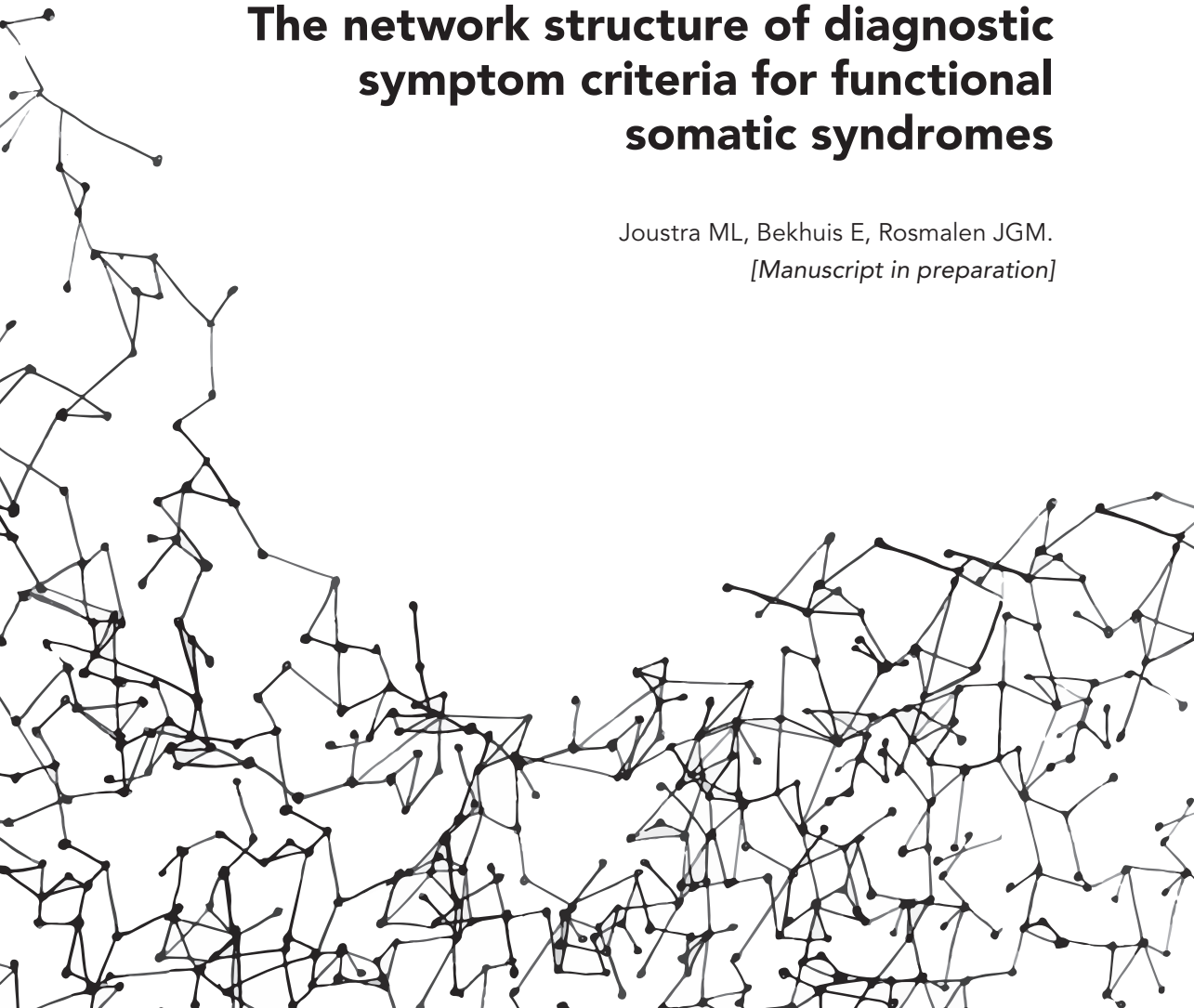
4

The network structure of diagnostic symptom criteria for functional somatic syndromes

Joustra ML, Bekhuis E, Rosmalen JGM.

[Manuscript in preparation]



ABSTRACT

Background: There is a longstanding discussion on whether functional somatic syndromes (FSS) are different names for the same problem, since they are known for substantial clinical and diagnostic overlap.

Objectives: The aim of this study was to investigate the co-occurrence of the most well-known FSS (i.e., chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS)) on a symptom-level using network analyses, in the general population and in a subgroup consisting of patients fulfilling the diagnostic criteria for FSS.

Method: This study was performed in 79,966 participants (age: 52.9±12.6 years, 59.2% female) of the LifeLines cohort study. The diagnostic symptoms of the three FSS were assessed by questionnaire. A partial correlation network of the diagnostic criteria was estimated to study how diagnostic symptoms were interrelated within and between diagnoses. Clustering of symptoms was examined using the walktrap algorithm.

Results: Network analyses showed that all diagnostic symptoms were highly connected, with similar levels of clustering in the general population and patients with FSS. The network density between diagnoses was in most cases slightly lower than within diagnosis, but differences were small. Clustering of diagnostic symptoms revealed a general, musculoskeletal and abdominal symptom cluster in the general population, which melted to an abdominal and combined general and musculoskeletal cluster in patients with FSS.

Conclusions: FSS may reflect the same underlying syndrome with different subtypes based on symptoms' bodily systems rather than their current classification as criteria for CFS, FMS or IBS. The diagnostic criteria for FSS should be further examined and reconsidered.

INTRODUCTION

Functional somatic syndromes (FSS) comprise clusters of persistent somatic symptoms for which no conclusive underlying organic pathology can be found (1). The main three syndromes are chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS). FSS are often co-morbid: patients with CFS, FMS or IBS are more likely to meet lifetime symptom and diagnostic criteria for other FSS than control subjects (2). For example, lifetime rates of IBS were significantly higher in patients with CFS (92%) or patient with FMS (64%) compared with controls (18%) (2).

Since the three main FSS are known for substantial clinical and diagnostic overlap, there is a longstanding discussion in the literature on whether these syndromes are different names for the same problem, also known as the lumper-splitter discussion (3). Lumpers state that the different FSS identify one group of patients, while splitters state that the different FSS should be considered as distinct entities. One argument in favour of the lumpers is that the case definitions of FSS overlap. For example, both CFS and FMS diagnostic criteria describe both musculoskeletal symptoms, fatigue, cognitive symptoms, and sleep disturbance or waking unrefreshed. More recently, it has been suggested that both lumpers and splitters are right and that there is commonality as well as heterogeneity between and within FSS in both onset-related factors and psychosocial or physiological patient characteristics (4).

In the current literature, attempts have been made to investigate whether FSS are different names for the same problem by examining the interrelatedness or clustering of symptoms that characterize FSS. Different statistical techniques have been used, including latent class analyses (5-7), principle component analysis (8-10), and cluster analysis (11,12). Most studies found multiple underlying classes or clusters and conclude that there are both similarities and dissimilarities between FSS. However, there were also some inconsistencies between these studies: some findings indicated that patients with FSS could be distinguished by the number of symptoms (7,9), while other findings suggested that both the number of symptoms and the type of symptoms were relevant (6,12,13). The number of classes or clusters also varied widely, ranging from two to eleven (9,12). A possible explanation for these inconsistencies is that different symptom clusters might be

the result of the experience of milder or lower numbers of symptoms, while in the more severe cases the overlap of clusters becomes larger (6,12-14). There are also several limitations of the current literature in the context of the lumper-splitter discussion: the somatic symptoms included more than those in the diagnostic algorithms of the different FSS, the time frame of symptom assessment was relatively long in most studies, and lastly, symptoms were frequently dichotomized (i.e. present or not), not taking into account the severity of symptoms.

Currently there is a new approach to analyze symptom patterns, known as the network approach (15). This approach focuses on individual symptoms and the unique patterns in which they co-occur with other symptoms (16). The advantage of the network approach compared to latent class analyses, principle component analysis, and standard cluster analysis, is that it naturally accommodates the unique role of each of the individual symptoms. As such, it can provide insight into how varying symptoms of a specific syndrome relate differentially to symptoms from the same or other syndromes. Recent studies have used the network approach to study co-morbidity and have shown promising results (13,17-19). One study investigated for example the network structure of psychiatric symptoms and showed that although clustering of the symptoms generally corresponded with the classification of symptoms in the DSM, symptoms within the same diagnosis could show unique patterns in which they co-occurred with each other (17). Another study showed that individual depressive/anxiety symptoms had different levels of importance in explaining their general co-occurrence with somatic symptoms (18). More recently, network analysis was performed in patients with CFS, FMS, or IBS and revealed that 61 symptoms could be classified into eleven categories, which showed more overlap as FSS severity increased (13). As the study did not focus on diagnostic criteria of the FSS and their individual roles in the network, however, important information about the role of individual diagnostic symptoms within the specific FSS syndromes as well as in their co-morbidity is missing in the context of the lumper-splitter discussion.

The aim of this study is to investigate networks of the diagnostic symptoms composing the criteria for the three most well-known FSS. To the best of our knowledge, no studies have investigated the relatedness of symptoms that compose the diagnostic algorithms of the different FSS using network analyses. This study will be performed in a large population-based cohort study. First, we

will examine the general network structure of the diagnostic criteria for FSS in both the entire cohort and in a subgroup consisting of patients with FSS experiencing more severe symptoms, to investigate the influence of experiencing more severe symptoms on network structure and clustering. Second, we will examine the role of the individual symptoms within and between the CFS, FMS and IBS diagnostic symptom criteria. Lastly, we will examine clustering of symptoms in the network models.

METHODS

Sampling frame

This study was conducted within the sampling frame of the LifeLines cohort study (20). LifeLines is a multi-disciplinary, prospective (three-generational) population-based cohort study examining health and health-related behaviors of more than 167,000 persons living in the North East part of The Netherlands. LifeLines employs a broad range of investigative procedures in assessing biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.

Participants

Participants of LifeLines were recruited in two ways. First, a number of general practitioners from the three northern provinces of the Netherlands invited all their listed patients between 25 and 50 years of age to participate. If they agreed to participate, these participants were asked to invite their partner(s), parents, parents in law, and children to participate as well. In this way participants of all ages were included. Eligibility for participation was evaluated by general practitioners. To ensure the reliability of the study, persons with severe psychiatric or physical illness, and those not being able to visit the general practitioner, to fill out the questionnaires, and/or to understand the Dutch language were excluded. Parents and children were not excluded in case of the mentioned criteria when a representative was willing to assist these participants in the performance of the study. Inclusion of pregnant women was rescheduled until six months after pregnancy or three months after breastfeeding. Second, persons who were interested to participate could register themselves via the LifeLines website and then participate.

All participants received written information on the purpose and methods of the study and written informed consent was obtained after the procedure was fully explained. All data are kept confidential and are only used for medical research. Approval by the Medical Ethical Committee of the University Medical Center Groningen was obtained for the study.

Data collection

The first participants were included at the end of 2006, and the recruitment period was closed after reaching the target number of participants in 2013. Participants who were included in the LifeLines study will be followed for at least 30 years. At baseline, participants visited one of the LifeLines research sites for a physical examination. Prior to these baseline visits, two extensive baseline questionnaires were completed at home. Follow-up questionnaires were administered to all participants approximately every 18 months, and participants have been invited for a renewed physical examination at the LifeLines research site on average every five years. During the second assessment, general physical examination was first performed, followed by medical examinations (e.g. ECG, lung function), and lastly, the CogState computerized cognitive battery and the digital neuropsychiatric questionnaire were conducted respectively. At the time of writing, data from baseline assessment, first and second follow-up questionnaires and data from the second assessment were available. Data of the second assessment was used in the current study, since the diagnostic algorithms for FSS were included in the second assessment.

FSS diagnostic criteria

The diagnostic criteria for the three FSS were included in the LifeLines questionnaire. The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention criteria (CDC) (21), FMS using the 2010 American College of Rheumatology criteria (ACR) (22), and the diagnosis for IBS was assessed using the ROME III criteria (23). However, the IBS criteria which were based on a minimal frequency of symptoms were adjusted in accordance with the ROME IV criteria (24),: instead of symptoms 3 days per month, participants should indicate that they have recurrent abdominal pain or discomfort at least 1 day per week (Appendix A: scoring algorithm).

Descriptives

Educational level was assessed using the question: "What is your highest completed education?", resulting in information about low (lower secondary education or less), middle (higher secondary education), and high (tertiary education) educational level. Medical diseases were assessed by a questionnaire asking to indicate for each disease whether the participant had or had had them.

Statistical analyses

The characteristics of the participants were described using SPSS version 22. For all continuous variables, means ± standard deviations (SDs) were calculated. Network analyses were performed on a combination of binary main criteria (fatigue for at least 6 months, locomotor pain complaints for at least 3 months, abdominal pain for at least 6 months with a frequency of at least 1 day/week), and categorical and continuous data on additional symptoms. Two diagnostic criteria of CFS and FMS were very similar, namely cognitive symptoms (forgetfulness or memory problems/difficulty with thinking or concentrating in CFS; thinking requires effort/I have trouble concentrating in FMS) and unrefreshed sleep (unrefreshing sleep in CFS; waking up unrefreshed in FMS). Therefore, these items were combined by taking the mean of the CFS and the FMS symptom. We performed the network analyses in both the general population cohort and in a subset with persons who fulfilled the diagnostic criteria for CFS, FMS and/or IBS. Weighted networks of symptoms for both the general population and FSS were estimated and visualized in R version 3.4.2 with package qgraph (25). A correlation matrix for all symptoms (with polyserial correlations for symptom pairs including categorical or binary symptoms and Pearson correlations for symptom pairs consisting only of continuous symptoms) was calculated. Partial correlations were calculated for all pairs of variables, which indicate correlations among symptoms while controlling for all other variables in the network. To prevent overfitting, an *l*1-penalty was used to estimate possible networks with different levels of sparsity (26). The model with the best fit to the data was selected using the extended Bayesian information criterion (EBIC) (27) with hyperparameter y=0.5 (28). This technique has been shown to yield adequate network structures (28-30). The accuracy of estimated connections in the networks was also investigated by calculating 95% confidence intervals around connection weights with R-package bootnet (31). Bootstrapped confidence intervals were calculated by drawing 1,000 bootstrap samples of the data and recalculating connection weights for each sample. The

lay-outs of the networks were based on the Fruchterman-Reingold algorithm, which places symptoms with stronger and/or more connections closer to each other (32).

First, we explored the general structure of the network. To examine the general connectivity of the network, the density of the network was calculated by determining the proportion of actual connections over the number of potential connections between all symptoms (33). In addition, the network clustering coefficient was calculated by determining the proportion of actual connections of adjacent nodes in the network over the number of potential connections between adjacent nodes. Subsequently, we focused on the strength of the individual FSS symptoms to symptoms of the same diagnosis, and the strength of all connections from an individual symptom to all symptoms of other FSS diagnoses by summing the weight of these connections (34). Strengths of 0.1, 0.3, and >0.5 were interpreted to reflect small, medium, large, and very large strengths, respectively (35). Lastly, clustering of symptoms was examined using the walktrap algorithm from package "Igraph" (36). This random walk method identifies groups of symptoms with high intragroup but low intergroup connectedness.

RESULTS

This study was performed in 79,966 participants (age: 52.9±12.6 years, 59.2% female) of the general-population cohort LifeLines. Of these participants, 11.5% (n=9,217) fulfilled criteria for one or more FSS: 3.1% of the participants fulfilled the CDC criteria for CFS, 6.4% fulfilled the ACR criteria for FMS, and 5.5% fulfilled the ROME IV criteria for IBS. Patients with FSS were more often female (75% female) and were slightly younger (52.3±12.4 years) than the general population (59.2%, 52.9±12.6; Table 1). In addition, patients with FSS were lower educated than the general population. The prevalence of medical health conditions is summarized in Table 2.

Table 1. General characteristics of the study groups.

	General population	One or more FSS	CFS	FMS	IBS
n (%)	79,966 (100)	9,217 (11.5)	2,490 (3.1)	5,122 (6.4)	4,377 (5.5)
Female n (%)	47,341 (59.2)	6,917 (75.0)	1,848 (74.2)	3,922 (76.6)	3,307 (75.6)
Age in years (SD)	52.9 (12.6)	52.3 (12.4)	54.2 (11.8)	52.8 (11.7)	50.9 (12.9)
Education (% low-middle- high)	2.6 65.9 29.2	3.5 69.9 24.0	4.7 72.7 19.6	3.9 73.6 19.9	2.5 66.4 28.6

FSS = functional somatic syndrome; CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

Table 2. Prevalence rates of medical and psychiatric health conditions in the general population (lifetime).

	n	%
Anxiety disorder	5,712	7.1
Cancer	1,625	2.0
Celiac disease	381	0.5
Dementia	74	0.1
Eating disorder	1,107	1.4
Functional somatic syndrome	9,217	11.5
Heart failure	1,603	2.0
Hepatitis B	66	0.1
Inflammatory bowel disease	924	1.2
Mood disorder	2,368	3.0
Multiple sclerosis	185	0.2
Rheumatoid arthritis	2,858	3.6
Schizophrenia	65	0.1

General network structure

The network structure of FSS diagnostic symptoms in the general population is presented in Figure 1A and in patients with FSS in Figure 1B. Tables S1A and S1B show that accuracy of connection weights was excellent, reflected in very small confidence intervals of associations. The diagnostic symptoms were highly connected: 89.2% of potential connections in the general population network and 90% in the FSS group network were observed, with a mean strength of connections of r=0.055 in the general population and r=0.048 in patients with FSS. In addition, both networks had a high level of clustering (i.e., clustering coefficient = 0.79 in the general population and 0.80 in patients with FSS). Most connections were positive or slightly negative, except for the association of the main criterion of IBS (mIBS) with the widespread pain index of FMS (WPI, r=-0.17) and fatigue of FMS (Fat, r=-0.07) in patients with FSS.

Associations of symptoms within diagnoses

The associations of symptoms within FSS diagnoses in the general population and patients with FSS can be found in Table S2. The within-diagnosis density for the CFS diagnostic symptom criteria was respectively 86.1% in the general population and 69.4% in the FSS group, with a mean strength of connections of r=0.52 in both groups. The CFS symptom post-exertional malaise (PEM) had the highest within-diagnosis strength (r=0.73 in the general population and r=0.87 in patients with FSS), while headaches (Hea) had the lowest within-diagnosis strength in both the general population (r=0.27) and patients with FSS (r=0.32). Although sore throat (Thr) and lymph node tenderness (Lym) had a high within-diagnosis strength (r=0.62 and 0.58 in the general population and r=0.55 and 0.54 in the FSS group), this was mainly the result of their strong associations with each other (r=0.43 in both groups).

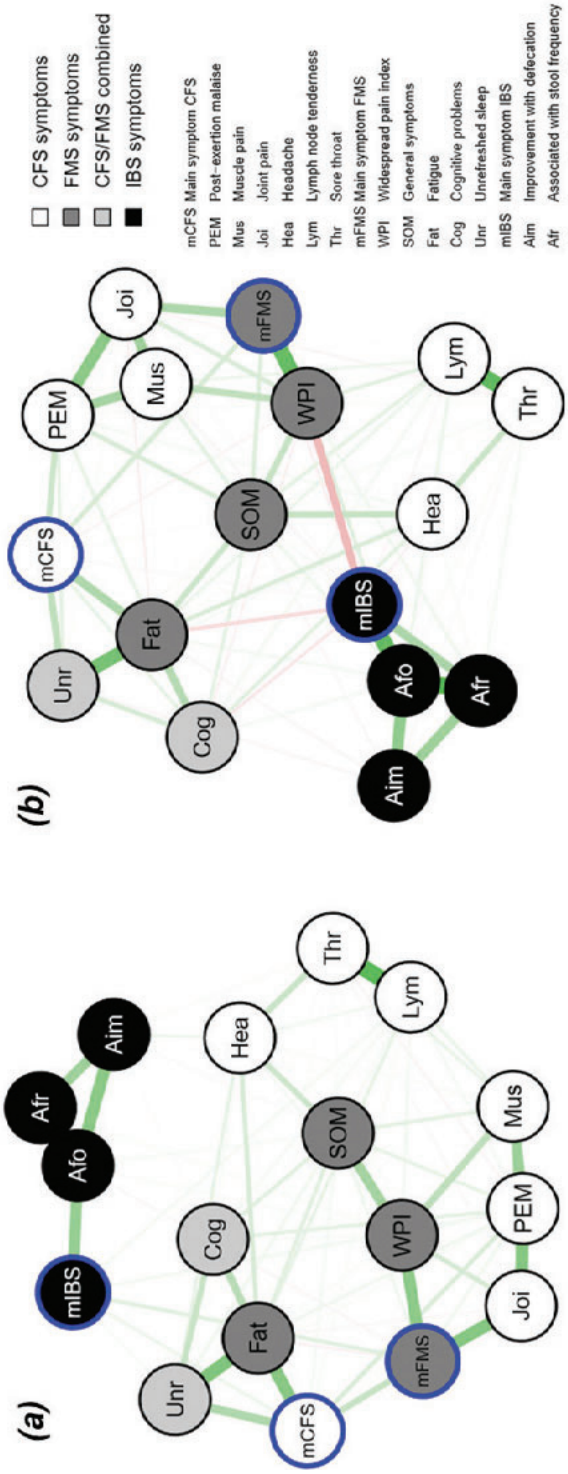


Figure 1. Estimated network structures of FSS diagnostic symptoms for (a) the general population and (b) patients with FSS.

Symptoms are represented by circles and associations between them by lines. The color of circles refers to the diagnosis symptoms belong to. Main criteria for CFS, FMS and IBS are delineated in blue. Green lines indicate positive associations and red lines negative associations. The thickness of lines is proportional to the strength of associations.

For the diagnostic symptom criteria of FMS, the within-diagnosis density was 80% in both the general population and patients with FSS, with a mean strength of connections of r=0.42 in the general population and r=0.51 in patients with FSS. The FMS symptom fatigue (Fat) had the highest within-diagnosis strength (r=0.57 in the general population and r=0.71 in patients with FSS), while the main criterion of FMS (mFMS) had the lowest within-diagnosis strength in the general population (r=0.24), and cognitive symptoms (Cog) in patients with FSS (n=0.34). The strongest connections between FMS symptoms were between the main criterion and the widespread pain index (WPI; r=0.26 in the general population and r=0.42 in patients with FSS), and fatigue and unrefreshed sleep (Unr; r=0.34 and r=0.37).

Lastly, the within-diagnosis density was 83.3% in the IBS symptom criteria of both groups, with a mean strength of connections of r=0.73 in the general populations and r=0.83 in patients with FSS. The IBS symptom abdominal pain associated with change in stool form (Afo) had the highest within-diagnosis strength (r=1.18 in both groups), while the symptoms with the lowest within-diagnosis strength were the main criterion in the general population (mIBS; r=0.15) and improvement of abdominal pain after defecation in patients with FSS (Aim; r=0.56). The strongest connections between IBS symptoms were between abdominal pain associated with change in stool form (Afo) and abdominal pain associated with change in stool frequency (Afr; r=0.73 in the general population and r=0.46 in patients with FSS).

Associations of symptoms between diagnoses

The associations of symptoms between FSS diagnoses in the general population and patients with FSS can be found in Table S3. The between-diagnosis density for CFS with FMS and IBS diagnostic symptom criteria was 66.2% in the general population and 74.6% in patients with FSS. The main criterion of CFS had the highest between-diagnosis strength (mCFS; r=0.92 in the general population and r=0.52 in patients with FSS respectively), while the symptom sore throat

(Thr) had the lowest between-diagnosis strength (r=0.10 in both groups). The strongest connections of CFS symptoms with FMS symptoms were between joint pain (Joi) and the main criterion of FMS (mFMS; r=0.23 in both groups), and with IBS symptoms between lymph node tenderness (Lym) and abdominal pain associated with change in form (Afo; r=0.05 in both groups).

The between-diagnosis density for FMS with CFS and IBS diagnostic symptom criteria was 73.1% in the general population and 80.8% in patients with FSS respectively. For FMS the symptom fatigue (Fat) had the highest between-diagnosis strength (r=1.07 in the general population and r=0.84 in patients with FSS), while cognitive symptoms in the general population (Cog; r=0.33) and the main criterion in FSS patients (mFMS; r=0.21) had the lowest between-diagnosis strength. The strongest connection between FMS and IBS symptoms was between the widespread pain index (WPI) and abdominal pain associated with change in form (Afo; r=0.08 in both groups).

Lastly, the between-diagnosis density was 44.2% and 50% for IBS with CFS and FMS diagnostic symptom criteria in the general population and patients with FSS respectively. The main symptom of IBS (mIBS) had the highest between-diagnosis strength in the general population (r=0.23), while it had a negative between-diagnosis strength in patients with FSS (r=-0.57).

Cluster analyses

Cluster analysis of the network in the general population revealed four clusters. Firstly, an abdominal symptom cluster with inclusion of all IBS diagnostic symptoms was found. Second, a general symptom cluster was identified including the main criterion of CFS (mCFS), the combined CFS/FMS symptoms cognitive problems (Cog) and unrefreshed sleep (Unr), and the FMS symptoms fatigue (Fat) and general somatic symptoms (SOM). Third, a musculoskeletal cluster was identified with inclusion of the main FMS criteria (mFMS), the widespread pain index (WPI), and the CFS diagnostic symptoms joint pain (Joi), muscle pain (Mus), and post-exertional malaise (PEM). Lastly, analyses revealed an "other symptoms" cluster with inclusion of the CFS criteria headaches (Hea), sore throat (Thr), and tender lymph nodes (Lym).

When analyzing clustering in the network of the FSS group, two clusters were found: one abdominal symptom cluster with inclusion of all IBS diagnostic symptoms, and a combined general and musculoskeletal symptom cluster including all diagnostic symptoms of CFS and FMS.

DISCUSSION

This was the first study that investigated the interrelatedness of symptoms that compose the diagnostic criteria of the different FSS using network analyses. First, we found that all diagnostic symptoms were connected, either directly or via other symptoms, with similar levels of clustering in the general population and patients with FSS. Second, the network density between diagnoses was in most cases slightly lower than within diagnosis, but differences were small. Main symptoms were important in connecting the different FSS diagnoses as they had high between-diagnoses strength. Lastly, clustering of symptoms in the general population revealed a general, musculoskeletal, abdominal, and other symptom cluster, but in patients with FSS only an abdominal and a combined general and musculoskeletal symptom cluster were found.

The main strength of the current study is that the symptoms that compose the diagnostic criteria for the three main FSS were assessed concurrently in one cohort. We were therefore able to examine the networks of the diagnostic symptoms criteria in a large population-based sample, as well as in a subgroup consisting of patients fulfilling the diagnostic criteria for one or more FSS. Since we assessed the diagnostic symptom criteria for all three FSS, it was possible to examine the relatedness of symptoms that compose the diagnostic criteria of the different FSS irrespective of help-seeking behaviour or diagnostic biases. Lastly, instead of dichotomized additional symptoms, we used the continuous symptom variables taking into account the severity or frequency of symptoms.

There are also limitations in the current study. First, the FSS symptoms and diagnoses were based on the responses to a questionnaire, without an assessment by a physician. Because LifeLines is a large population cohort study that aims to study a wide spectrum of mental and somatic disorders, it was not feasible to determine whether participants met the diagnostic criteria for FSS based on clinical

examinations. Second, co-morbid conditions that could explain the FSS symptoms were not excluded when determining the FSS diagnoses, mainly because only the CFS diagnostic criteria and not the FMS and IBS criteria specifically mention the exclusion of medical health conditions. Nevertheless, FSS diagnoses rely heavily on subjective symptoms and to a lesser extent on the absence of objective clinical or laboratory findings. Furthermore, although we combined items with the same definitions (i.e., cognitive problems and unrefreshed sleep), the estimated network structures contained several symptoms with partially overlapping definitions. Examples include the main criterion of CFS and the additional symptom fatigue in FMS, and muscle pain or joint pain in CFS and the main symptom or the widespread pain index in FMS. The correlations between these variables will naturally be stronger, and therefore these (partially) overlapping symptoms might have changed clustering in the network structure. We decided not to combine these partially overlapping symptoms as they are included in this way in the diagnostic criteria and they differ in important aspects (e.g., their time frame).

Our networks had high density, and many connections within and between the different FSS diagnostic symptoms were found. The between-diagnosis density was comparable to the within diagnosis density for CFS and FMS, indicating that overlap among CFS and FMS diagnostic symptoms is very high. Despite strong within diagnosis connectedness of IBS symptoms, this symptom cluster seemed to be more isolated from the rest due to its lower between-diagnosis density. Within and between diagnoses of FSS, individual diagnostic criteria had differential roles. The highest within-diagnosis strengths were found for the additional criteria of post-exertional malaise in CFS, fatigue in FMS, and abdominal pain associated with change in stool frequency in IBS, while the syndromes' main criteria had low within-diagnosis. Main criteria, however, were important in connecting the different FSS diagnoses as they had high between-diagnoses strength. This is interesting as it would be expected that main criteria have a central role in strengthening the internal connectedness of the diagnostic criteria of a syndrome, while they separate a syndrome from criteria of other syndromes. Indeed, previous studies have identified main criteria of mental disorders as the most central within-diagnosis symptoms (37,38).

Symptoms in the networks clustered based on bodily systems rather than their current classification into CFS, FMS and IBS symptoms. Recently, the Institute of

Medicine (IOM) published a new proposal for diagnostic criteria for CFS based on extensive literature review (39). These criteria are based on three main symptoms: disabling fatigue, post-exertional malaise and unrefreshing sleep; with at least one of two mentioned additional symptoms (cognitive impairment or orthostatic intolerance). In line with the literature review of the IOM, the networks revealed that fatigue symptoms clustered with cognitive problems and unrefreshed sleep, and that sore throat, lymph node tenderness, and headaches formed a separate symptom cluster. One remarkable finding is that the CFS symptom post-exertional malaise was included in the musculoskeletal cluster in the general population. In contrast to the 1990 diagnostic criteria (40), the revised 2010 FMS criteria also include non-pain symptoms that overlap with the CFS diagnostic symptom criteria such as fatigue, cognitive symptoms, unrefreshed sleep, and general symptoms (22). As mentioned by the IOM, the revised ACR diagnostic criteria for FMS may therefore greatly increase the overlap between CFS and FMS (39). Based on our results, the classification of the current diagnostic criteria for CFS or FMS could be questioned.

The level of clustering was similar in the general population and the FSS group. Nevertheless, the between-diagnosis density was higher in the FSS group than in the general population. In addition, the four clusters in the general population melted to an abdominal and combined general and musculoskeletal symptom cluster in the FSS group. This could have been the result of negative associations in the network of FSS patients, which may have been caused by the selection of patients based on the fulfilment of the criteria of either of the three syndromes. However, it is in line with an earlier network study showing that difference between network structure and symptom clusters in patient with FSS decreased as symptom severity increased (13). Furthermore, our findings may suggest that one mechanism underlies FSS which could be divided into a modest single-organ type with symptoms primarily from one bodily system (6,12,14). But also in a more severe, multiorgan type, which may have led to stronger symptom overlap in FSS patients than in the general population. Rather than the presence of such a latent variable, it has also been suggested that direct causal relations among symptoms, as is central in the network approach, could explain this higher overlap in patients with more severe symptomatology (13).

In summary, we revealed that all FSS diagnostic symptoms were connected, either directly or via other symptoms. Furthermore, we found that symptoms clustered based on bodily systems rather than their current classification into the different FSS. Our results are therefore in line with recent suggestions supporting both the lumpers' and splitters' views in that there is commonality as well as heterogeneity within and between FSS (4). Future studies will be necessary to examine and reconsider the diagnostic criteria for FSS.

REFERENCES

1 Buffington CT. Developmental influences on medically unexplained symptoms. Psychother Psychosom 2009;78(3):139-144.
2 Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med 2000;160(2):221.
3 Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354(9182):936-939.
4 White PD. Chronic fatigue syndrome: Is it one discrete syndrome or many? Implications for the "one vs. many" functional somatic syndromes debate. J Psychosom Res 2010 May;68(5):455-459.
5 Robbins JM, Kirmayer LJ, Hemami S. Latent variable models of functional somatic distress. J Nerv Ment Dis 1997;185(10):606-615.
6 Kato K, Sullivan PF, Pedersen NL. Latent class analysis of functional somatic symptoms in a population-based sample of twins. J Psychosom Res 2010 May;68(5):447-453.
7 Rosmalen JG, Tak LM, de Jonge P. Empirical foundations for the diagnosis of somatization: implications for DSM-5. Psychol Med 2011 Jun;41(6):1133-1142.
8 Tsai C. Factor analysis of the clustering of common somatic symptoms: a preliminary study. BMC health services research 2010;10(1):160.
9 Fink P, Toft T, Hansen MS, Ornbol E, Olesen F. Symptoms and syndromes of bodily distress: an exploratory study of 978 internal medical, neurological, and primary care patients. Psychosom Med 2007 Jan;69(1):30-39.
10 Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms: an epidemiological study in seven specialities. J Psychosom Res 2001;51(1):361-367.
11 Lacourt T, Houtveen J, van Doornen L. "Functional somatic syndromes, one or many?" An answer by cluster analysis. J Psychosom Res 2013 Jan;74(1):6-11.
12 Gara MA, Silver RC, Escobar JI, Holman A, Waitzkin H. A hierarchical classes analysis (HICLAS) of primary care patients with medically unexplained somatic symptoms. Psychiatry Res 1998 Oct 19;81(1):77-86.
13 Melidis C, Denham SL, Hyland ME. A test of the adaptive network explanation of functional disorders using a machine learning analysis of symptoms. BioSystems 2018;165:22-30.
14 Fink P, Schröder A. One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. J Psychosom Res 2010;68(5):415-426.
15 Borsboom D, Cramer AO. Network analysis: an integrative approach to the structure of psychopathology. Annual review of clinical psychology 2013;9:91-121.
16 Cramer A, Waldorp L, van der Maas H, Borsboom D. Comorbidity: a network perspective. Behav Brain Sci 2010(33(2-3)):37 – 150; discussion 150 – 193.

17 Boschloo L, van Borkulo CD, Rhemtulla M, Keyes KM, Borsboom D, Schoevers RA. The network structure of symptoms of the diagnostic and statistical manual of mental disorders. PLoS One 2015;10(9):e0137621.
18 Bekhuis E, Schoevers R, van Borkulo C, Rosmalen J, Boschloo L. The network structure of major depressive disorder, generalized anxiety disorder and somatic symptomatology. Psychol Med 2016;46(14):2989-2998.
19 Bekhuis E, Schoevers R, de Boer M, Peen J, Dekker J, Van H, et al. Symptom-Specific Effects of Psychotherapy versus Combined Therapy in the Treatment of Mild to Moderate Depression: A Network Approach. Psychother Psychosom 2018;87(2):121-123.
20 Scholtens S, Smidt N, Swertz MA, Bakker SJ, Dotinga A, Vonk JM, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. Int J Epidemiol 2015 Aug;44(4):1172-1180.
21 Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121(12):953-959.
22 Wolfe F, Clauw DJ, Fitzcharles M, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis care & research 2010;62(5):600-610.
23 Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology 2006;130(5):1377-1390.
24 Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. Gastroenterology 2016;150(6):1262-1279. e2.
25 Epskamp S, Cramer AO, Waldorp LJ, Schmittmann VD, Borsboom D. qgraph: Network visualizations of relationships in psychometric data. Journal of Statistical Software 2012;48(4):1-18.
26 Tibshirani R. Regression shrinkage and selection via the lasso. Journal of the Royal Statistical Society.Series B (Methodological) 1996:267-288.
27 Chen J, Chen Z. Extended Bayesian information criteria for model selection with large model spaces. Biometrika 2008;95(3):759-771.
28 Extended Bayesian information criteria for Gaussian graphical models. Advances in neural information processing systems; 2010.
29 Van Borkulo CD, Borsboom D, Epskamp S, Blanken TF, Boschloo L, Schoevers RA, et al. A new method for constructing networks from binary data. Scientific reports 2014;4:5918.
30 Borsboom D, Fried EI, Epskamp S, Waldorp LJ, van Borkulo CD, van der Maas, Han LJ, et al. False alarm? A comprehensive reanalysis of "Evidence that psychopathology symptom networks have limited replicability" by Forbes, Wright, Markon, and Krueger (2017). 2017.
31 Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: A tutorial paper. Behavior Research Methods 2018;50(1):195-212.

32 Fruchterman TM, Reingold EM. Graph drawing by force- directed placement. Software: Practice and experience 1991;21(11):1129-1164.
33 Kolaczyk E. Statistical Analysis of Network Data: Springer: New York; 2009.
34 Barrat A, BarthÃ©lemy M, Pastor-Satorras R, Vespignani A. The architecture of complex weighted networks. Proc Natl Acad Sci U S A 2004 Mar 16;101(11):3747-3752.
35 Cohen J. Statistical power analysis for the behavioral sciences. 2nd. 1988.
36 Csardi G, Nepusz T. The igraph software package for complex network research. InterJournal, Complex Systems 2006;1695(5):1-9.
37 Boschloo L, van Borkulo CD, Borsboom D, Schoevers RA. A Prospective Study on How Symptoms in a Network Predict the Onset of Depression. Psychother Psychosom 2016;85(3):183-184.
38 van Borkulo C, Boschloo L, Borsboom D, Penninx BW, Waldorp LJ, Schoevers RA. Association of symptom network structure with the course of depression. JAMA psychiatry 2015;72(12):1219-1226.
39 IOM (Institute of Medicine). 2015. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness. Washington, DC: The National Academies Press.
40 Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis & Rheumatism 1990;33(2):160-172.

APPENDIX A: SCORING ALGORITHM TO DETERMINE THE FUNCTIONAL SOMATIC SYNDROME DIAGNOSIS

Chronic fatigue syndrome

The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention (CDC) criteria (1). To meet the CDC diagnostic criteria participants had to indicate [1] that they had experienced chronic fatigue for 6 or more months (box 1), and [2] that the fatigue significantly interfered with daily activities and work (box 2). In addition, [3] the participant had to report concurrently four or more of the eight mentioned additional symptoms (box 3)

BOX 1
Question chronic fatigue duration:

"I have had my tiredness complaints for about:"

Code	Label
1	not applicable because I do not have tiredness complaints
2	shorter than 3 months
3	3 months to 6 months
4	6 months to 1 year
5	longer than 1 year: ….. years and ... months
6	I have been feeling tired my entire life

To meet the CDC diagnostic criteria, participants had to indicate that they experienced chronic fatigue for 6 or more months (code 4-6).

BOX 2
Question interference:
"To what extent did your tiredness hamper your normal activities (both work outside the home and household chores) in the past 6 months?"

Code	Label
1	not applicable, because I did not have any tiredness in the past 6 months
2	not at all
3	a little bit
4	quite a bit
5	a lot
6	very much

To meet the CDC diagnostic criteria, participants had to indicate that the fatigue significantly interfered with daily activities and work quite a bit, a lot or very much the past 6 months (code 4-6).

BOX 3
Question additional symptoms (items from the CDC CFS Symptom Inventory):
"How often did you have the complaints listed below in the past 6 months?
- *Sore throat;*
- *Tender lymph nodes;*
- *Muscle pain;*
- *Joint pain;*
- *Headaches;*
- *Unrefreshing sleep;*
- *Unusual fatigue after exertion;*
- *Forgetfulness or memory problems;*
- *Difficulty with thinking or concentrating."*

Code	Label
1	not at all
2	several times a month
3	several times a week
4	every day

To meet the CDC diagnostic criteria, participants had to indicate that they had concurrently four or more of the mentioned complaints several times a week or every day in the past 6 months (code 3 or 4), where forgetfulness and/or difficulty concentrating were scored as one symptom.

Fibromyalgia syndrome

The diagnosis for FMS was assessed using the 2010 American College of Rheumatology (ACR) criteria (2). To meet the ACR criteria participants had to indicate that they experienced pain symptoms for at least 3 months (box 4). Participants were asked to indicate in which of 19 mentioned body areas they had had pain during the last week using the widespread pain index (WPI, box 5). The Symptom Severity (SS) scale was calculated based on the severity of fatigue, cognitive symptoms, waking unrefreshed and somatic symptoms participants reported (box 6). The severity of fatigue and cognitive symptoms were determined using items of the Checklist Individual Strength (CIS) (3). An additional item that determined to which extent participants are waking unrefreshed was added. To determine the level of somatic symptoms, the 12-item somatization scale of the Symptom Checklist-90 (SCL-90 SOM) was used (4). To meet the ACR diagnostic criteria, participants were required to have a WPI score ≥7 and an SS-scale score ≥5 or a WPI score of 3-6 and an SS-scale score of ≥9.

BOX 4

Question musculoskeletal pain complaints duration:
"I have had my musculoskeletal pain complaints for about:"

Code	Label
1	not applicable because I do not have musculoskeletal pain complaints
2	shorter than 3 months
3	3 months to 6 months
4	6 months to 1 year
5	longer than 1 year: ... years and ... months

To meet the ACR diagnostic criteria, participants had to indicate that they experienced musculoskeletal pain complaints for 3 or more months (code 3-6).

BOX 5

Questions Widespread Pain Index:
"Please indicate whether the parts of the body listed below were painful and/or tender in the past 7 days:
- *Abdomen;*
- *Chest;*
- *Left hip;*
- *Left lower arm;*
- *Left lower leg;*
- *Left shoulder;*
- *Left side of jaw;*
- *Left upper arm;*
- *Left upper leg;*
- *Lower back;*
- *Neck;*
- *Right hip;*
- *Right lower arm;*
- *Right lower leg;*
- *Right shoulder;*
- *Right side of jaw;*
- *Right upper arm;*
- *Right upper leg;*
- *Upper back."*

Code	Label
1	yes
2	no

The WPI score was determined by counting the number of body areas in which the participant had pain during the last week.

BOX 6

Questions symptom severity scale:

"The last two weeks in general:

- *I feel tired;*
- *I have difficulty thinking;*
- *It takes an effort to concentrate;*
- *I do not wake up rested."*

Code	Label
1	yes, true
2	2
3	3
4	4
5	5
6	6
7	no, not true

This scale was converted into a 0-3 scale (0) "No problem" (score 7), (1) "Slight or mild problems" (score 4-6); (2) "Moderate to considerable problems" (score 2, 3); and (3) "Severe, pervasive, continuous problems" (score 1).

Questions somatic symptoms (SCL-90 SOM items):

"In the previous week, how much were you bothered by:

- *Headaches;*
- *Faintness or dizziness;*
- *Pains in heart or chest;*
- *Pains in lower back;*
- *Nausea or upset stomach;*
- *Soreness of your muscles;*
- *Trouble getting your breath;*
- *Hot or cold spells;*
- *Numbness or tingling in parts of your body;*
- *A lump in your throat;*
- *Feeling weak in parts of your body;*
- *Heavy feeling in your arms or legs."*

Code	Label
1	not at all
2	a little bit
3	moderately
4	quite a bit
5	extremely

The symptoms of 12 items of the SCL-90-SOM were summed, and converted into (0) "No problem" (0 symptoms), (1) "Slight or mild problems" (1-3 symptoms); (2) "Moderate to considerable problems" (4-5 symptoms); and (3) "Severe, pervasive, continuous problems" (>=6 symptoms).
The SS scale score was created by summing the 0–3 scores of fatigue, cognitive symptoms, waking unrefreshed and somatic symptoms into a 0–12 scale.

Irritable bowel syndrome

The diagnosis for IBS was assessed using the ROME III criteria (5). However, the criteria including occurrence of symptoms was adjusted in accordance to the ROME criteria (6), namely participants should indicate that they have recurrent abdominal pain or discomfort at least 1 day per week (instead of 3 days per month), with a symptom onset at least 6 months in the past to meet the research diagnosis. And for women, this abdominal pain or discomfort should not only occur during menstrual bleeding (box 7). Participants were asked if [1] this recurrent abdominal pain or discomfort was associated with improvement after defecation, [2] the onset was associated with change in stool frequency or [3] the onset was associated with change in (appearance) of stool (box 8). To meet the ROME III diagnostic criteria participants should have indicated that the recurrent abdominal pain or discomfort was sometimes to always accompanied by at least 2 of the 3 additional symptoms.

REFERENCES

1 Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994; 121(12): 953-9.

2 Wolfe F, Clauw DJ, Fitzcharles M, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis care & research* 2010; 62(5): 600-10.

3 Vercoulen JH, Swanink CM, Fennis JF, et al. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994; 38(5): 383-92.

4 Arrindell WA, Ettema J. SCL-90: Handleiding bij een multidimensionele psychopathologie-indicator. Swets test publishers; 1986.

5 Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006; 130(5): 1377-90.

6 Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. *Gastroenterology* 2016; 150(6): 1262-1279.

Table S1. Connection weights of the estimated network structures of FSS diagnostic symptoms for (A) the general population and (B) patients with FSS.

A. General population

	mCFS	PEM	Mus	Joi	Hea	Lym	Thr	mFMS	WPI	SOM	Fat	mIBS	Aim	Afr	Afo	Cog	Unr
mCFS	-																
PEM	0.08	-															
Mus	-0.01	0.26	-														
Joi	-0.01	0.32	0.15	-													
Hea	0.01	0	0.03	-0.03	-												
Lym	0.03	0.01	0.03	0.01	0.02	-											
Thr	-0.01	-0.03	0.08	-0.02	0.15	0.43	-										
mFMS	0.17	0.05	0	0.35	0.01	-0.01	-0.01	-									
WPI	0	0.04	0.16	0.12	0.05	0.05	-0.01	0.26	-								
SOM	0.04	0.06	0.07	0.03	0.13	0.03	0.02	0.05	0.17	-							
Fat	0.33	0.04	0	-0.02	0.10	0.04	0.02	-0.04	0.02	0.07	-						
mIBS	0.07	0	0.08	-0.05	-0.02	0.14	0.03	-0.06	0.01	0.03	0	-					
Aim	0.01	0	0.01	0	0.07	0	0.03	0	0.01	0	0.03	0	-				
Afr	0	0	0	0	0	0	0	0	0.01	0	0	0.03	0.26	-			
Afo	0	0	0	0	0.01	0	0	0	0.02	0.02	0	0.13	0.32	0.73	-		
Cog	0.08	0.07	0	0	0.02	0.04	-0.01	-0.03	0	0.05	0.19	-0.02	0	0.01	0	-	
Unr	0.23	0.01	0.01	0	0.07	0	0.02	0	0	0.03	0.34	0.03	0	0	0.01	0.14	-

Table S1. Continued.

B. FSS patients

	mCFS	PEM	Mus	Joi	Hea	Lym	Thr	mFMS	WPI	SOM	Fat	mIBS	Aim	Afr	Afo	Cog	Unr
mCFS	-																
PEM	0.14	-															
Mus	0.02	0.25	-														
Joi	0.02	0.32	0.26	-													
Hea	0	0.03	0	-0.01	-												
Lym	-0.01	0	0.05	0	0.03	-											
Thr	0	0	0	-0.03	0.14	0.43	-										
mFMS	0.10	0	0	0.23	0	-0.01	0	-									
WPI	-0.03	0.02	0.17	0.10	0	0.08	0.02	0.42	-								
SOM	0.02	0.10	0.07	0.02	0.15	0.07	0.03	0.09	0.15	-							
Fat	0.22	0.02	-0.01	-0.04	0.10	0.05	0.02	0.01	0	0.14	-						
mIBS	-0.02	-0.01	-0.03	-0.02	-0.04	-0.03	-0.01	-0.04	-0.19	-0.02	-0.09	-					
Aim	-0.01	0	0	-0.01	-0.01	-0.02	-0.02	0	0	-0.03	-0.03	0	-				
Afr	0	0	0	0	0.02	0.01	0.03	-0.02	0.05	0.02	0	0.23	0.26	-			
Afo	0	0	0	-0.01	0.03	0.05	0.02	-0.04	0.08	0.05	0.04	0.42	0.30	0.46	-		
Cog	0.07	0.07	0	0	0.08	0.04	0	0	-0.04	0.07	0.20	-0.06	0	0	0.03	-	
Unr	0.17	0.07	0.01	0.02	0.03	0	0.01	0	-0.01	0.02	0.37	-0.01	-0.03	0	0	0.10	-

mCFS = main symptom chronic fatigue syndrome; PEM=post-exertion malaise; Mus = muscle pain; Joi = joint pain; Hea = headaches; Lym = lymph node tenderness; Thr = sore throat; ACR = main symptom fibromyalgia syndrome; WPI = widespread pain index; SOM = general symptoms; Fat = fatigue; ROME = main symptom irritable bowel syndrome; Aim = improvement with defecation; Afr = associated with stool frequency; Afo = associated with stool form; Cog = cognitive problems; Unr = unrefreshed sleep.

Table S2. Associations of symptoms within FSS diagnoses in the general population and patients with FSS. Symptoms are ordered based on the strength of their connections.

CFS				**FMS**				**IBS**			
Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients
PEM	0.73	=	0.87	Fat	0.57	=	0.71	Afo	1.18	=	1.18
Thr	0.62	↑Mus	0.58	Unr	0.51	↑mFMS	0.52	Afr	0.95	=	0.95
Lym	0.58	↑Joi	0.57	WPI	0.45	=	0.52	Aim	0.65	↑mIBS	0.65
Mus	0.54	↓Thr	0.55	SOM	0.37	↓Unr	0.49	mIBS	0.56	↓Aim	0.56
Unr	0.49	↓Lym	0.54	Cog	0.36	↓SOM	0.46				
Joi	0.43	↓Unr	0.41	mFMS	0.24	↓Cog	0.34				
mCFS	0.4	=	0.4								
Cog	0.34	=	0.35								
Hea	0.27	=	0.32								

CFS = chronic fatigue syndrome; PEM = post-exertional malaise; Mus = musculoskeletal pain; Joi = joint pain; Thr = sore throat; Lym = tender lymph nodes; mCFS = main criteria chronic fatigue syndrome; Unr = unresreshed sleep; Cog = cognitive symptoms; Hea = headaches; FMS = fibromyalgia syndrome; Fat = fatigue; mFMS = main criteria fibromyalgia syndrome; WPI = widespread pain index; SOM = symptoms in general; IBS = irritable bowel syndrome; Afo = abdominal pain associated with change in form; Afr = abdominal pain associated with change of frequency; mIBS = main criteria irritable bowel syndrome; Aim: improvement of abdominal pain after defecation.

Table S3. Associations of symptoms between FSS diagnoses in the general population and patients with FSS. Symptoms are ordered based on the strength of their connections.

CFS				**FMS**				**IBS**			
Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients
mCFS	0.92	=	0.52	Fat	1.07	=	0.84	mIBS	0.23	↑Afo	0.26
Unr	0.55	=	0.45	SOM	0.52	=	0.59	Aim	0.12	↑Afr	0.12
Hea	0.43	=	0.36	mFMS	0.47	↑Unr	0.38	Afo	0.02	↓Aim	-0.15
Joi	0.42	↑Cog	0.31	WPI	0.46	↑Cog	0.33	Afr	0	↓mIBS	-0.57
Cog	0.35	↓Joi	0.29	Unr	0.38	↓WPI	0.25				
Mus	0.33	↑PEM	0.26	Cog	0.33	↓mFMS	0.21				
Lym	0.31	=	0.25								
PEM	0.28	↓Mus	0.22								
Thr	0.1	=	0.1								

CFS = chronic fatigue syndrome; mCFS = main criteria chronic fatigue syndrome; Unr = unresreshed sleep; Hea = headaches; Cog = cognitive symptoms; Joi = joint pain; PEM = post-exertional malaise; Lym = tender lymph nodes; Mus = musculoskeletal pain; Thr = sore throat; FMS = fibromyalgia syndrome; Fat = fatigue; SOM = symptoms in general; WPI = widespread pain index; mFMS = main criteria fibromyalgia syndrome; IBS = irritable bowel syndrome; Afo = abdominal pain associated with change in form; Afr = abdominal pain associated with change of frequency; Aim: improvement of abdominal pain after defecation; mIBS = main criteria irritable bowel syndrome.