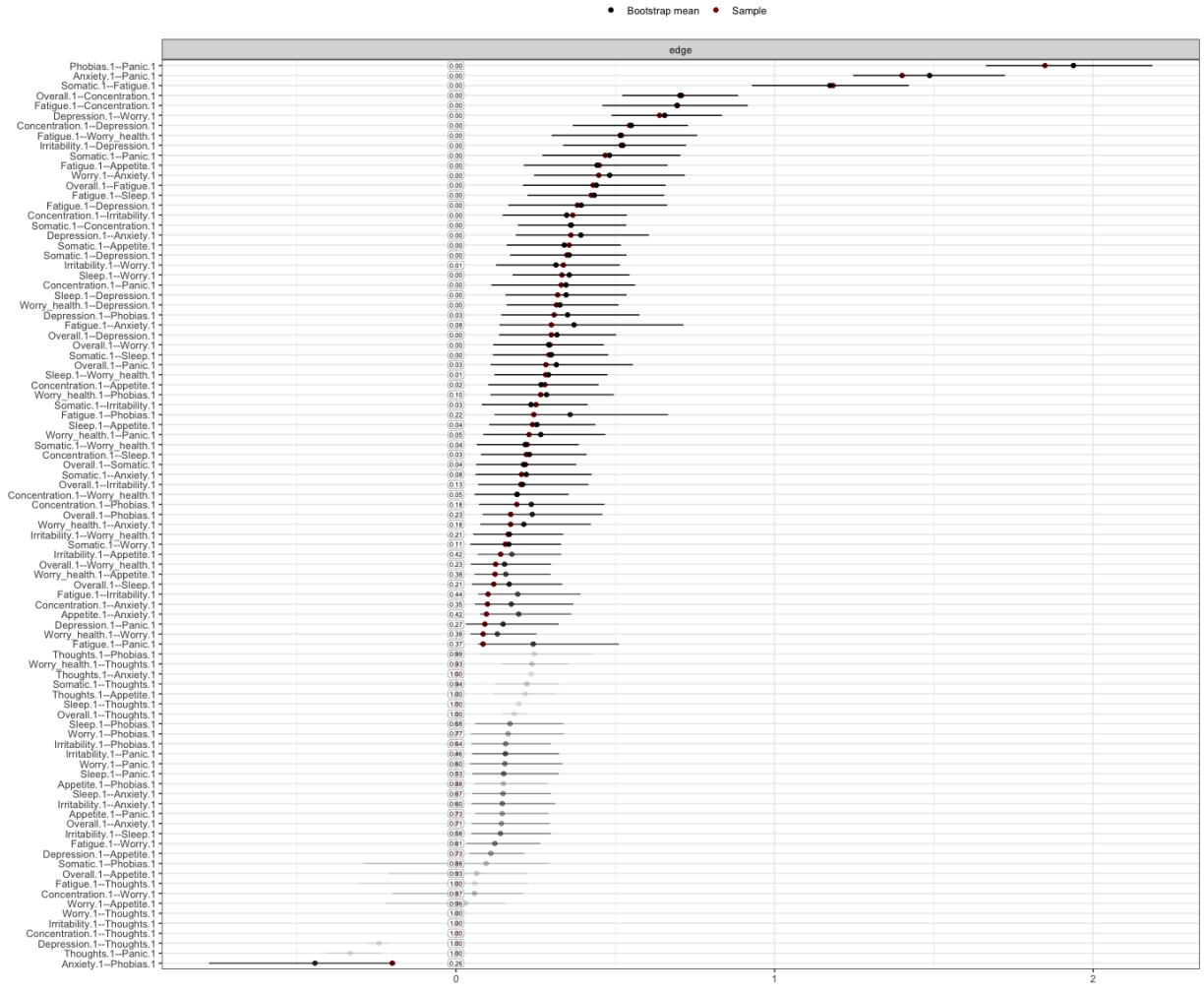


Figure 19: Centrality indices (standardized values) across three models, mgm, ggm, Ising model

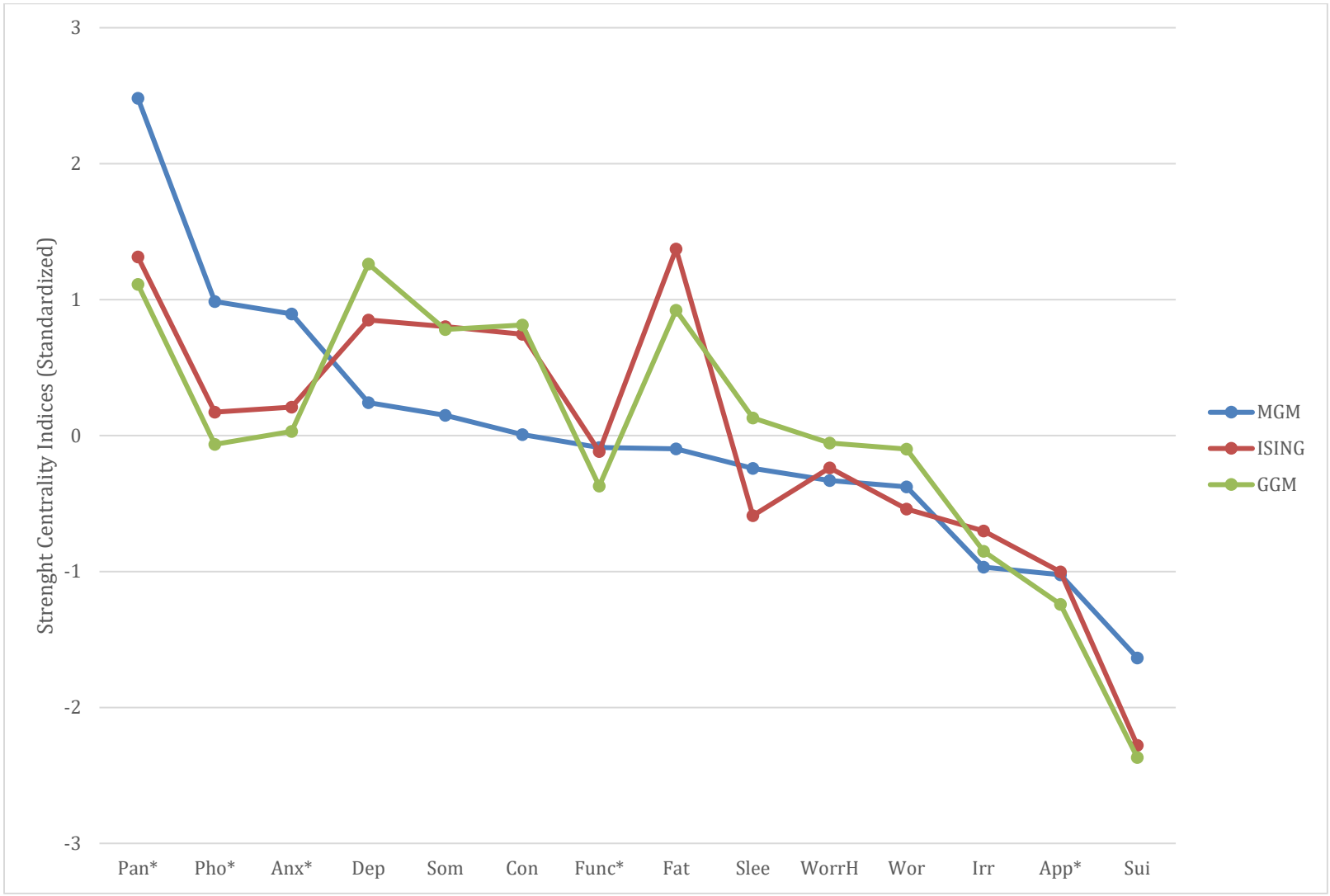
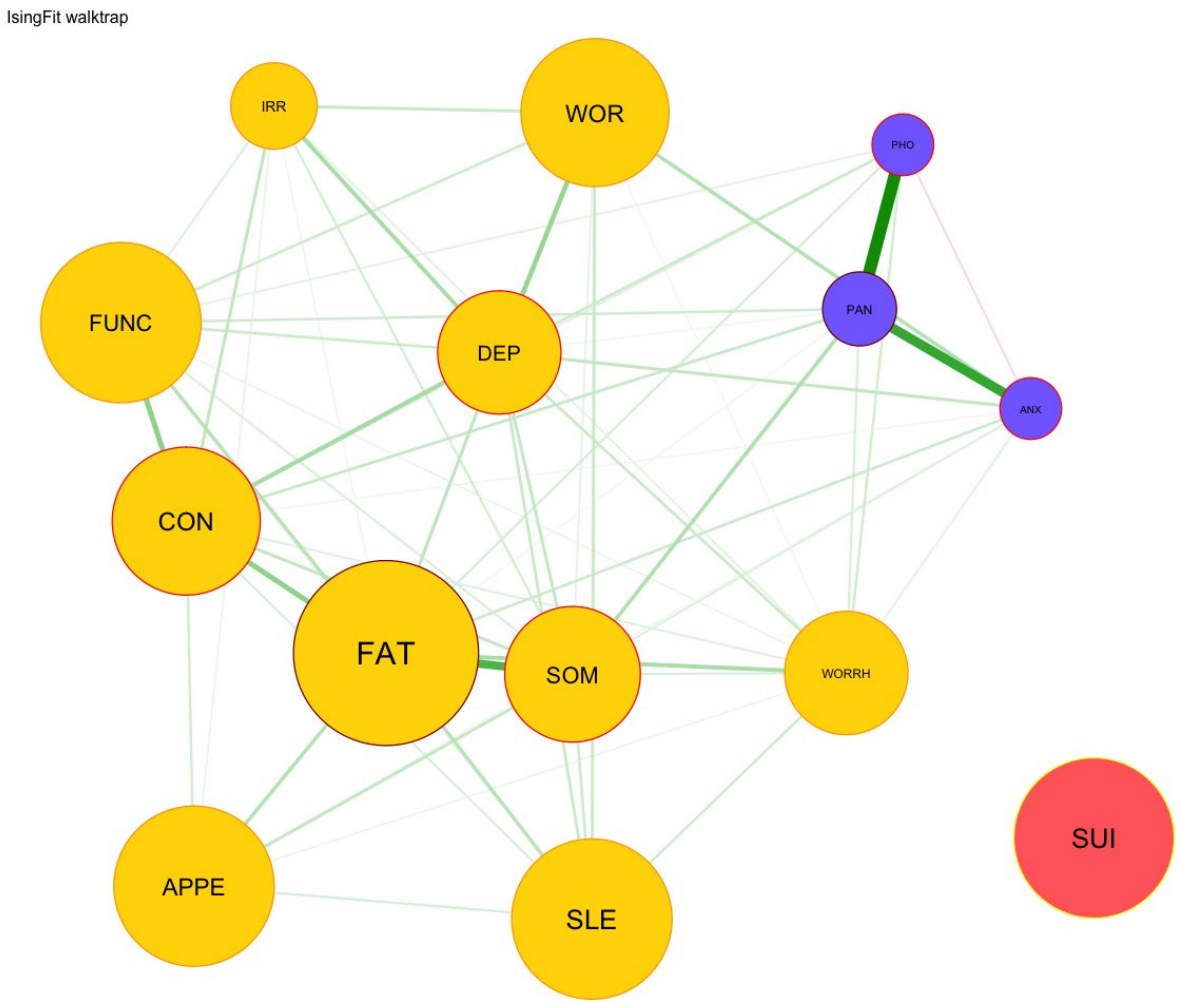


Figure 20: Ising network showing the communities obtained with the Walktrap alogorithm (modularity = 0.17)



Note: The node colors represent the communities for each symptom.

Figure 21: The gaussian graphical model of the 14 CIS-R symptoms across males and females

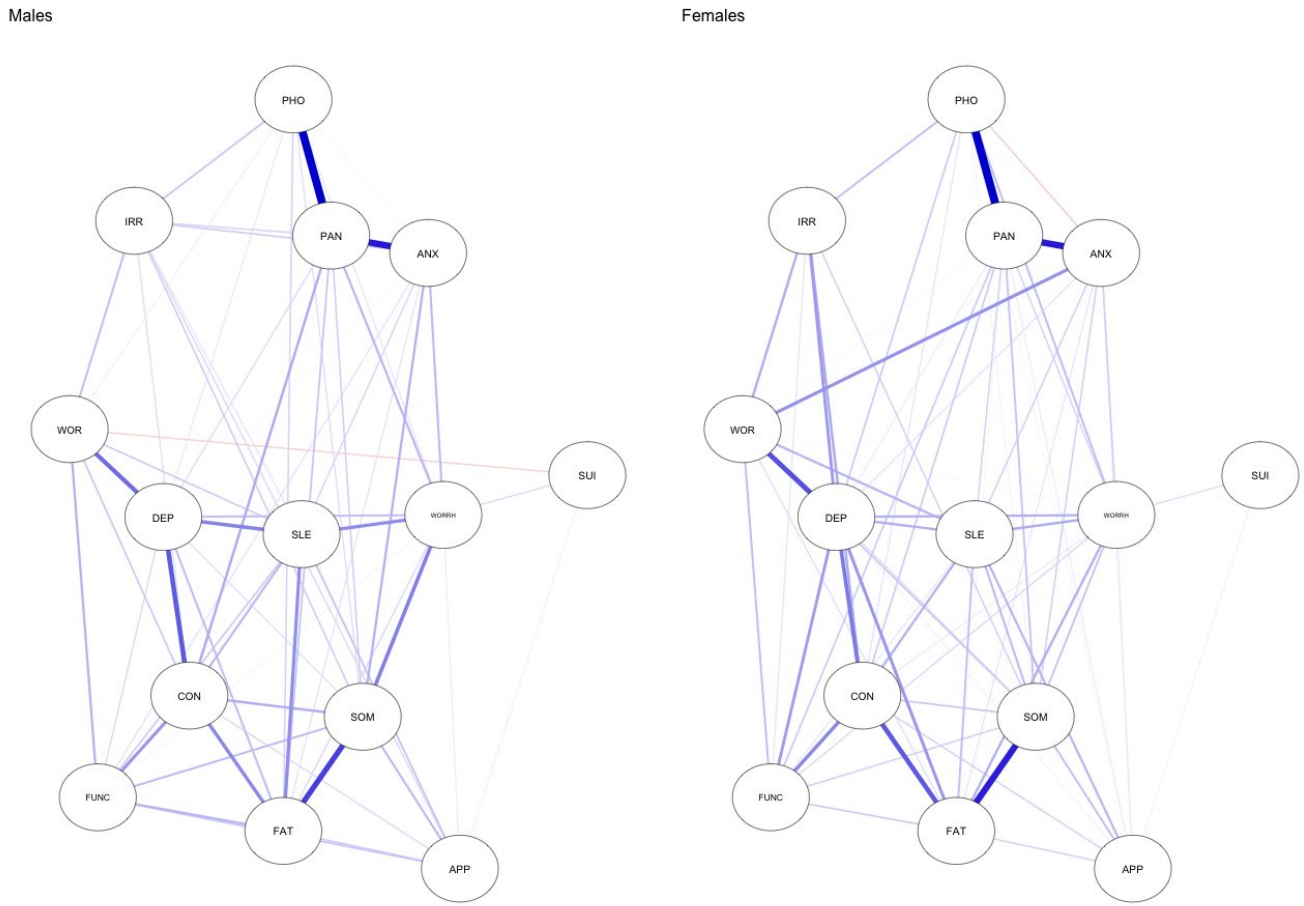


Figure 22: The gaussian graphical model of the 14 CIS-R symptoms across private and public settings

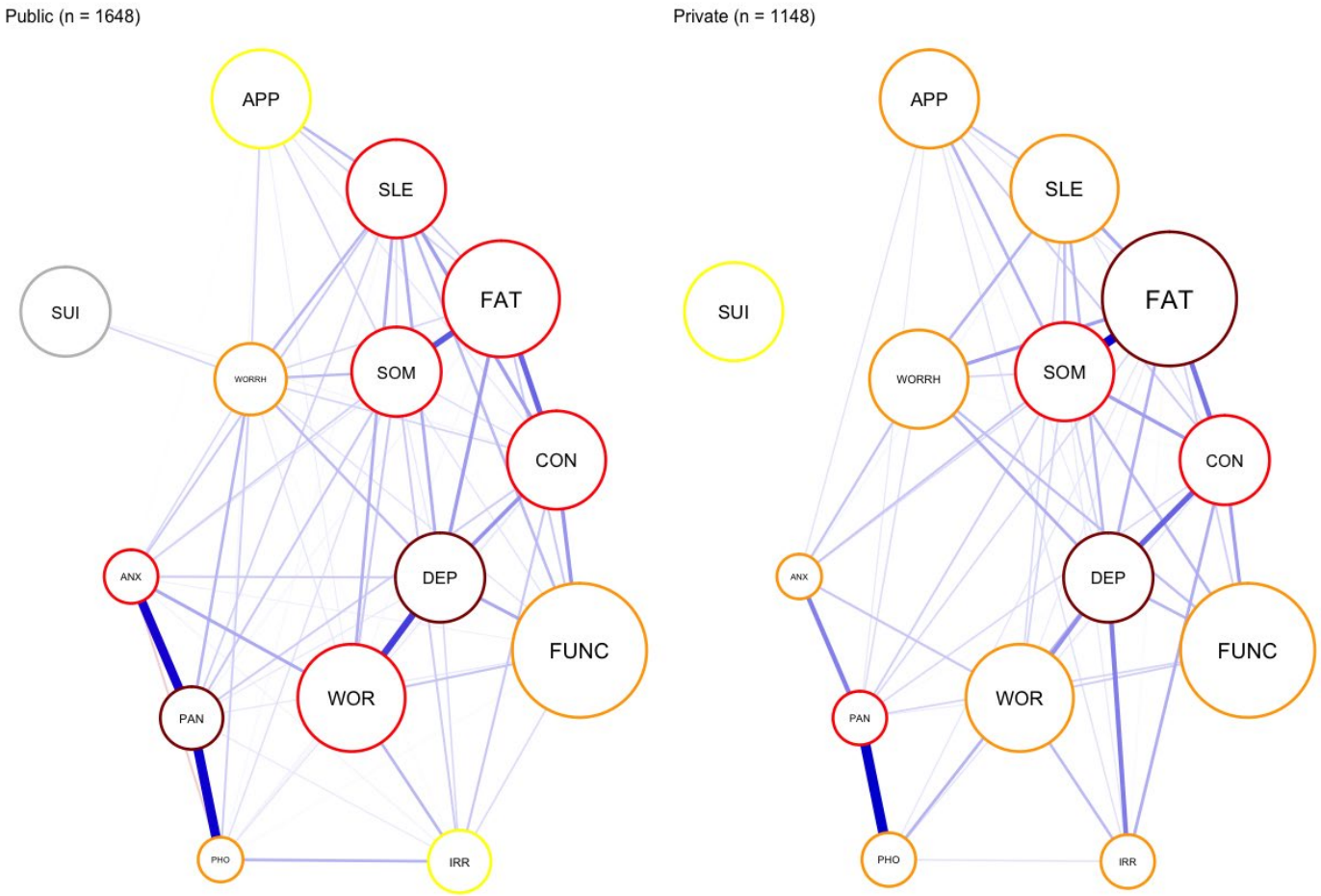


Figure 23: The centrality indices of the CMD symptom network in public settings

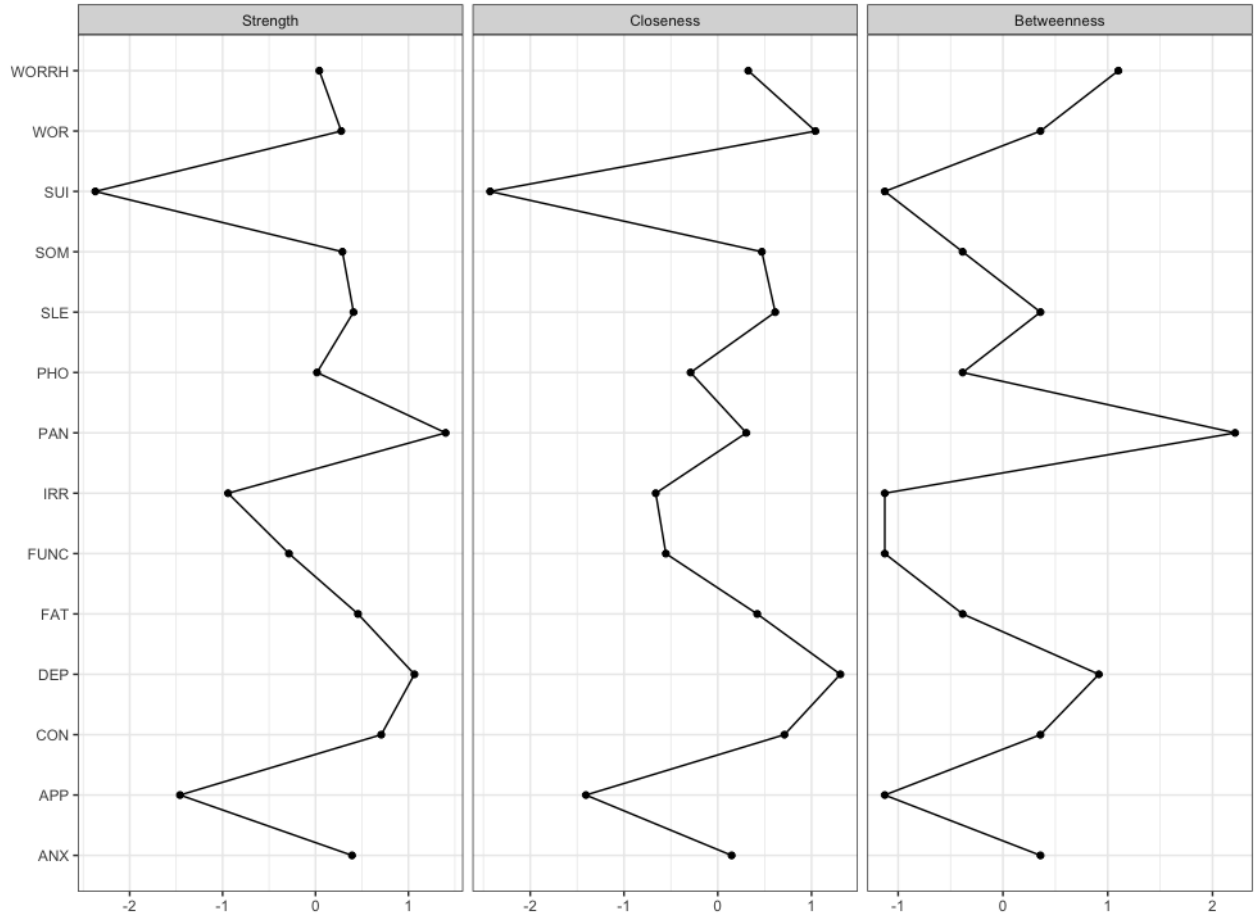


Figure 24: The centrality indices of the CMD symptom network in private settings

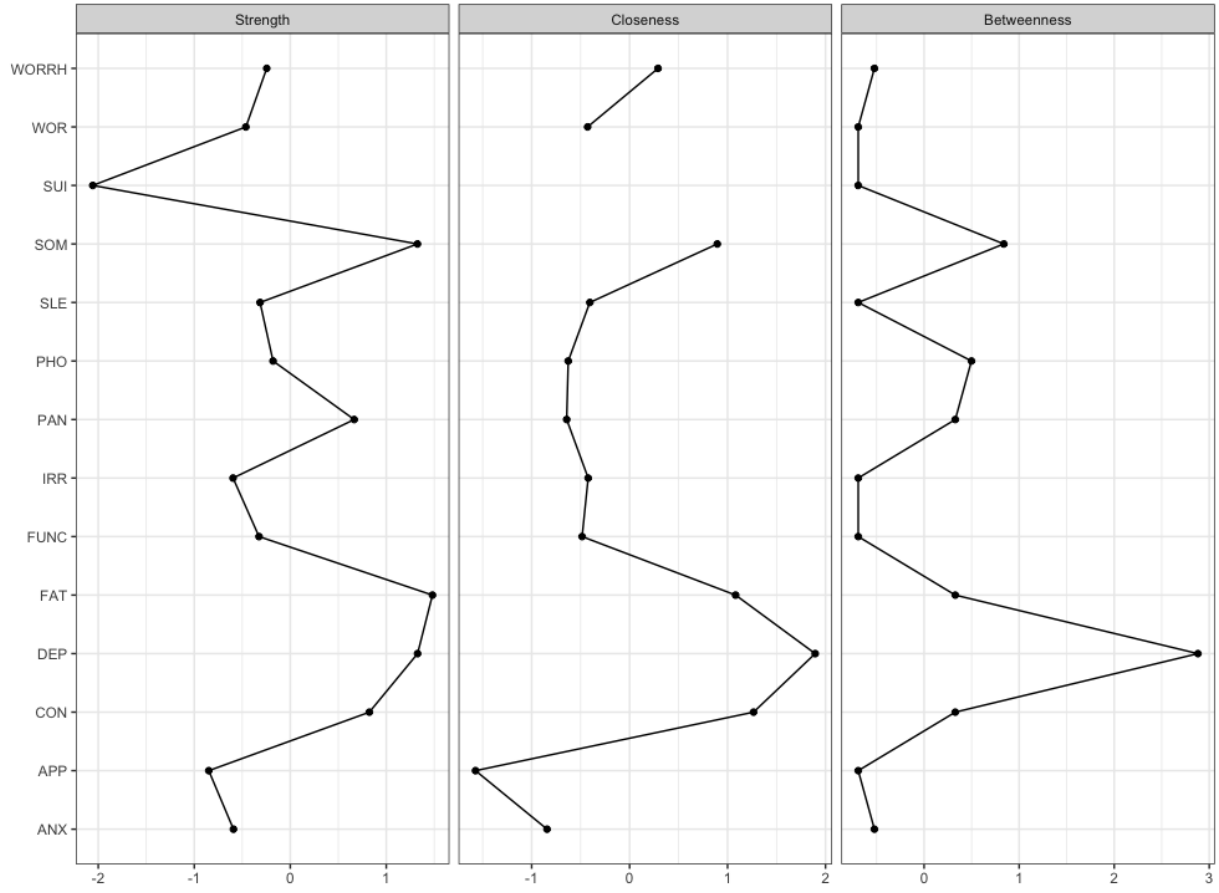


Figure 25: The bootstrapped edge-weights and the % of times an edge was estimated as zero in public settings

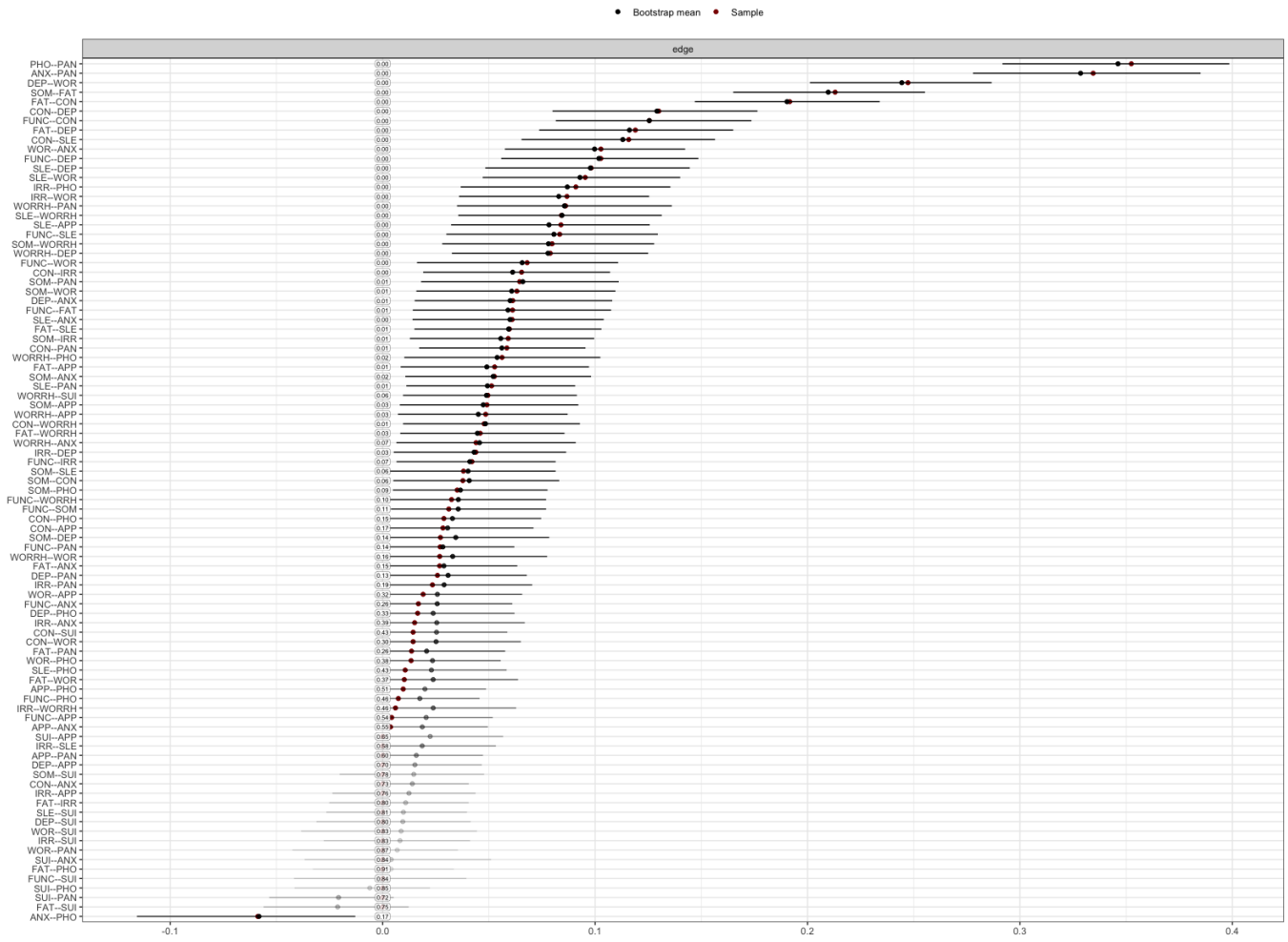


Figure 26: The bootstrapped edge-weights and the % of times an edge was estimated as zero in private settings

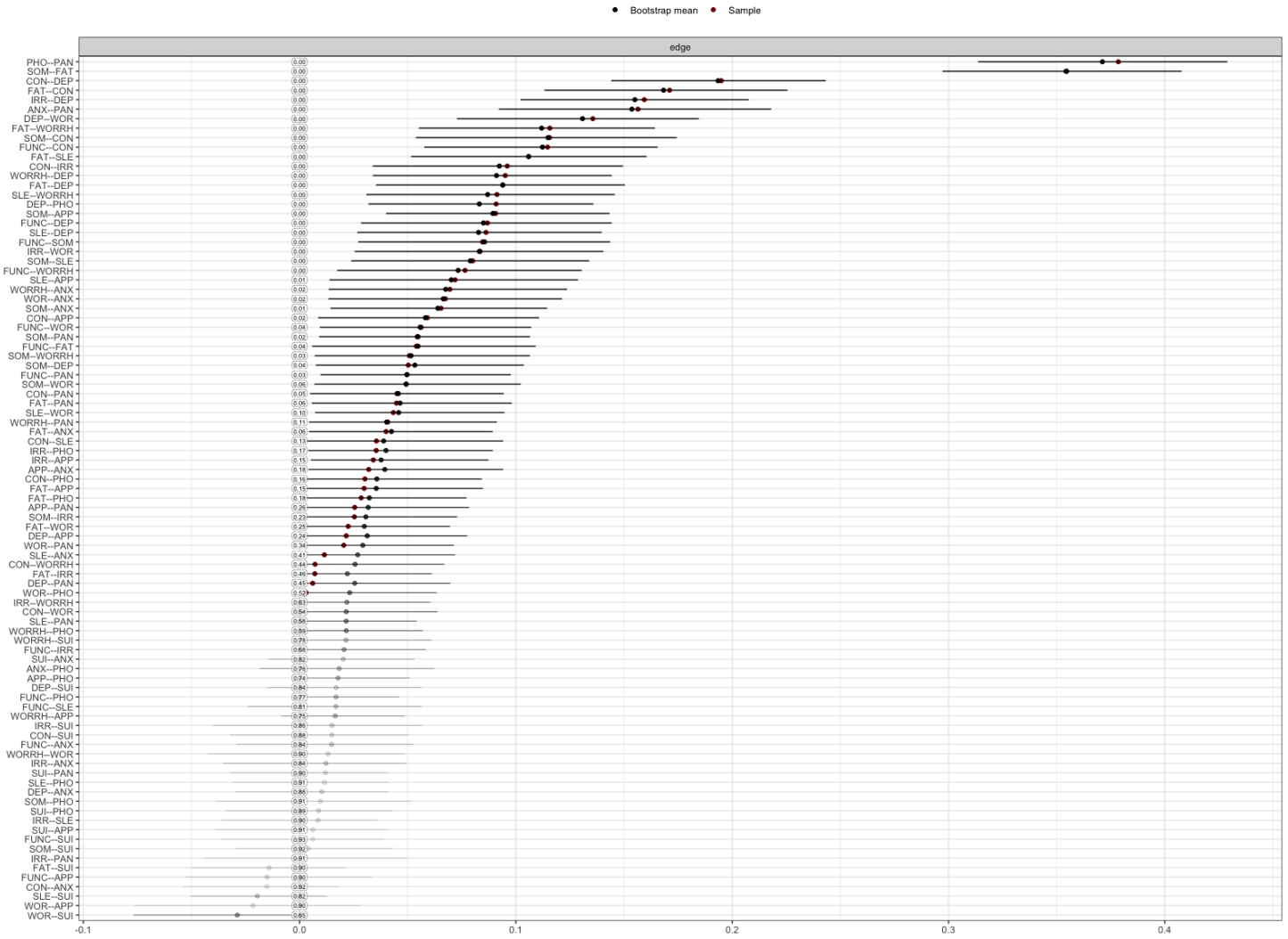


Figure 27: The gaussian graphical model of the 14 CIS-R symptoms across sustained and non-remission (i.e., nonresponse) groups

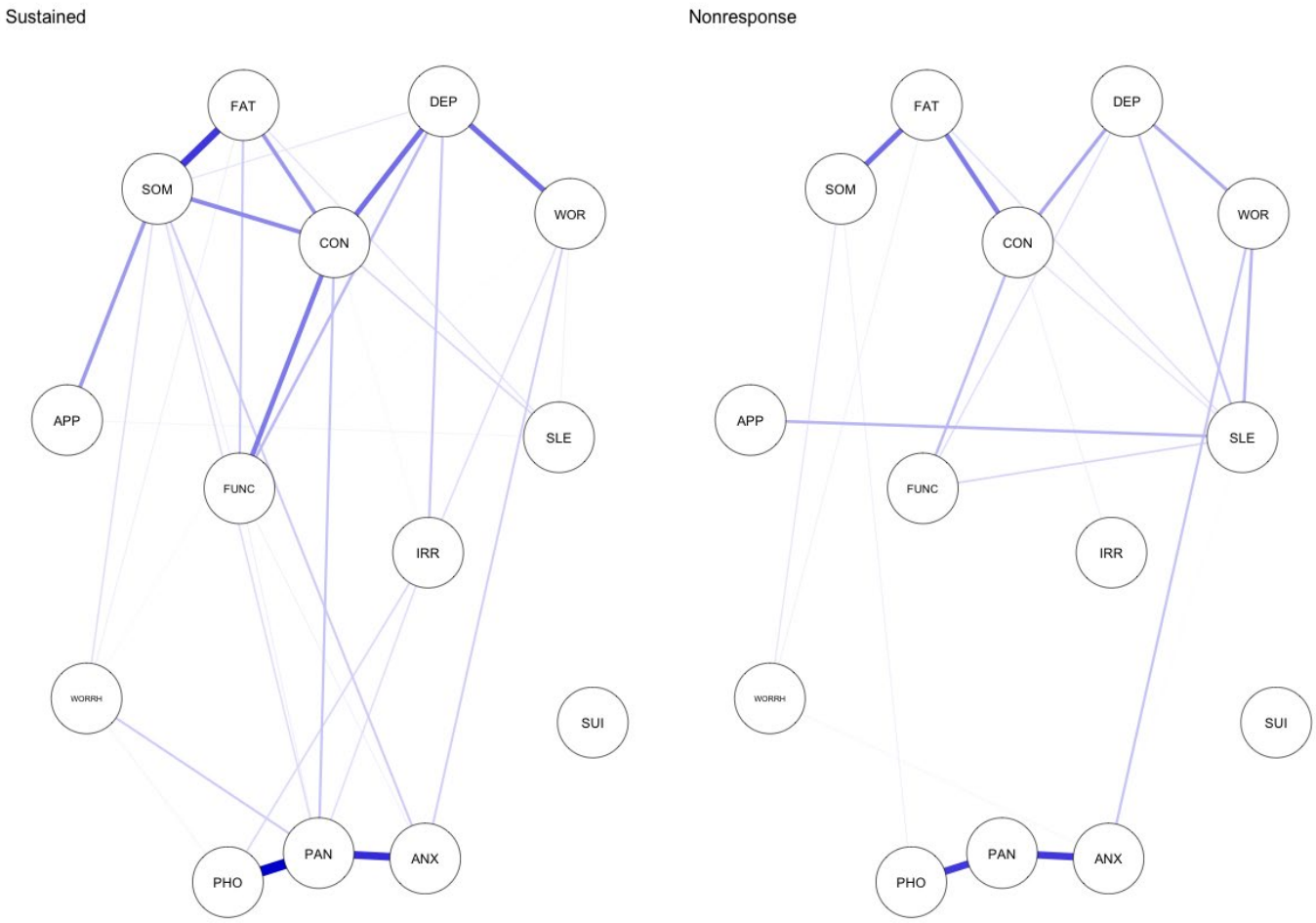


Figure 28: The gaussian graphical model of the 14 CIS-R symptoms across sustained and not sustained remitter groups

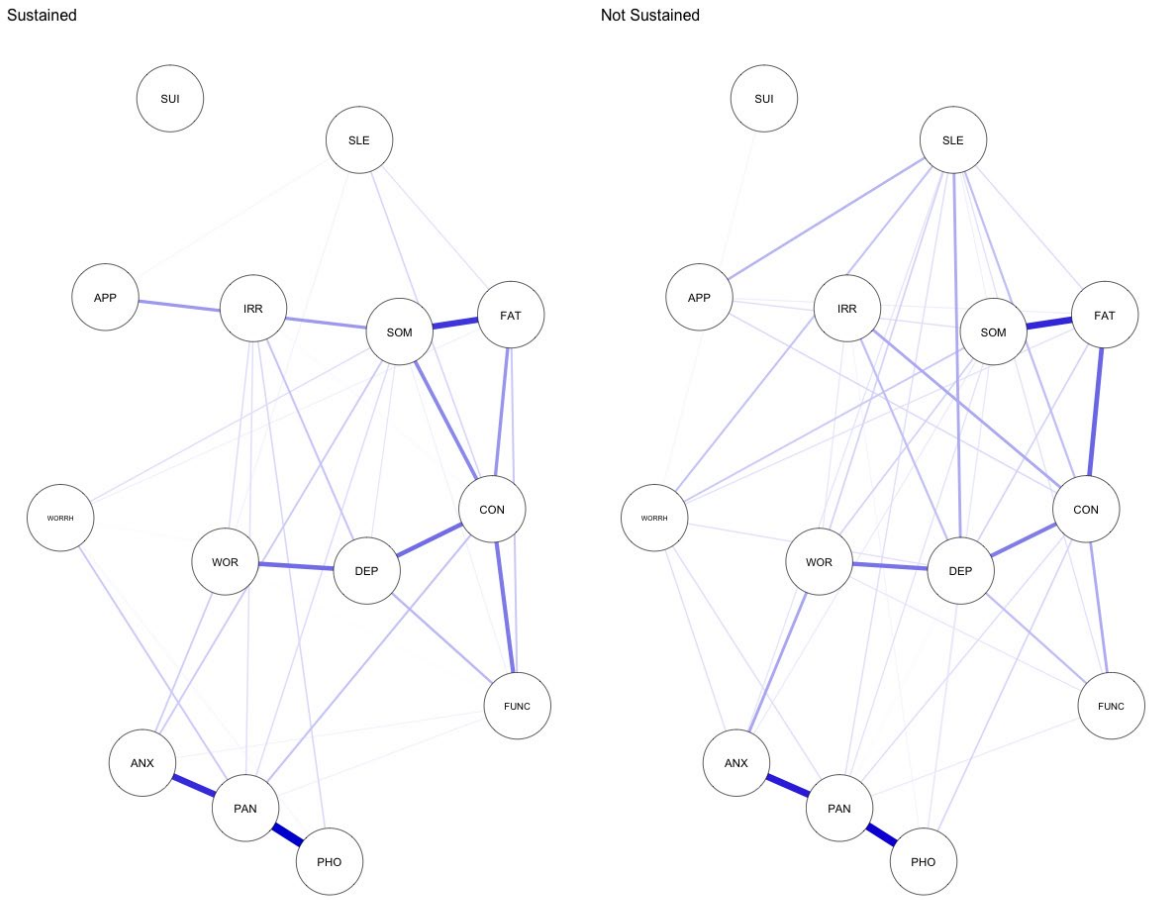


Figure 29: One clinical hypothesis about the onset of CMD among primary care patients in India