The Interplay of Biopsychosocial Factors and Quality of Life in Inflammatory Bowel Diseases

A Network Analysis

Anne K. Thomann, MD, Laura-Louise Knödler,**
Sandeep Karthikeyan, MSc, MPhil,† Konstantina Atanasova, MSc,†
Charles N. Bernstein, MD,‡ Matthias P. Ebert, MD, Stefanie Lis, PhD,†*
*and Wolfgang Reindl, MD**

Goal: The aim of this study was to investigate the network of biopsychosocial factors and quality of life (QoL) in persons with inflammatory bowel diseases (IBDs) and explore the influence of psychological factors on the course of the disease.

Background: QoL of persons with IBD depends on disease activity but also on numerous interacting psychosocial factors. The influence of psychosocial factors on the disease course in controversially discussed.

Materials and Methods: In 2 independent IBD samples (sample 1: n = 209, anonymous internet survey; sample 2: n = 84, outpatients with active disease), we measured QoL, anxiety, depression, illness identity, self-esteem, loneliness, childhood trauma, and visceral sensitivity with questionnaires. In addition, fatigue, hemoglobin levels, and response to therapy were assessed in sample 2. We estimated multiple regularized partial correlation networks and conducted accuracy and stability tests of the networks.

Results: In both samples, QoL had the strongest relationships with visceral sensitivity and the illness identity engulfment. Depression was the most central factor in the networks. Baseline depression scores, visceral sensitivity, and engulfment were associated with response to therapy in sample 2.

Conclusions: This first network study to assess the interplay between biopsychosocial factors and QoL in IBD reveals a comparable network structure in 2 samples. Results partly replicate findings from previous studies with regard to the importance of depression and yield information on the central role of the newly introduced concepts of illness identity and visceral sensitivity. Preliminary findings point to an influence of these parameters on the disease course, which indicates their role as a possible target in individualized therapy.

Key Words: quality of life, network analysis, fatigue, inflammatory bowel diseases, visceral sensitivity

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Inflammatory bowel diseases (IBDs) as chronic-relapsing gastrointestinal disorders do not only burden patients with physical symptoms like abdominal pain, diarrhea, or fatigue but also psychosocial issues like stress generated by an unpredictable disease course a reduced level of social and occupational functioning[1] and stigmatization.[2] Moreover, the prevalence of mood disorders like anxiety and depression is increased in IBD.[3–5] Assessments of a patient's health state and of therapeutic efficacy in IBD should not be limited to "objective" inflammatory markers but also include patient-reported outcomes including subjective measurements of well-being and response to therapy. To this end, health-related quality of life (QoL) has emerged as one of the most important patient-reported outcome in patients with IBD.[6] The impact of depression, anxiety, and fatigue on QoL in IBD patients is indisputable,[3,7] and studies on other psychosocial concepts in IBD like self-esteem[8] and loneliness[9] are emerging. The prevalence of childhood trauma is higher in IBD than in the general population[10,11], and effects of adverse childhood events on the immune system have been discussed as a potential pathway to IBD development.[12–15] The identification of psychological and social factors that show the strongest relations to QoL and their relative impact could optimize therapeutic approaches to improve QoL in persons with IBD. The following promising concepts have been shown to influence QoL in other somatic disorders and may also prove relevant in IBD but have yet to be scientifically addressed:

Visceral sensitivity (VS) focuses on anxiety related to bowel symptoms and can be described as hypervigilance towards gastrointestinal symptoms.[16] While VS was originally introduced and shown to influence QoL in the context of irritable bowel syndrome (IBS),[17] the concept can also be useful in IBD, where IBS-like symptoms can occur after remission of inflammation.[18] VS as "gastrointestinal anxiety" could depict IBD-specific issues more robustly than "general" anxiety.

The burden of a chronic disease relates to the way an individual integrates the illness into the self-concept. The

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From the *Department of Medicine II, University Medical Centre Mannheim; †Institute of Psychiatric and Psychosomatic Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; and ‡Faculty of Medicine, University of Manitoba, Winnipeg, MB, Canada.

A.K.T., L.-L.K., S.L., and W.R. contributed equally.
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Address correspondence to: Anne K. Thomann, MD, Department of Medicine II, University Medical Center Mannheim, Theodor-Kutzer-Ufer 1-3, Mannheim 68167, Germany (e-mail: anne.thomann@medma.uni-heidelberg.de).

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concept of illness identity (IID) describes this integration and comprises the dimensions acceptance, enrichment, engulfment, and rejection.[19] These dimensions are differentially related to QoL, to psychopathologic symptoms, and also to treatment adherence in several other chronic illnesses.[20,21] In IBD, due to the often young age at disease onset and the high symptom burden, the way of adaptation to the disease could be especially important.

Obviously, many psychosocial factors are highly interrelated. Assuming that QoL in patients with IBD depends on numerous biological and psychosocial factors, it is desirable to comprehensively consider these variables and their unique connections to identify variables with the closest connections to QoL. One approach to address the interplay of variables and study their unique associations is the network analytical approach. This approach has recently gained increasing importance for understanding the interplay between biological, psychological, and social factors in complex systems, displaying multiple variables and their associations in intelligible network structures.[22,23] Network analytical approaches are increasingly being used in meta-analyses or in the analysis of empirical data, such as the clinical and patient-reported variables retrieved in the present study. Understanding health as a network of biopsychosocial factors reflects a holistic view of our patients' well-being and may help to identify highly connected and thus important variables as potential targets for specific therapeutic approaches.

In this study, we used network analysis (NA) to investigate the interplay between different psychosocial factors in IBD and their associations with QoL. The primary aim of this study was to determine which variables are reproducibly connected to QoL in biopsychosocial networks of 2 independent samples with IBD and which factors show the strongest connections to QoL in these networks. We further explored the relationship between QoL-relevant variables and measures of clinical importance including response to biological therapy in a sample with active IBD, to investigate the possible influence of these variables on the disease course.

MATERIALS AND METHODS

Two independent cohorts were included in this study. The first cohort (sample 1, n = 209) consisted of persons with IBD from an anonymous nationwide German online survey. The recruitment process was conducted by publishing study announcements on the Web site, via social media accounts, and the member magazine of the "Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung" (DCCV), the largest self-help association for patients with IBD in Germany.

The second cohort (sample 2, n = 84) consisted of persons with active IBD from the IBD outpatient unit at Department of Medicine II, Medical Faculty Mannheim, Heidelberg University. Active disease was defined by the presence of intestinal inflammation, determined by any of endoscopy, magnetic resonance imaging, sonography, and/or repeatedly elevated fecal calprotectin (fC) levels (> 250 mg/kg). Patients were recruited in the study and completed the questionnaires before the beginning of treatment with biologics (adalimumab, certolizumab, golimumab, infliximab, ustekinumab, vedolizumab). Response to therapy was assessed 3 to 6 months later (t_2) regarding subjective and objective measures:

"Subjective" response to therapy (TR_{subj}) was defined as changes in Harvey Bradshaw Index (HBI), an activity score for Crohn's disease (CD), or in partial Mayo Score (pMS), an activity score for ulcerative colitis (UC) at t_2 in relation to the baseline value.

$$TR_{subj} = \frac{HBI_{baseline} \text{ or } pMS_{baseline} - HBI_{t_2} \text{ or } pMS_{t_2}}{HBI_{baseline} \text{ or } pMS_{baseline}}.$$

"Objective" response to therapy (TR_{obj}) was defined as the arithmetic mean of relative changes in inflammatory markers: fC and C-reactive protein (CRP) if both measures were available (n = 38). If only one measure was available (delta CRP only: n = 31; delta fC only: n = 1), relative changes in the available one were included in the analysis.

$$TR_{obj} = \frac{\left(\frac{CRP_{baseline} - CRP_{t_2}}{CRP_{baseline}}\right) + \left(\frac{fC_{baseline} - fC_{t_2}}{fC_{baseline}}\right)}{2}.$$

Ethical Considerations

The described procedures were approved by the local ethics committee (Ethikkommission II, Medical Faculty Mannheim, Heidelberg University; 2018-589N-MA and 2014-633N-MA) and conducted in accordance with the declaration of Helsinki.

Questionnaires

To investigate associations between QoL and psychosocial factors, we chose to include variables that have previously been shown to impact QoL in persons with IBD[3,7,8,24] and further concepts that are connected to QoL in other disorders,[25–27] but have not been studied in IBD.

In both samples, we assessed disease-specific health-related QoL with the German version of Inflammatory Bowel Disease Questionnaire (IBDQ-D, range 0 to 224 with higher scores indicating higher QoL), anxiety and depression with the Hospital Anxiety and Depression Score (range 0 to 21 each for anxiety and depression, with higher scores indicating a higher level of anxiety and depressive symptoms, respectively), VS with the Visceral Sensitivity Index[16] (range 0 to 75 with higher scores indicating a higher VS), IID with the Illness Identity Questionnaire,[19] which includes the 4 dimensions of IID rejection, engulfment, acceptance, and enrichment (range 1 to 5 with higher scores indicating stronger rejection, engulfment, acceptance, and enrichment), self-esteem with the Rosenberg Self-esteem Scale[28] (range 0 to 30 with higher scores indicating more self-esteem), loneliness by the UCLA Loneliness Scale[29] (range: 0 to 100 with higher scores indicating higher levels of loneliness), and childhood maltreatment with the short version of the Childhood Trauma Questionnaire[30] (range: 25 to 125 with higher scores indicating more severe trauma). In sample 2, we additionally measured fatigue with the "Würzburger Erschöpfungs-Inventar bei Multipler Sklerose"[31] (range 0 to 68 with higher scores indicating higher levels of fatigue).

Data Analysis

Statistical analyses were performed using SPSS 25 (RRID:SCR_002865) for Windows for the descriptive statistics. The NAs were performed using R (RRID: SCR_001905, version 1.2.1335), together with the R package

"bootnet" (version 1.2.4). We used a Gaussian Graphical Model which is a form of pairwise Markov Random Field.

In NA, variables are considered as nodes in a network connected by edges. We chose a partial correlation network approach, in which the edges represent partial correlations between nodes, that is, unique associations between 2 variables that cannot be explained by the variation in other nodes of the network.[32] The description of a network structure is possible by estimating edges, that is, the connections between nodes and the centrality of single nodes, that is, the extent to which a node connects to other nodes in the network. In the visualization, the thickness of the edge displays the strength of the association with the gray-colored edges indicating positive partial correlations and the black-colored edges negative ones. The partial correlation network was regularized by using the graphical least absolute shrinkage and selection operator (LASSO) which sets small edges to zero to avoid false-positive connections in combination with extended Bayesian Information Criterion (EBIC). EBIC is used to select the optimal regularization parameter (lambda). The hyperparameter, the gamma, for the EBIC is kept at 0.5 (default).

We estimated the strength centrality (ie, the sum of the absolute values of the edge weights connected to a node) of the variables. In line, a high centrality score of a node depends on both the strength and the number of its edges. To assess the inferred network parameters, we applied accuracy and stability tests. The accuracy of the edge weights is calculated by estimating a 95% confidence interval around bootstrapped edge weights. The stability of the centrality indices is calculated as the correlation stability (CS) coefficient via subset-drop bootstrapping by which some portion of the sample is dropped in successive iterations and correlating the centrality values with that of the original sample. CS > 0.5 indicate stable estimates. To test whether there is a significant difference between any 2 given edge weights or centrality measures, we calculated edge-weight and centrality bootstrap difference tests.

In total, we estimated 4 network models: NA1 is based on the psychosocial variables measured in sample 1, NA2 on the same variables measured in sample 2. To investigate the association with clinical factors, we calculated 2 additional network models based on the data derived for sample 2. Following a step-up-approach using the nodes of NA2 that showed unique relations to QoL, we included fatigue and hemoglobin levels of sample 2 to calculate NA3 and added measures of "subjective" (changes in HBI or pMS) and "objective" (changes in CRP and/or fC) response to therapy, resulting in NA4.

To assess the stability and reproducibility of the networks estimations in both samples, we calculated the Spearman correlation coefficients for edge weights and node centrality measures between both networks. In addition, we used the structure and global strength invariance tests of the R package "NetworkComparisonTest" to test for differences in structure and node centrality between the networks NA1 and NA2.

RESULTS

Sample Description

Sample 1: A total of 209 patients (female: 73.2%, mean age: 40.51 SD: 13.07) with IBD (54.1% UC, 44.5% CD, 1.4% IBD-type unclassified) completed the anonymous online survey.

Sample 2: A total of 84 outpatients (female: 54.8%; mean age: 39.96; SD: 15.84) with active IBD (21.4% UC, 78.6% CD) answered the questionnaires before the beginning of treatment with biologics. Response to therapy at t_2 was assessed in 71 of those patients, 13 patients were lost to follow-up.

Three patients reported the diagnosis of a depressive disorder and were on antidepressant medication. For further details on the samples' features, see Table 1.

TABLE 1. Sample Characteristics

	n (%)/Mean ± SD			
Demographic/ Clinical Data	**Sample 1**	**Sample 2**	***t*/χ^2**	***P***
Gender				
Male	55 (26.3)	38 (45.2)	10.162	0.006
Female	153 (73.2)	46 (54.8)		
Nonbinary	1 (0.5)	0 (0)		
Age (y)	40.51 ± 13.07	39.96 ± 15.84	−0.273	0.785
Diagnosis				
CD	93 (44.5)	66 (78.6)	28.301	< 0.001
UC	113 (54.1)	18 (21.4)		
IBD unclassified	3 (1.4)	0 (0)		
Montreal class				
L1 (CD)	NA	15 (22.7)		
L2 (CD)	NA	15 (22.7)		
L3 (CD)	NA	31 (47)		
L4 (CD)	NA	10 (15.2)		
B1 (CD)	NA	18 (27.3)		
B2 (CD)	NA	18 (27.3)		
B3 (CD)	NA	33 (50)		
E1 (UC)	NA	0 (0)		
E2 (UC)	NA	9 (52.9)		
E3 (UC)	NA	8 (47.1)		
Current IBD medication				
Steroids	81 (38.8)	34 (40.5)		
Biologics	94 (45.0)	15 (17.8)		
5-ASA	102 (48.8)	13 (15.4)		
IS	31 (14,8)	7 (8.3)		
Illness duration (y)	14.11 ± 11.35	11.11 ± 10.86	−1.996	0.047
Prior systemic medications	1.37 ± 1.62	2.69 ± 1.43	6.458	< 0.001
History of IBD-related surgery	75 (35.9)	42 (50)	5.76	0.016
Years of education	14.42 (4.1)	11.973 (3.3)	5.348	< 0.001
IID				
Rejection	2.54 ± 0.82	2.46 ± 0.92	−0.672	0.502
Acceptance	3.48 ± 0.92	3.46 ± 1.02	−0.213	0.831
Engulfment	2.6 ± 0.95	2.65 ± 1.03	0.451	0.652
Enrichment	3.3 ± 0.98	3.21 ± 0.97	−0.742	0.458
QoL	148.35 ± 35.64	133.73 ± 42.2	−2.801	0.006
Childhood trauma	39.88 ± 15.94	31.95 ± 7.49	−5.78	< 0.001
Anxiety	7.92 ± 4.16	7.14 ± 4.33	−1.419	0.157
Depression	6.22 ± 4.2	5.72 ± 4.18	−0.911	0.363
Visceral sensitivity	36.47 ± 16.66	37.73 ± 20.82	0.492	0.624
Self-esteem	21.65 ± 6.41	22.68 ± 6.29	1.225	0.21
Loneliness	43.13 ± 16.27	34.53 ± 12.12	−4.935	< 0.001
Fatigue	NA	30.33 ± 15.63	NA	NA
HBI	NA	9.47 ± 6.77	NA	NA
pMS	NA	5.0 ± 1.82	NA	NA

5-ASA indicates 5-aminosalicylic acid; CD, Crohn's disease; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; IID, illness identity; IS, immunosuppressants; NA, not available; pMS, partial Mayo Score; QoL, quality of life; UC, ulcerative colitis.

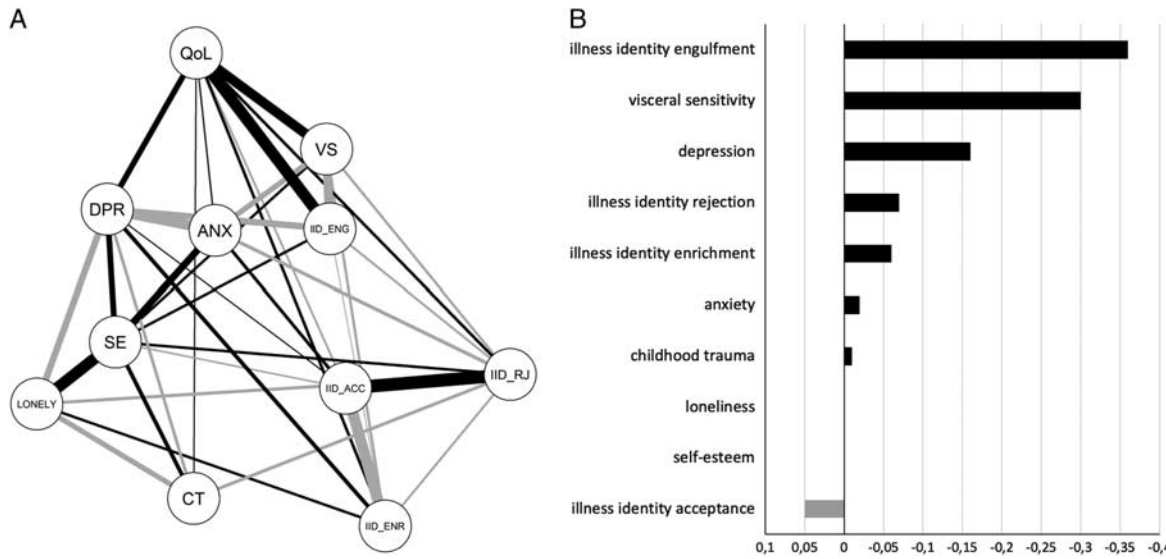

FIGURE 1. Regularized partial correlation networks of sample 1 (A) and edge weights of the partial correlations to QoL in network analysis 1 (B). The black line indicates a negative partial correlation, the gray line indicates a positive partial correlation. ANX indicates anxiety; CT, childhood trauma; DPR, depression; IID_ACC, illness identity acceptance; IID_ENG, illness identity engulfment; IID_ENR, illness identity enrichment; IID_RJ, illness identity rejection; LONELY, loneliness; QoL, quality of life; SE, self-esteem; VS, visceral sensitivity.

NA

Four NAs (1 to 4) were performed. Figure 1 displays the network structures of NA1 (sample 1, Fig. 1A) and the edge weights (eg, the strength of unique correlation) of the partial correlations to QoL in sample 1 (Fig. 1B). Figure 2 displays the network structure (Fig. 2A) and the edge weights to QoL (Fig. 2B) of sample 2 with identical nodes. NA3 includes the variables of NA2 that showed unique relations to QoL plus fatigue and hemoglobin levels (Fig. 3A). NA4 additionally explores connections between variables of NA3 and objective/subjective levels of response to biological therapy (Fig. 3B).

NAs 1 and 2

In both IBD samples, QoL showed the strongest negative unique associations with VS, IID engulfment, and depression, that is, these variables revealed an association with QoL that was present after taking all connections with other variables of the network into account. Additional relationships with QoL emerged for anxiety in both samples, and childhood trauma and the other IID dimensions in sample 1 (Figs. 1, 2).

The 3 key nodes/variables with regard to QoL (VS, depression, and IID engulfment) were also strongly connected to each other in sample 2, while a direct link between VS and depression was not detected in sample 1. Both depression and VS were positively associated with anxiety, and IID engulfment was connected to anxiety in sample 2.

Depression revealed the highest centrality and thus relevance within both networks (Fig. 4). Besides connections to QoL and anxiety, it is related to self-esteem and loneliness. These 2 variables were strongly related to each other and also connected to childhood trauma in both samples.

Self-esteem is additionally connected to anxiety and IID rejection and IID engulfment in both samples, to VS and IID acceptance in sample 1, and IID-enrichment in sample 2.

NA1 and NA2 showed a comparable network structure with correlation coefficients indicating 64% shared variance for edge weights (correlation $r = 0.811$, $P < 0.01$) and 45% shared variance for centrality strength (correlation $r = 0.67$, $P = 0.024$). Invariance tests by network comparison revealed no significant differences between NA1 and NA2 for centrality and edge weights (global strength invariance $P = 0.4$, global structure invariance $P = 0.81$). CS coefficients of NA1 and NA2 were 0.517 and 0.131, respectively.

NA3—Fatigue and Hemoglobin Levels

Fatigue and hemoglobin levels were assessed in sample 2 and included in the network estimation. Due to the smaller size of sample 2, we restricted the nodes of the network to those related to QoL in the previous analyses. In NA3, QoL was also uniquely related to the 3 key factors as described in NA1 and NA2 and additionally to anxiety and fatigue, with a stronger association to QoL for fatigue than for depression. Fatigue was associated with lower QoL and higher depression and anxiety. Higher hemoglobin levels were linked to lower fatigue and depression. CS coefficient of NA3 was 0.357 (Fig. 3A).

NA4—Response to Therapy

Adding objective and subjective measures of response to biological therapy to NA3 revealed a strong positive association between objective and subjective response. Furthermore, both subjective and objective response to therapy were related to higher baseline hemoglobin and lower baseline depression. Moreover, higher VS at baseline was correlated with lower subjective response to therapy, while higher IID engulfment was associated with stronger objective response to therapy. CS coefficient of NA4 was 0.357 (Fig. 3B).

DISCUSSION

Previous studies on psychosocial factors in IBD show associations between several factors, for example, using multiple linear regression.[8] While regression analyses undoubtedly detect important associations, network approaches offer

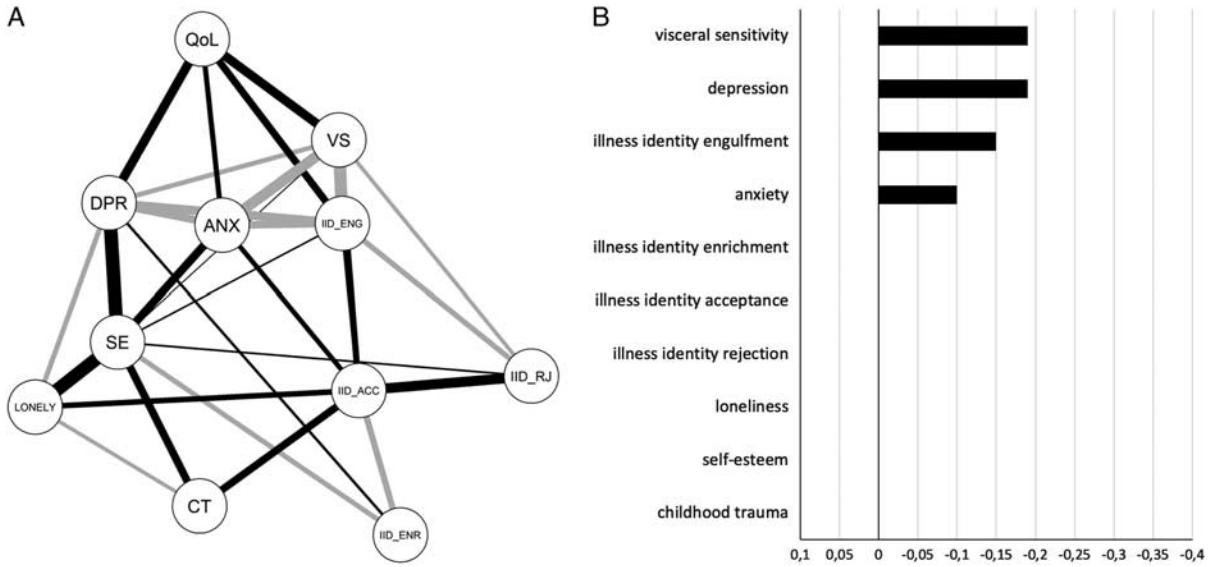

FIGURE 2. Regularized partial correlation networks of sample 2 (A) and edge weights of partial correlations to QoL in network analysis 2 (B). The black line indicates a negative partial correlation, the gray line indicates a positive partial correlation. ANX indicates anxiety; CT, childhood trauma; DPR, depression; IID_ACC, illness identity acceptance; IID_ENG, illness identity engulfment; IID_ENR, illness identity enrichment; IID_RJ, illness identity rejection; LONELY, loneliness; QoL, quality of life; SE, self-esteem; VS, visceral sensitivity.

certain advantages compared with conventional regression analyses. They allow testing of the interplay between a multitude of variables without a prior definition of independent and dependent variables, which is especially useful in the exploration of new psychosocial concepts where the directionality of relationships is unknown. Furthermore, the detection of unique associations between psychosocial factors is possible by controlling for all other variables within the network by using a partial correlation network,[32] which reduces the number and strength of edges (connections) to unique relations between the nodes (variables). In this study, the network estimation of psychosocial variables of 2 independent IBD samples formed a widely reproducible general network structure.

QoL was highly connected within these networks, shaping an interrelated complex with depression, anxiety, VS, and IID engulfment in which VS as gastrointestinal hypervigilance showed an even stronger association to QoL than general anxiety symptoms. Screening for general anxiety and depression as part of IBD care is often

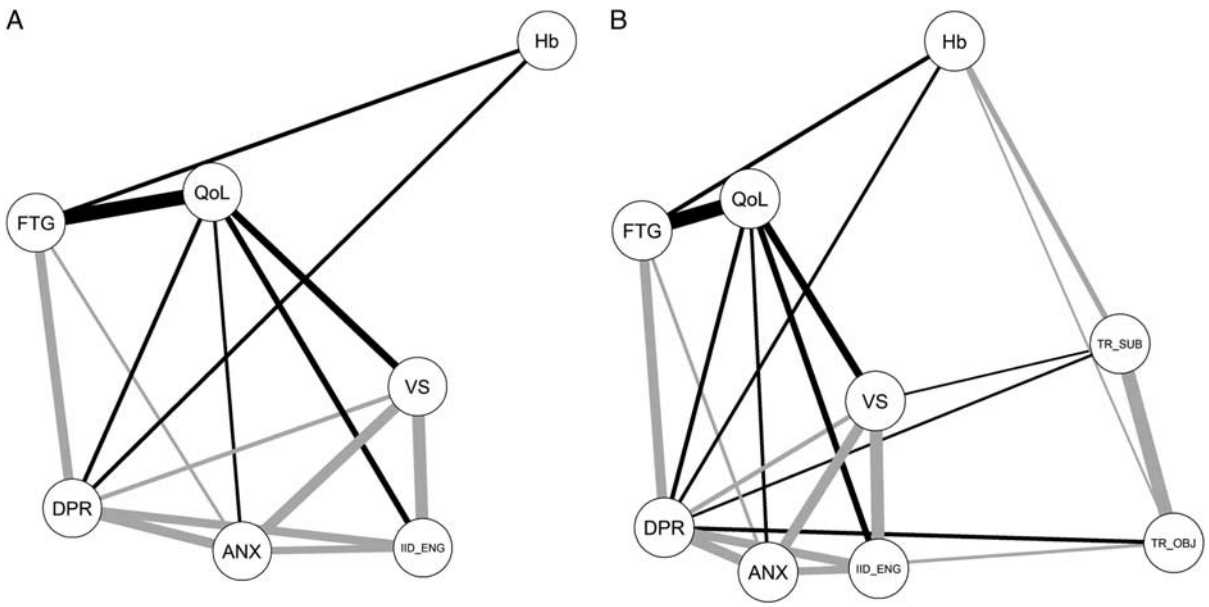

FIGURE 3. Regularized partial correlation networks of sample 2 including fatigue and hemoglobin levels (A) as well as subjective and objective response to therapy (B). The black line indicates a negative partial correlation, the gray line indicates a positive partial correlation. ANX indicates anxiety; DPR, depression; FTG, fatigue; Hb, hemoglobin levels; IID_ENG, illness identity engulfment; QoL, quality of life; TR_OBJ, objective response to therapy; TR_SUB, subjective response to therapy; VS, visceral sensitivity.

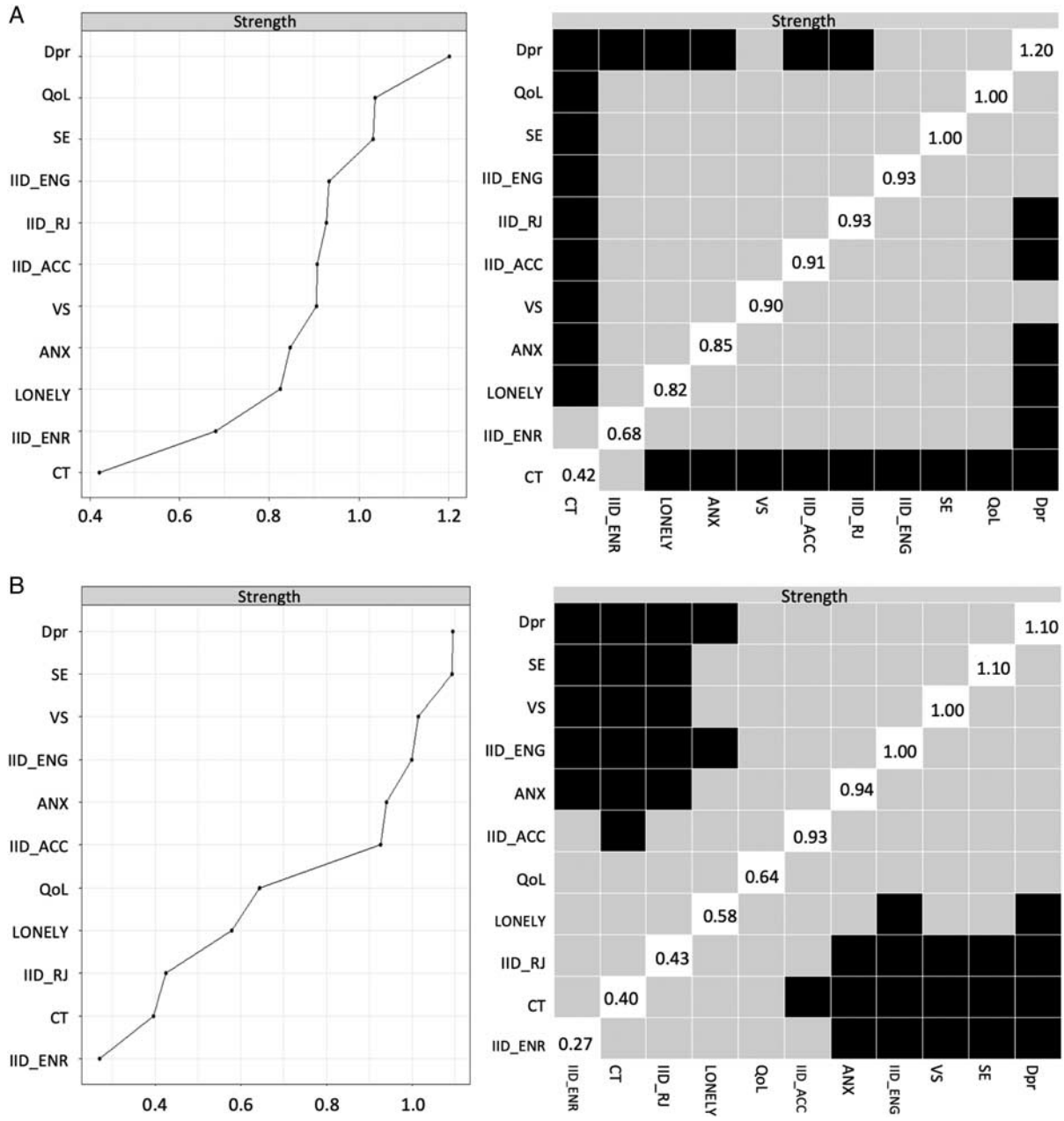

FIGURE 4. Strength centrality (left) and strength centrality difference (right) of sample 1 (A) and sample 2 (B). Black boxes indicate the presence of significant difference, gray boxes indicate the nonsignificant difference. ANX indicates anxiety; CT, childhood trauma; DPR, depression; IID_ACC, illness identity acceptance; IID_ENG, illness identity engulfment; IID_ENR, illness identity enrichment; IID_RJ, illness identity rejection; LONELY, loneliness; QoL, quality of life; SE, self-esteem; VS, visceral sensitivity.

recommended,[33,34] but the particularly strong connection between VS and QoL implies that VS should also be addressed and implemented in the patients' treatment plan. Functional gastrointestinal disorders such as IBS have been classified as disorders of brain-gut interactions, and these interactions have recently gained increasing attention in IBD.[35] Gastrointestinal hypervigilance and anxiety are suggested to modulate pain sensitization, pointing to an important pathway in the occurrence of IBS-like symptoms in IBD.[36] VS can reflect IBS-like symptoms in patients in remission[37] and correlates with subjective measures of disease activity.[38] However, the variance of VS in sample 2 of the present study, which only consists of patients with confirmed inflammation, indicates different levels of VS also in patients with objectively active disease. There is a need for approaches that will help to further distinguish between symptoms of disease activity and increased VS, as this is a common problem in the treatment of patients with IBD. In this study, the link between higher VS and lower subjective response to therapy in sample 2 indicates a possible influence of IBS-like symptoms on the perceived effectiveness of a treatment, which may lead to complications such as unnecessary diagnostic procedures or premature treatment changes.

Future research on IBS-like symptoms should implement assessments of VS in IBD patients to quantify the influence of VS on IBS-like symptoms and assess its role as a possible treatment target.

We introduced the analysis of IID in IBD patients to analyze how the individual patients integrate their disease into their self-image and how this relates to QoL. Strong connections between IID engulfment and the complex of health-related QoL, anxiety, depression,, and VS indicate that this IID dimension interacts with the acute symptom burden of a patient more than the other IID dimensions. Since our analyses rely on cross-sectional data, we cannot infer a causal relationship between these factors. IID engulfment may reflect a patient's predisposition to strongly emphasize visceral and psychopathologic symptoms as part of the self, being overwhelmed by the disorder during everyday life causing reduced QoL. However, IID engulfment may also simply reflect the severity of the disorder which may require an adjustment of lifestyle leaving no space for other aspects of the patient's identity. This is in line with findings of Oris et al[20] that show higher levels of engulfment in patients with disorders that are considered more complex or more disabling. The positive link between IID engulfment and objective response to therapy in sample 2 may relate to an increased focus on the disorder, causing stronger adherence to therapeutic recommendations and thus to increased therapeutic efficacy.

Self-esteem, loneliness, childhood trauma, and IID dimensions other than engulfment are components of the network with unique associations between each other, but not directly to QoL. Self-esteem may play a central role in the interplay of psychosocial factors and potentially mediate between social vulnerabilities and psychopathologic symptoms that are related to the patients' well-being. The relevance of childhood trauma remains inconclusive. The prevalence of adverse childhood events in our samples was lower compared with other IBD cohorts[11] but higher than expected in the general population, especially with regard to emotional abuse.[39] While the level of traumatization showed a unique but the weak association with QoL in sample 1, we did not replicate this finding for sample 2. One reason may be that the prevalence of childhood trauma is lower in sample 2 compared with sample 1, emphasizing the need for further studies with larger sample sizes.

Fatigue and anemia are highly prevalent, especially during active disease.[40] Investigating patients with active disease (sample 2) revealed fatigue as an important factor impacting QoL that was additionally associated with high levels of depression and anxiety. Though fatigue is increasingly perceived as an important issue in IBD, a clear understanding of the mechanisms behind this symptom and established treatment options for fatigue are still lacking.[40] The results of the present study indicate a mediating role of fatigue symptoms in the connection between QoL and depression and anxiety, respectively. This may relate to symptom overlap and high degrees of co-occurrence as also described in previous research.[41] In IBD, the feeling of exhaustion could be the most debilitating symptom in patients suffering from comorbid depression or vice versa, fatigue symptoms may lead to depression.

The reciprocal interaction between mental health and disease activity is a controversial topic. Numerous studies have examined the relationship and report partly contradicting results.[42–44] An important question for evaluating the importance of biopsychosocial factors in IBD is to which extent they may impact patient's adherence with IBD therapies.[45–47] For instance, childhood trauma may be accompanied by medical neglect and therefore indirectly associated with low therapy adherence in young persons with IBD still depending on caretakers.[48] To our knowledge, there are no studies examining the relationship between VS and adherence to medical therapy in IBD. One might speculate that persons with VS show greater adherence due to more general awareness and focus on symptoms. In contrast, persistent symptoms after treatment may lead to disappointment and consecutive discontinuation of a given therapeutic approach. This is an important question to address in future research. Further, there is an ongoing discussion whether the impact of affective symptoms or psychiatric comorbidities on the course of the disease is limited to subjective measures of well-being without an influence on inflammation.[43,49–51] To explore the influence of psychopathologic symptoms on the disease course in terms of response to treatment, we included measures of „subjective" and „objective" parameters of response in the NA. Our analyses suggest that neither were strongly connected with any psychosocial factor in the networks. This may relate to the small sample size in cohort 2, to sample heterogeneity, and to the short follow-up time of 3 to 6 months. As consecutive patients were screened, the sample includes patients with UC and CD, some naive to biologicals, some with extensive previous therapy, heterogenous in age and gender as well as the chosen therapy, and perhaps most importantly, in symptoms and thus the subjective burden of disease. We are aware that our definitions of subjective and objective responses are not standardized. Although subjective and objective outcome measures were similarly related to depression, a differential link to the levels of VS and IID engulfment, which are highly interrelated, suggests that a general division between "objective" and "subjective" response is a promising concept to help unravel the still unknown interplay between psychosocial and biological features of the disease course in IBD. A longer observation period and larger samples may yield more distinct results of bidirectional associations between psychosocial factors and clinical outcomes.

We need to address some limitations of our study. The sizes of both samples, and especially sample 2, were rather limited. Low CS coefficients secondary to limited sample sizes indicate that the centrality of nodes in the generated networks of sample 2 should be interpreted with care.[32] A simulation study we performed to estimate the required sample size to replicate network parameters of sample 1 suggests that the size of sample 2 was large enough to reproduce most parts. However, for more accurate reproduction of centrality estimates, a sample size of at least 250 is recommended.

Although the assessment of 2 IBD samples in different settings is an important strength of this work, the design is susceptible to bias. Sample 1 is larger and anonymous. This may lead to more honest answers in sensitive issues like childhood trauma or loneliness but has disadvantages such as the lack of clinical information. Regarding QoL, it is not surprising that the mean IBDQ scores were lower in sample 2, given the known active disease of all participants in that sample. The samples also showed significant demographic differences with regard to gender distribution (more females in sample 1), diagnosis (more UC in sample 1), and education (higher in sample 1); and sample 2 had a shorter but more severe IBD history (more prior systemic medication and surgeries in sample 2).

Regardless of these limitations and differences, the fact that the main features of the networks were largely comparable between 2 independent samples of different sizes strengthens the reliability of the conclusions. A replication of the findings of the current undirected NA in larger, clinically well-characterized samples and longitudinal settings is desirable to confirm the connections and identify causal relationships. If the high impact of VS, fatigue, and IID engulfment on QoL is confirmed, a screening of these symptoms in clinical practice seems desirable. However, in the usual patient care, an assessment with multiple different scales as conducted in this study is not easy to implement. While the assessment of QoL as the most important depiction of a patient's state of well-being is feasible with several established tools, it would be useful to also screen for the extent by which QoL in a single patient is impacted by each of the aforementioned factors, to target these factors separately, for example, in psychotherapeutic approaches. The development of a simple, short, and standardized scale with selected items to measure symptoms of increased VS, fatigue, and IID engulfment would be helpful in this regard and could be investigated in future research. Knowledge of individual patterns and predominance of factors impacting a patient's QoL may help to identify effective supportive therapeutic strategies: Studies of persons with functional gastrointestinal disorders suggest a benefit for hypnotherapy, which could also prove useful in persons with IBD and dominating increased VS.[52] Patients with fatigue may benefit from yoga or solution-focused therapy.[53,54] Maladaptive coping strategies such as a dominance of the disease in a patient's self-concept (ie, IID engulfment) might be successfully targeted by mindfulness-based approaches like acceptance and commitment therapy,[55] while a high level of depressive symptoms may require a psychotherapeutic intervention such as cognitive-behavioral therapy or antidepressant medication.[56]

In conclusion, this study was the first to address psychosocial and clinical aspects of IBD in a biopsychosocial network approach, which yielded a coherent network of biopsychosocial items influencing QoL in persons with IBD, and preliminary findings with regard to the influence of psychosocial factors on the disease course. NA seems suitable for assessments in complex, multifactorial disorders like IBD, where the patients' well-being is influenced by several issues interacting in a causal system. Future research on biopsychosocial networks in IBD should include longitudinal studies in larger samples to detect temporal dynamics and identify causal associations within the system, which will help clinicians in understanding the complex interactions in these disorders, and help to identify important targets in holistic approaches to IBD treatment.

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