Inflammatory Bowel Diseases, 2022, **28**, 393–408
DOI: 10.1093/ibd/izab083
Advance access publication 13 April 2021
Original Research Articles - Clinical

Randomized Controlled Trial of Cognitive-Behavioral and Mindfulness-Based Stress Reduction on the Quality of Life of Patients With Crohn Disease

Ganit Goren, MSW,[*,a] Doron Schwartz, MD,[†,‡,a] Michael Friger, PhD,[§] Hagar Banai, MD,[¶,‖] Ruslan Sergienko, MA,[‡] Shirley Regev, PhD,[*] Heba Abu-Kaf, MD,[†,‡] Dan Greenberg, PhD,[**] Anna Nemirovsky, MA,[‖] Karny Ilan,[††] Livnat Lerner,[††] Alon Monsonego, PhD,[††] Iris Dotan, MD,[¶,‖] Henit Yanai, MD,[¶,‖] Rami Eliakim, MD,[‖,‡‡] Shomron Ben Horin MD,[‖,‡‡] Vered Slonim-Nevo, PhD,[*] Shmuel Odes, MD,[‡,b] and Orly Sarid, PhD[*,b]; on behalf of the Israeli IBD Research Nucleus

From the *Spitzer Department of Social Work, Ben-Gurion University of the Negev, Beer Sheva, Israel
[†]Department of Gastroenterology and Hepatology, Soroka Medical Center, Beer Sheva, Israel
[‡]Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
[§]Department of Public Health, Ben-Gurion University of the Negev, Beer Sheva, Israel
[¶]Division of Gastroenterology, Rabin Medical Center, Petah Tikva, Israel
[‖]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[**]Department of Health Systems Management, School of Public Health, Guilford Glazer Faculty of Business and Management, Ben-Gurion University of the Negev, Beer Sheva, Israel
[††]The Shraga Segal Department of Microbiology and Immunology, Faculty of Health Sciences, The National Institute for Biotechnology in the Negev, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[‡‡]Department of Gastroenterology, Sheba Medical Center, Tel Hashomer, Israel
[a]These authors share first authorship.
[b]These authors share senior authorship.
Supported by: The Leona M. and Harry B. Helmsley Charitable Trust generously funded the study.

Address correspondence to: Shmuel Odes, MD, Faculty of Health Sciences, Third Floor Room 306, Ben-Gurion University of the Negev, P.O. Box 653, Beer Sheba 8410500, Israel (odes@bgu.ac.il).

Background: Patients with Crohn disease have debilitating psychological symptoms, mental fatigue, and poor quality of life. Psychological intervention may improve these symptoms.

Methods: We performed a randomized parallel-group physician-blinded trial of cognitive-behavioral and mindfulness-based stress reduction (COBMINDEX) on quality of life and psychological symptoms in adults with mild-moderate Crohn disease. COBMINDEX was taught by social workers in one-on-one video conferences over 3 months; quotidian home practice was mandated.

Results: Fifty-five COBMINDEX and 61 waitlist control patients completed the study; mean age was 33 years and 65% of participants were women. At 3 months, COBMINDEX patients had significantly reduced disease activity (per Harvey-Bradshaw Index score, C-reactive protein level, and calprotectin level), increased quality of life (Short Inflammatory Bowel Disease Questionnaire [SIBDQ] score increased from baseline 41 to 50; $P < 0.001$), decreased psychological symptoms (Global Severity Index [GSI], 0.98-0.70; $P < 0.001$), reduced fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue, 26-33; $P < 0.001$), and increased mindfulness disposition (Freiburg Mindfulness Inventory, 33-38; $P < 0.001$). Waitlist patients had a significant but small change in Harvey-Bradshaw Index, SIBDQ, and GSI scores, without improvement in fatigue or mindfulness. There were significant correlations ($0.02 > P < 0.002$) in COBMINDEX patients between baseline SIBDQ, GSI, Freiburg Mindfulness Inventory, and Functional Assessment of Chronic Illness Therapy-Fatigue scores with a relative change (baseline to 3 months) of the SIBDQ score, but none among waitlist patients. Predictors of relative change of the SIBDQ score in COBMINDEX patients included the GSI score (90% quantile; coefficient 0.52; $P < 0.001$), somatization (90%; 0.20; $P = 0.001$), depression (75%; 0.16; $P = 0.03$), and phobic anxiety (75%; 0.31; $P = 0.008$).

Conclusions: COBMINDEX was effective in increasing patients' quality of life and reducing psychological symptoms and fatigue. Patients with severe baseline psychological symptoms benefited the most from COBMINDEX.

Key Words: inflammatory bowel disease, fatigue, psychological intervention, somatization, depression

Introduction

Crohn disease (CD) is a common form of chronic inflammatory bowel disease (the other common forms are ulcerative colitis and microscopic colitis).[1,2] The peak age incidence of CD is in the third decade of life.[3] It runs a relapsing-remitting course that may complicate with bowel perforation, obstruction, and extraintestinal manifestations.[4-6] Corticosteroids, immunomodulators, and biologics decrease inflammation but expose the patient to possible serious adverse events.[7,8] Many patients fail medical treatment and require surgery.

Received for publications: December 29, 2020. **Editorial Decision:** March 15, 2021. **Published online:** 13 April 2021

Sudden abdominal pain with the need to defecate may be quite embarrassing for patients. Work, educational, and social activities are often compromised by the need to be close to a toilet.[9] Social dysfunction and isolation result.[10]

Patients with CD suffer considerable psychological symptoms (anxiety, depression, somatization) during active and quiescent disease,[11-16] leading to a poor quality of life.[17-19] Mental fatigue also occurs frequently,[11] and it too is associated with a decreased quality of life.[20] Longitudinal studies have shown an association between psychological distress and worsening of the disease course.[15, 21]

Several psychotherapeutic interventions have been studied in patients with CD, including cognitive-behavioral techniques and mindfulness meditation.[22] Interventions targeting psychological distress may improve quality of life in patients with CD.[23] The relationships between thoughts, behavior, physical sensations, and emotions are the basis of cognitive-behavioral therapy, where patients learn to identify, intervene, and attempt to modify their reactions.[24] Cognitive-behavioral therapy has benefited some patients with CD.[25] Two pilot studies of mindfulness-based distress reduction found an improved quality of life and reduced fatigue in patients with CD[26, 27] and others have not.[28, 29] These trials were all limited by small-sized cohorts, lack of control patients, and failure to separate patients with CD from those with ulcerative colitis. Furthermore, previous studies neither required nor monitored the daily practice of learned skills and did not examine for any impact of baseline psychological symptoms on change in quality of life. This missing information is important given the observation that not all but rather selected patients with CD seem to benefit most from psychological interventions.[30]

We postulated that the COgnitive Behavioral and MINdfulness-based stress reduction with Daily EXercise (COBMINDEX) program would improve quality of life by reducing both distress and fatigue in patients with CD. Our first aim was to test this hypothesis by performing a controlled trial of COBMINDEX in patients with mild or moderately active CD. A second aim was to identify which domains of quality of life would be most improved by COBMINDEX. Our third aim was to determine the impact of baseline medical and psychological characteristics on any enhancement of quality of life, which could inform the triaging of patients requiring psychosocial interventions when resources are limited.

METHODS

Study Design

This study was a randomized (separately for each sex) parallel-design (COBMINDEX or waitlist control patients) trial of the effect of COBMINDEX on patients with CD. Patients were recruited from July 2018 to July 2020 by advertising at outpatient clinics of participating hospitals, on the website of The Israel Foundation for Crohn's Disease and Ulcerative Colitis, and on social media. Patients aged ≥18 years and with a Harvey-Bradshaw Index (HBI) of disease activity in the range of 5 to 16 were eligible for inclusion. Social workers performed the initial screening for eligible patients, and study gastroenterologists did the final screening and enrolled suitable patients. Patients were then randomized (separately for each sex) to the COBMINDEX or waitlist control group. Exclusion criteria included age <18 years, no diagnosis of CD, <1 year of follow-up since diagnosis, change of diagnosis in study period, new medication started in the past 3 months, surgery in the past 6 months, planned surgery, acute surgery during the study, pregnancy, planned pregnancy during the study period, present/past psychiatric disease/medication, irritable bowel syndrome, and not being fluent in Hebrew. Patients' electronic medical and pharmacy records were reviewed by the study gastroenterologists to determine whether they had any of the exclusion criteria. Irritable bowel syndrome was excluded on clinical grounds. Persistent mild diarrhea and/or abdominal pain in treated patients with CD is a known entity[31] (attributed to subclinical inflammation associated with increased colonic paracellular permeability[32]) and does not imply a comorbidity of irritable bowel syndrome.

Randomization was performed using the cluster random sampling method with a proportionate allocation strategy, where the fractions were defined by the sex variable. Thus, patients interested in participating in the study were scheduled to meet with the social workers in no particular order. Those satisfying the entry criteria were divided by sex. Next, for each sex the first, third, fifth, seventh, and continuing odd-numbered participants were entered into the intervention group, whereas the second, fourth, sixth, and continuing even-numbered patients were entered into the control group.

Follow-Up Procedures

Patients were taught COBMINDEX over 3 months. The instruction was given by clinical social workers who had undergone a special training course in cognitive-behavioral and mindfulness-based stress reduction. Instruction was one-on-one in 7 video conferences of at least 1 hour and according to a structured protocol set out in a printed manual. The techniques that were taught included the following: breathing awareness, body scanning and progressive muscle relaxation, guided imagery techniques, coping, creating healthy and adaptive ways of thinking, and being mindful of unpleasant experiences. Quotidian practice of learned skills was to be performed at home twice daily, with a minimum of 10 minutes per exercise. Periodic text reminders to practice were sent to the patients. Patients reported their exercises daily by using an app; nonreporting led to a call from the patient's assigned social worker. In addition, a series of podcasts was created and made available to the COBMINDEX patients throughout the study.

Patients randomized to the waitlist constituted the control group. They understood that they would not receive any form of psychological instruction during the study period but would receive it after 3 months. During this waiting period, we kept in touch with the control group to be sure they were not lost to the study but rather felt that they were part of a cohort. We contacted them periodically regarding completion of the blood tests and returning the completed questionnaires, and we encouraged them to make contact if there were any medical problems so that they could be referred to a gastroenterologist. However, study materials like the podcasts were not made available to them. (After 3 months, the waitlist patients were taught COBMINDEX; a description of their outcomes exceeds the scope of this report).

All patients continued their regular medical follow-up with their respective physicians. Patients who required a change of medication during the study period could continue the trial.

Outcome Measures

Before randomization, and again after 3 months, all patients self-completed several questionnaires, and a gastroenterologist blinded to the randomization completed the HBI and medical details and ordered C-reactive protein (CRP) and calprotectin measurements. The questionnaires are in the public domain, have validated Hebrew translations, and were used previously by patients with CD.[13, 14, 29] Participants provided information about sex, age, education, family status, religious observance, and economic status (self-rated on an arbitrary scale of 1 to 5, where 1 = poor and 5 = well-to-do).

HBI

The HBI is a questionnaire that evaluates disease activity in 5 questions pertaining to the past day's symptoms regarding general well-being, abdominal pain, number of liquid/soft stools, presence of an abdominal mass, and number of complications from a list of 8. Responses are summed to provide the HBI score. An HBI score ≤ 4 indicates disease remission, 5 to 7 indicates mild disease, 8 to 16 indicates moderate disease, and >16 indicates severe disease.[33]

Brief Symptom Inventory

This instrument[34] measures psychological symptoms in the past month. Its 53 questions assess 9 dimensions (depression, somatization, obsessive-compulsive disorder, interpersonal sensitivity, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) on a 0 to 4 Likert scale (0 = not at all, 4 = extremely). A higher score implies more severe symptoms. The Brief Symptom Inventory yields a score for each dimension and a summary score called the Global Severity Index (GSI), also with a range of 0 to 4.

Short Inflammatory Bowel Disease Questionnaire

The Short Inflammatory Bowel Disease Questionnaire (SIBDQ), a disease-specific quality-of-life questionnaire, relates to the past 2 weeks' symptoms, general feeling, and mood in 10 items graded on a 7-point Likert scale (1 = all the time, 7 = never). The results are expressed as a general score (range, 10-70), which is the sum of the scores of 4 domains: emotional (range, 3-21), systemic (range, 2-14), bowel (range, 3-21) and social (range, 2-14). A higher score indicates a better quality-of-life.[35]

Medical Outcomes Study 12-Item Short Form Survey Instrument

This generic quality-of-life measure[36] has 12 items that assess physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-model, and mental health over the past 4 weeks. Scores are summed to yield physical health and mental health composites, each with a range of 0 to 100. A higher score indicates a better quality of life.

3-Level EuroQual Five-Dimensional Questionnaire

This generic questionnaire[37] comprises a comprehensive descriptive system in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) scored in 3 levels and a visual analogue scale. For ease of comparison, the EuroQual Five-Dimensional Questionnaire (EQ-5D) was converted into a single summary index. A higher index indicates a better quality of life.

Freiburg Mindfulness Inventory

This questionnaire[38, 39] has 14 items to be answered on a 4-point Likert scale regarding the patient's perceived mindfulness disposition during the past 7 days. The score range is 14 to 56; a higher score indicates a greater self-perceived mindfulness level. The Freiburg Mindfulness Inventory (FMI) can be used in persons without meditation experience.

Functional Assessment of Chronic Illness Therapy-Fatigue

This tool assessing mental fatigue comprises 13 questions that relate to the past 7 days. Responses are scored on a 5-point Likert scale. The total score range is 0 to 52; a higher score means less fatigue. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is a valid instrument in patients with CD.[40]

Statistical Analysis

Categorical variables were summarized using frequencies and percentages and quantitative variables used mean and SD if normally distributed or median and interquartile range (25th and 75th percentile) if nonnormally distributed. Statistical differences were appraised by *t* test or Pearson χ^2 for normally distributed variables and by Mann-Whitney *U* and Wilcoxon signed-rank test for nonparametric data. Correlations were determined by Spearman's rho.

We calculated the percent relative change of the SIBDQ over the study period by the following formula:

$$(SIBDQ\ after\ 3\ months - SIBDQ\ at\ study\ entry)/(SIBDQ\ at\ study\ entry) * 100.$$

The relative change in the 4 SIBDQ domains was calculated similarly. These values were used as the dependent variable in a quantile regression analysis (10%, 25%, 50%, 75%, 90% quantiles) performed to determine the predictors of the relative change of the SIBDQ (or its domains), using independent variables that were significant in the correlation analysis or had clinical interest. A series of models incorporating various independent variables was developed; given the cohort size, we limited each model to 3 variables. The independent variables were the baseline values of the HBI; the FMI; the FACIT-F; the BSI scales of depression, somatization, obsessive-compulsive disorder, interpersonal sensitivity, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism; and the GSI score. Results are presented separately for the COBMINDEX and waitlist groups. Only models with significant coefficients for any independent variable at more than the 10% quantile in either the COBMINDEX or waitlist groups are shown. Analyses were performed using IBM SPSS Statistics 23 for Windows (IBM Corp., Armonk, NY); $P < 0.05$ was considered statistically significant.

ETHICAL CONSIDERATIONS

The institutional review boards of Soroka Medical Center (Beer Sheva, Israel) and Rabin Medical Center (Petah Tikva, Israel) approved the trial. Participants were given a detailed

written and oral description of the research project and provided written informed consent.

RESULTS

Baseline Characteristics

Of 646 patients expressing interest in the research, 139 met the inclusion criteria and underwent randomization. Fifty-five COBMINDEX and 61 waitlist patients completed the 3-month study (Fig. 1). Across groups, patients had a mean age of 33 years, and 65% were women. Education, working status, and smoking habit were similar in the 2 groups (Table 1). The HBI score, the Montreal classification characteristics, and the drug treatments were comparable between groups. However, the COBMINDEX patients reported a significantly higher economic status than the waitlist patients.

Medical and Psychological Outcomes

Baseline HBI, CRP, calprotectin, SIBDQ (with the emotional, physical, bowel, and social domains), the 12-Item Short-Form Survey Instrument (SF-12) Physical Health Composite (PH) and Mental Health Composite (MH), EQ-D5, psychological symptoms (GSI), mindfulness disposition (FMI), and fatigue (FACIT-F) scores were similar in the groups (Table 2). Patients practiced self-exercise of the skills taught on more than 80% of the study days. Two patients in the COBMINDEX group and 4 in the waitlist group deteriorated clinically during the study, and biologic agents were added to their treatment regimens. Other changes of medications are noted in Table 1. These changes in medication did not impact the outcome of the study. The median HBI decreased in both patient groups during the 3-month study period. The reduction of HBI was greater in the COBMINDEX patients (50% decrease; $P < 0.001$) than in the waitlist patients (12.5% decrease; $P = 0.005$). The markers of inflammation, CRP and calprotectin, both decreased significantly in the COBMINDEX patients but not in the waitlist patients. The psychological scores on the SIBDQ, SF-12 PH, SF-12 MH, and EQ-D5 all improved in the COBMINDEX patients (most at $P < 0.001$). The SIBDQ score increased from the baseline 41 to 50 at 3 months ($P < 0.001$), mainly from the increments in the emotional and bowel domains. In the waitlist patients there was a lesser increase in the SIBDQ score (from 38 to 41; $P = 0.016$) that resulted from an increment in the systemic domain. The SF-12 PH score increased in the waitlist patients, but the SF-12 MH and EQ-D5 did not. The GSI score decreased more in the COBMINDEX patients than in the waitlist patients. The FMI and FACIT-F scores increased in the COBMINDEX patients only.

Correlations

All demographic, medical, and psychological measures at baseline were examined for possible correlations with the relative change in the SIBDQ score. Significant correlations ($0.02 > P < 0.002$) were found in the COBMINDEX group between the baseline SIBDQ, GSI, somatization, interpersonal sensitivity, depression, phobic anxiety, paranoid ideation, psychoticism, FMI, and FACIT-F scores with the relative change in the SIBDQ score (Table 3). However, waitlist patients had no significant correlations for any of these variables. Interestingly, no correlations were found in either group between baseline demographic data, economic status, and medical measures with the relative change in the SIBDQ score.

Predictors of Relative Change of SIBDQ Score

Nine models, each with 3 independent variables, are shown in Table 4. In model 1, the independent variables are the HBI, FMI, and FACIT-F. In this model, the FMI predicted a decrease in the relative change of the SIBDQ score in the 10%, 25%, and 50% quantiles, and the HBI predicted a decrease in the 25% quantile, in the COBMINDEX group; there were no significant predictions in the waitlist group. The FACIT-F was not a significant predictor in either the COBMINDEX or waitlist patients in this model.

In models 2 to 5, the HBI and FMI constituted 2 of 3 independent variables. In these models, most predictions were found in the COBMINDEX patients. The FMI was a predictor in models 2 through 5, more often in the 25% and 50% quantiles. In model 2, GSI was a predictor in COBMINDEX patients in the 90% quantile (coefficient 0.52; $P < 0.001$). In model 3, somatization was a predictor in the 75% and 90% quantiles in COBMINDEX patients. Depression (model 4) was a predictor in both COBMINDEX and waitlist patients in the 75% quantile. Phobic anxiety (model 5) was a predictor in COBMINDEX patients in the 75% and 90% quantiles.

In models 6 through 9, the HBI and FACIT-F were 2 of 3 independent variables. The GSI was a predictor in COBMINDEX patients in the 90% quantile (coefficient 0.53) in model 6. Somatization (model 7) was a predictor in COBMINDEX patients in the 90% quantile and in waitlist patients in the 25% quantile. Depression was a predictor in waitlist patients in the 10% and 90% quantiles but not at all in COBMINDEX patients. Phobic anxiety was a predictor in COBMINDEX patients in the 75% (coefficient 0.25) and 90% quantiles (coefficient 0.34) and in waitlist patients in the 10% quantile (coefficient –0.17). Finally, in models 6, 7, and 9, the HBI was a negative predictor in the 50% quantile in COBMINDEX patients.

Results of the quantile regression analysis of predictors of the relative change of the 4 SIBDQ domains are presented in Table 5. Regarding the SIBDQ emotional domain, the significant predictors in COBMINDEX patients were as follows: model 1: FMI and FACIT-F, both in 25% quantile; model 2: GSI in 10%, 25%, 50%, and 75% quantiles; model 3: FMI in 10% and 75% quantiles and somatization in 10%, 25%, and 50% quantiles; model 4: depression in 10% and 25% quantiles; model 5: phobic anxiety in 25% and 50% quantiles; model 6: GSI in 10%, 25%, and 50% quantiles; model 7: FACIT-F in 10% quantile; model 8: FACIT-F and depression, both in 10% and 25% quantiles; and model 9: phobic anxiety in 25% and 50% quantiles. In the waitlist patients, however, there were few significant predictors of relative change in the SIBDQ emotional domain. In the models of the SIBDQ systemic domain, there were actually more significant predictors of relative change of SIBDQ in waitlist patients than in COBMINDEX patients. In the SIBDQ bowel domain, there were 7 significant predictors in COBMINDEX patients and 3 in waitlist patients. Finally, in the SIBDQ social domain, 9 significant predictors were found in COBMINDEX patients and 5 in waitlist patients.

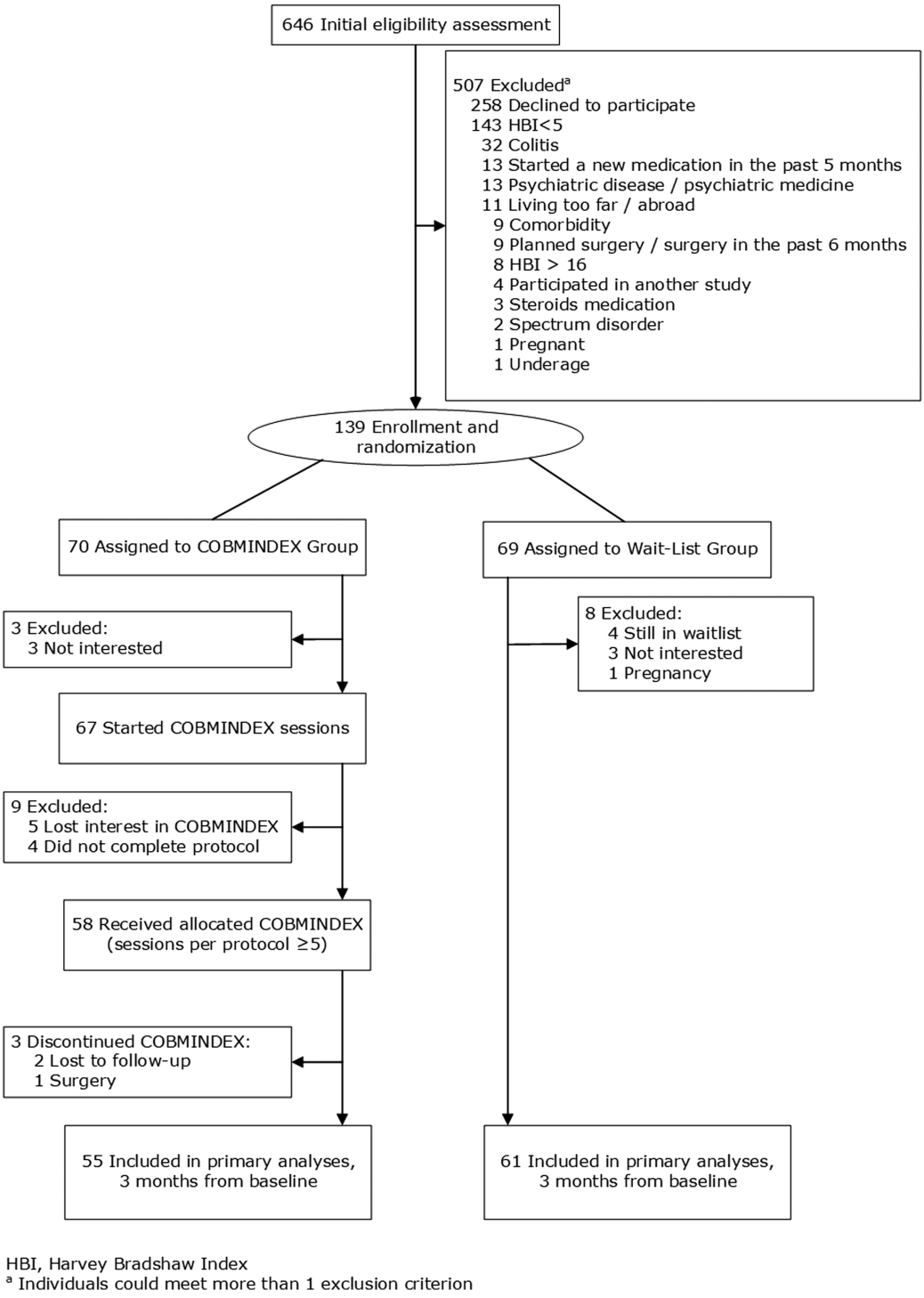

Figure 1. Flow of participants: CONSORT diagram.

Discussion

In a randomized parallel-design trial, we showed that COBMINDEX instruction to patients with mild-moderate CD resulted in an increase of their quality of life and a reduction of psychological symptoms and fatigue over a short time period. It could be argued that patients in both the COBMINDEX and waitlist groups were receiving anti-inflammatory medication, which of itself would result in an increased quality of life.[41] However, after 3 months the SIBDQ score had increased by 22% in the COBMINDEX patients vs only an 8% increase in the waitlist patients, implying that the difference was attributable to the psychological instruction of the COBMINDEX program. The increment in the disease-specific instrument SIBDQ after COBMINDEX instruction was caused primarily by improvement in the emotional domain, followed by the bowel domain, and least from the systemic and social domains. By comparison, the SIDBQ

Table 1. Cohort Characteristics at Baseline

	Number (%) of Participants	
	COBMINDEX (n = 55)	Waitlist (n = 61)
Age, mean (SD), y	33.6 (13)	32.4(11)
Women	38 (69)	37 (61)
Married/paired	28 (51)	29 (48)
Religious	19 (35)	25 (41)
Education		
High school or vocational studies	19 (35)	22 (36)
College or university	36 (66)	39 (64)
Economic status		
Low	6 (11)	23 (38)[§]
Middle-high	49 (89)	38 (62)
Working	40 (73)	48 (79)
Current smoking	6 (11)	8 (13)
Body mass index, median (IQR)	21.1 (19.6-25.1)	22.4 (20.0-25.4)
Illness duration, mean (SD), y	9.1 (8.8)	8.9 (8.1)
HBI		
Mild disease (5-7)	25 (45)	29 (48)
Moderate disease (8-16)	30 (55)	32 (52)
Medications*		
Steroids	1 (2)	6 (10)
Immunomodulators	12 (22)	10 (16)
Biologics	24 (44)	23 (38)
Opiates	0	0
Complementary medications[†]	37 (67.3)	39 (63.9)
Montreal classification		
Age at diagnosis, y		
A1: ≤16	8 (15)	4 (7)
A2: 17-40	43 (78)	55 (90)
A3: ≥40	4 (7)	2 (3)
Location		
L1: Ileal	33 (60)	34 (56)
L2: Colonic	3 (6)	7 (12)
L3: Ileocolonic	19 (35)	19 (31)
L4: Isolated upper disease	0 (0)	1 (2)
Behavior		
B1: Nonstricturing, nonpenetrating	31 (56)	38 (62)
B2: Stricturing	15 (29)	17 (28)
B3: Penetrating	6 (12)	5 (8)
Perianal	12 (22)	9 (15)
Extraintestinal manifestations[‡]	38 (69)	40 (66)

*There were 8 COBMINDEX and 6 waitlist patients who discontinued medications by T2, and 5 and 6 patients, respectively, who began new medications ($0.133 \le P \ge 0.941$).
[†]There were 13 COBMINDEX patients and 12 waitlist patients who discontinued complementary medications by T2, and 2 and 5 patients, respectively, who started taking complementary medications ($P = 0.516$).
[‡]Patients with ≥1 of arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, fistula, and abscess.
[§]$P < 0.001$ between COBMINDEX and waitlist groups.

emotional and bowel domains were unaltered in waitlist patients. Interestingly, the increase in the systemic domain over the study period was similar in both patient groups, raising the possibility that the increase was not related to any psychological instruction. Whether the increase was related to the decrease of the HBI is uncertain, because the decrease of the HBI was much greater in COBMINDEX patients than in waitlist patients. Like the disease-specific SIBDQ measure, the generic instruments SF-12 PH, SF-12 MH, and EQ-D5 all showed an increase of quality of life in COBMINDEX patients. Only the SF-12 PH increased in the waitlist patients; this is possibly the explanation for the results of the quan-

Table 2. Score of Medical and Psychological Characteristics of Participants at Baseline and After 3 Months

	COBMINDEX			Waitlist		
	Baseline	After 3 Months	*P*[a]	Baseline	After 3 Months	*P*[a]
HBI	8.00 (7.0-10.00)	4.00 (2.00-5.00)	<0.001	8.00 (6.50-10.50)	7.00 (4.50-9.00)	0.005
CRP	0.60 (0.23-1.20)	0.39 (0.18-0.85)	0.004	0.50 (0.18-1.00)	0.36 (0.10-0.72)	0.193
Calprotectin	83.50 (38.00-360.00)	75.30 (32.95-275.75)	0.022	142.50 (39.88-516.50)	67.95 (21.10-422.50)	0.808
SIBDQ	41.00 (34.00-46.00)	50 (42.00-54.00)	<0.001	38.00 (33.00-46.50)	41.00 (32.00-50.00)	0.016
Emotional	11.00 (9.00-14.00)	15 (13.00-17.00)	<0.001	11.00 (8.50-13.00)	11.00 (9.00-15.00)	0.083
Systemic	7.00 (5.00-9.00)	9.00 (6.00-11.00)	0.004	7.00 (5.00-9.00)	9.00 (5.00-10.00)	0.020
Bowel	12.00 (10.00-14.00)	15.00 (11.00-18.00)	<0.001	13.00 (10.00-14.50)	13.00 (10.00-16.00)	0.064
Social	10.00 (7.00-12.00)	11.00 (9.00-13.00)	<0.001	08.00 (6.00-11.00)	9.00 (6.00-11.50)	0.232
SF-12 PH	44.44 (38.36-48.31)	47.38 (41.87-47.38)	<0.001	41.76 (34.44-45.27)	43.88 (37.28-47.22)	0.004
SF-12 MH	39.12 (36.61-42.45)	42.36 (39.49-45.00)	0.001	39.83 (35.28-43.57)	38.20 (36.07-42.16)	0.353
EQ-D5	0.58 (0.49-0.70)	0.59 (0.53-0.77)	<0.001	0.58 (0.42-0.66)	0.58 (0.44-0.77)	0.163
GSI	0.98 (0.72-1.55)	0.70 (0.45-0.98)	<0.001	1.08 (0.68-1.95)	0.98 (0.58-1.63)	0.046
FMI	33.00 (28.00-40.00)	38.00 (34.00-44.00)	<0.001	32.00 (29.00-36.50)	33.00 (28.00-40.50)	0.444
FACIT-F	26.00 (20.00-31.00)	33.00 (24.00-41.00)	<0.001	25.00 (15.50-32.00)	24.00 (17.50-37.00)	0.106

Values are median and IQR (interquartile range). HBI: remission 0-4; mild 5-7; moderate 8-16; severe >16. CRP: normal < 0.5 mg/dL. Calprotectin: normal < 50 µg/g. SIBDQ: possible range 10-70, with emotional (3-21), physical (2-14), bowel (3-21), and social (2-14) domains. SF-12 PH: 0-100. SF-12 MH: 0-100. GSI: 0-4. FMI: 14-56. FACIT-F: 0-52.
[a]There were no statistically significant differences at baseline between COBMINDEX and waitlist patients in all measures shown ($0.203 < P < 0.923$).

Table 3. Correlations Between Medical and Psychological Measures at Baseline and Relative *C*hange of SIBDQ in COBMINDEX and Waitlist Patients

	COBMINDEX		Waitlist	
	Correlation Coefficient	*P*	Correlation Coefficient	*P*
HBI	–0.00	0.978	0.14	0.295
CRP	0.02	0.892	–0.12	0.364
Calprotectin	0.05	0.722	0.15	0.305
GSI	0.37	0.005	0.10	0.415
SIBDQ*	–0.63	<0.001	–0.22	0.091
Somatization	0.32	0.018	0.54	0.678
Interpersonal sensitivity	0.34	0.012	–0.09	0.497
Depression	0.32	0.016	0.21	0.112
Phobic anxiety	0.32	0.017	0.08	0.537
Paranoid ideation	0.39	0.003	0.08	0.561
Psychoticism	0.37	0.005	0.05	0.684
FMI	–0.40	0.002	0.03	0.800
FACIT-F	–0.31	0.020	–0.07	0.570

There were no significant correlations in the COBMINDEX or waitlist groups between the relative change in the SIBDQ and the following demographic, medical, and psychological variables: sex, family status, religious practice, education, social-economic status, working status, body mass index, current smoking, age at entry to study, duration of disease, age at disease onset, disease location, disease behavior, perianal disease, medications, hostility, anxiety, and obsessive-compulsive disorder.
*Percentage change from baseline to 3 months.

tile regression models of the SIBDQ systemic domain (also termed physical) in that group.

Previous studies of the effect of mindfulness-based cognitive therapy on quality of life in cohorts comprising both patients with CD and patients with ulcerative colitis reported mixed outcomes, such as no effect,[28] some increase but without reaching statistical significance,[29] or a significant increase of quality of life.[27] A pan-European study of 402 newly diagnosed patients with CD followed for 1 year found a significant increase in the SIBDQ in all 4 domains: emotional, systemic, bowel, and social.[41] The increase of quality of life in that study clearly resulted from the effect of treatment in the first year after diagnosis. This finding is different from the results in our cohort, where all patients were beyond the first year after diagnosis at study entry.

We noted a much greater reduction in the HBI in the COBMINDEX patients compared with the waitlist patients. If we assume that drug treatment could plausibly account for an equal reduction in the HBI (1 point) in both patient groups, then it is reasonable to presume that the further

Table 4. Predictors of Relative Change of SIBDQ[a] in Patients With CD by Quantile Regression Analysis

Model	Independent Variables at Baseline	Group	Regression Coefficient (*P*)				
			10%	25%	50%	75%	90%
1	HBI	COBMINDEX	–0.02 (0.51)	**–0.04 (0.03)**	–0.02 (0.32)	0.01 (0.70)	–0.01 (0.86)
		Waitlist	–0.01 (0.73)	0.02 (0.38)	0.01 (0.29)	0.01 (0.73)	0.04 (0.14)
	FMI	COBMINDEX	**–0.02 (0.03)**	**–0.02 (0.01)**	**–0.01 (0.03)**	–0.01 (0.46)	0.00 (0.98)
		Waitlist	0.00 (0.71)	0.01 (0.21)	0.00 (0.63)	0.00 (0.74)	0.00 (0.90)
	FACIT-F	COBMINDEX	0.00 (0.47)	0.00 (0.24)	–0.01 (0.16)	–0.01 (0.25)	–0.02 (0.32)
		Waitlist	0.01 (0.13)	0.00 (0.74)	0.00 (0.86)	0.00 (0.38)	0.00 (0.57)
2	HBI	COBMINDEX	–0.02 (0.51)	–0.04 (0.06)	–0.01 (0.54)	0.01 (0.69)	0.00 (0.87)
		Waitlist	–0.00 (0.54)	0.01 (0.44)	0.01 (0.28)	0.01 (0.74)	0.04 (0.26)
	FMI	COBMINDEX	–0.01 (0.13)	**–0.01 (0.03)**	–0.01 (0.10)	0.00 (0.62)	0.01 (0.40)
		Waitlist	**0.02 (0.001)**	0.01 (0.11)	0.00 (0.61)	0.00 (0.63)	0.00 (0.94)
	GSI	COBMINDEX	0.08 (0.48)	0.08 (0.34)	0.09 (0.34)	0.20 (0.06)	**0.52 (<0.001)**
		Waitlist	**0.17 (0.003)**	0.02 (0.78)	0.01 (0.81)	0.05 (0.52)	0.04 (0.77)
3	HBI	COBMINDEX	–0.02 (0.48)	–0.04 (0.10)	–0.03 (0.19)	0.01 (0.73)	0.03 (0.15)
		Waitlist	–0.01 (0.72)	0.01 (0.51)	0.01 (0.25)	0.01 (0.76)	0.04 (0.26)
	FMI	COBMINDEX	**–0.02 (0.01)**	**–0.01 (0.04)**	**–0.02 (0.02)**	–0.01 (0.28)	0.00 (0.76)
		Waitlist	0.01 (0.47)	0.01 (0.14)	0.00 (0.62)	0.00 (0.71)	0.00 (0.99)
	Somatization	COBMINDEX	0.09 (0.28)	0.10 (0.21)	0.12 (0.13)	**0.20 (0.04)**	**0.32 (0.001)**
		Waitlist	0.06 (0.36)	–0.01 (0.93)	0.01 (0.84)	0.02 (0.67)	0.03 (0.74)
4	HBI	COBMINDEX	–0.02 (0.53)	–0.03 (0.10)	0.00 (0.91)	–0.01 (0.75)	–0.01 (0.86)
		Waitlist	–0.01 (0.80)	0.01 (0.57)	0.01 (0.29)	0.00 (0.94)	–0.03 (0.30)
	FMI	COBMINDEX	–0.01 (0.13)	**–0.02 (0.001)**	**–0.02 (0.03)**	–0.01 (0.26)	0.00 (0.90)
		Waitlist	0.01 (0.22)	0.01 (0.07)	0.00 (0.61)	0.01 (0.39)	0.01 (0.62)
	Depression	COBMINDEX	0.05 (0.50)	0.04 (0.47)	0.02 (0.74)	**0.16 (0.03)**	0.29 (0.07)
		Waitlist	0.14 (0.06)	0.05 (0.33)	0.04 (0.34)	**0.11 (0.03)**	0.20 (0.06)
5	HBI	COBMINDEX	–0.02 (0.61)	–0.02 (0.19)	–0.01 (0.60)	–0.01 (0.82)	0.03 (0.40)
		Waitlist	–0.01 (0.45)	0.02 (0.38)	0.01 (0.24)	0.01 (0.76)	0.03 (0.22)
	FMI	COBMINDEX	–0.01 (0.26)	**–0.02 (0.001)**	–0.01 (0.11)	0.00 (0.87)	0.00 (1.0)
		Waitlist	0.01 (0.14)	0.01 (0.14)	0.00 (0.57)	0.00 (0.73)	0.00 (0.94)
	Phobic anxiety	COBMINDEX	0.11 (0.40)	0.04 (0.60)	0.07 (0.41)	**0.31 (0.008)**	**0.34 (0.02)**
		Waitlist	0.11 (0.13)	0.01 (0.90)	0.01 (0.84)	0.04 (0.55)	–0.01 (0.96)
6	HBI	COBMINDEX	–0.03 (0.42)	**–0.04 (0.02)**	0.00 (0.86)	0.02 (0.53)	–0.01 (0.79)
		Waitlist	0.02 (0.24)	0.03 (0.05)	0.01 (0.34)	0.01 (0.78)	0.04 (0.06)
	FACIT-F	COBMINDEX	–0.00 (0.80)	0.00 (0.34)	–0.01 (0.25)	0.00 (0.44)	0.00 (0.76)
		Waitlist	**0.01 (0.05)**	0.01 (0.08)	0.00 (0.52)	0.00 (0.56)	–0.01 (0.48)
	GSI	COBMINDEX	0.13 (0.41)	0.07 (0.37)	0.11 (0.24)	0.13 (0.22)	**0.53 (<0.001)**
		Waitlist	0.17 (0.07)	0.08 (0.29)	0.06 (0.40)	0.01 (0.96)	–0.05 (0.74)
7	HBI	COBMINDEX	–0.03 (0.38)	**–0.04 (0.03)**	0.00 (0.86)	0.00 (0.85)	0.00 (0.84)
		Waitlist	0.02 (0.18)	0.01 (0.31)	0.02 (0.20)	0.01 (0.76)	**0.05 (0.04)**
	FACIT-F	COBMINDEX	0.00 (0.94)	–0.01 (0.20)	–0.01 (0.17)	–0.01 (0.28)	–0.01 (0.32)
		Waitlist	0.01 (0.11)	**0.01 (0.01)**	0.00 (0.66)	0.00 (0.51)	–0.01 (0.29)
	Somatization	COBMINDEX	0.07 (0.62)	0.08 (0.30)	0.06 (0.43)	0.18 (0.05)	**0.34 (<0.001)**
		Waitlist	0.13 (0.10)	**0.13 (0.02)**	0.03 (0.62)	0.01 (0.95)	–0.06 (0.53)
8	HBI	COBMINDEX	–0.03 (0.38)	–0.04 (0.06)	0.01 (0.76)	0.00 (0.90)	–0.02 (0.74)
		Waitlist	0.00 (0.97)	0.02 (0.08)	0.01 (0.28)	0.00 (0.83)	–0.02 (0.28)
	FACIT-F	COBMINDEX	0.00 (0.90)	–0.01 (0.23)	–0.01 (0.15)	–0.01 (0.33)	–0.01 (0.53)
		Waitlist	**0.01 (0.002)**	0.01 (0.08)	0.00 (0.62)	0.00 (0.91)	0.01 (0.38)
	Depression	COBMINDEX	0.08 (0.38)	0.04 (0.47)	0.05 (0.45)	0.08 (0.28)	0.15 (0.44)
		Waitlist	**0.15 (0.001)**	0.07 (0.23)	0.04 (0.38)	0.08 (0.23)	**0.21 (0.02)**

Table 4. Continued

Model	Independent Variables at Baseline	Group	Regression Coefficient (*P*)				
			10%	25%	50%	75%	90%
9	HBI	COBMINDEX	–0.02 (0.55)	**–0.04 (0.05)**	–0.03 (0.13)	0.00 (0.91)	0.02 (0.58)
		Waitlist	0.02 (0.18)	0.02 (0.10)	0.02 (0.18)	0.01 (0.77)	0.04 (0.11)
	FACIT-F	COBMINDEX	0.00 (0.77)	0.00 (0.38)	–0.01 (0.11)	0.00 (0.51)	0.00 (0.60)
		Waitlist	**0.01 (0.02)**	**0.01 (0.02)**	0.00 (0.81)	0.00 (0.50)	–0.01 (0.46)
	Phobic anxiety	COBMINDEX	0.13 (0.41)	0.08 (0.35)	0.14 (0.06)	**0.25 (0.02)**	**0.34 (0.04)**
		Waitlist	**0.17 (0.03)**	0.09 (0.11)	0.02 (0.76)	0.00 (0.96)	–0.05 (0.70)

Only models with significant coefficients at more than the 10% quantile in the COBMINDEX or waitlist groups are shown. The bold-face values are statistically significant.
*Percentage change from baseline to 3 months.

Table 5. Predictors of Relative Change of SIBDQ Subscales in Patients With CD by Quantile Regression Analysis

Emotional*

Model	Independent Variables at Baseline	Group	Regression Coefficient (*P*)				
			10%	25%	50%	75%	90%
1	HBI	COBMINDEX	–0.01 (0.87)	0.01 (0.85)	0.01 (0.71)	0.03 (0.14)	0.01 (0.50)
		Waitlist	**–0.09 (0.004)**	–0.04 (0.11)	–0.01 (0.42)	–0.02 (0.31)	–0.02 (0.31)
	FMI	COBMINDEX	0.02 (0.32)	**0.02 (0.03)**	0.01 (0.13)	0.01 (0.11)	0.00 (0.94)
		Waitlist	–0.01 (0.59)	–0.01 (0.40)	0.00 (0.65)	0.00 (0.84)	–0.01 (0.39)
	FACIT-F	COBMINDEX	0.02 (0.11)	**0.02 (0.02)**	0.01 (0.32)	0.00 (0.78)	0.00 (0.68)
		Waitlist	0.01 (0.38)	0.00 (0.99)	0.00 (0.66)	0.00 (0.50)	–0.01 (0.33)
2	HBI	COBMINDEX	0.02 (0.64)	0.03 (0.08)	0.02 (0.36)	0.02 (0.43)	0.01 (0.76)
		Waitlist	**–0.05 (0.004)**	–0.03 (0.12)	–0.01 (0.46)	0.00 (0.99)	–0.02 (0.46)
	FMI	COBMINDEX	0.00 (0.72)	0.00 (0.98)	0.00 (0.71)	0.01 (0.38)	0.00 (0.83)
		Waitlist	**–0.02 (0.006)**	–0.01 (0.17)	0.00 (0.63)	–0.01 (0.23)	–0.01 (0.34)
	GSI	COBMINDEX	**–0.54 (0.002)**	**–0.61 (<0.001)**	**–0.31 (0.01)**	**–0.22 (0.04)**	–0.11 (0.21)
		Waitlist	**–0.20 (0.007)**	–0.15 (0.11)	–0.13 (0.07)	–0.09 (0.21)	0.01 (0.88)
3	HBI	COBMINDEX	0.03 (0.14)	–0.02 (0.39)	0.02 (0.42)	0.02 (0.42)	0.02 (0.60)
		Waitlist	–0.05 (0.06)	–0.04 (0.12)	–0.01 (0.61)	–0.01 (0.52)	–0.02 (0.49)
	FMI	COBMINDEX	**0.03 (0.001)**	0.01 (0.22)	0.01 (0.26)	**0.02 (0.02)**	0.01 (0.35)
		Waitlist	0.00 (0.84)	–0.01 (0.36)	0.00 (0.72)	0.00 (0.74)	–0.01 (0.31)
	Somatization	COBMINDEX	**–0.42 (<0.001)**	**–0.34 (0.002)**	**–0.26 (0.01)**	–0.14 (0.08)	–0.13 (0.28)
		Waitlist	–0.12 (0.15)	0.00 (0.99)	–0.06 (0.25)	0.01 (0.92)	0.01 (0.86)
4	HBI	COBMINDEX	–0.01 (0.73)	–0.01 (0.85)	0.02 (0.55)	0.02 (0.31)	0.01 (0.69)
		Waitlist	**–0.07 (<0.001)**	–0.04 (0.08)	–0.02 (0.35)	0.01 (0.39)	0.00 (0.90)
	FMI	COBMINDEX	0.01 (0.30)	0.02 (0.08)	0.01 (0.13)	0.01 (0.22)	0.00 (0.96)
		Waitlist	–0.01 (0.16)	–0.01 (0.12)	–0.01 (0.29)	–0.01 (0.14)	**–0.01 (0.04)**
	Depression	COBMINDEX	**–0.31 (0.006)**	**–0.31 (0.002)**	–0.16 (0.05)	–0.06 (0.30)	–0.04 (0.59)
		Waitlist	**–0.18 (<0.001)**	–0.13 (0.08)	**–0.15 (0.03)**	–0.09 (0.13)	**–0.12 (0.02)**
5	HBI	COBMINDEX	–0.03 (0.59)	0.00 (0.87)	0.02 (0.42)	0.01 (0.48)	0.01 (0.50)
		Waitlist	**–0.06 (<0.001)**	–0.04 (0.12)	–0.01 (0.57)	0.01 (0.64)	–0.02 (0.49)
	FMI	COBMINDEX	0.03 (0.14)	0.02 (0.12)	0.00 (0.98)	0.01 (0.15)	0.00 (0.96)
		Waitlist	–0.01 (0.33)	–0.01 (0.37)	0.00 (0.59)	–0.01 (0.08)	–0.01 (0.33)
	Phobic anxiety	COBMINDEX	–0.17 (0.46)	**–0.31 (0.02)**	**–0.27 (0.03)**	–0.09 (0.24)	–0.08 (0.36)
		Waitlist	**–0.25 (<0.001)**	0.00 (0.99)	–0.11 (0.12)	–0.12 (0.08)	0.02 (0.85)
6	HBI	COBMINDEX	0.02 (0.62)	0.03 (0.09)	0.02 (0.49)	0.02 (0.43)	0.01 (0.72)
		Waitlist	–0.04 (0.13)	–0.03 (0.07)	–0.02 (0.25)	–0.01 (0.49)	0.00 (0.93)
	FACIT-F	COBMINDEX	0.00 (0.62)	0.00 (0.98)	0.00 (0.71)	0.00 (0.67)	0.00 (0.84)
		Waitlist	–0.02 (0.07)	**–0.02 (0.003)**	–0.01 (0.06)	–0.01 (0.17)	**–0.02 (<0.001)**
	GSI	COBMINDEX	**–0.51 (0.007)**	**–0.61 (<0.001)**	**–0.31 (0.02)**	–0.20 (0.05)	–0.09 (0.36)
		Waitlist	–0.33 (0.06)	**–0.37 (0.001)**	–0.19 (0.05)	–0.15 (0.20)	**–0.24 (0.001)**

Table 5. Continued

Model	Independent Variables at Baseline	Group	Regression Coefficient (*P*)				
			10%	25%	50%	75%	90%
Emotional*							
7	HBI	COBMINDEX	0.02 (0.65)	0.00 (0.92)	0.00 (0.94)	0.05 (0.09)	0.01 (0.56)
		Waitlist	–0.05 (0.09)	–0.04 (0.10)	–0.01 (0.47)	–0.02 (0.20)	–0.03 (0.13)
	FACIT-F	COBMINDEX	**0.03 (0.03)**	0.01 (0.33)	0.01 (0.39)	0.00 (0.81)	0.00 (0.70)
		Waitlist	0.00 (0.84)	–0.01 (0.47)	–0.01 (0.27)	–0.01 (0.30)	–0.01 (0.28)
	Somatization	COBMINDEX	–0.12 (0.56)	–0.29 (0.06)	–0.21 (0.05)	–0.18 (0.09)	–0.02 (0.82)
		Waitlist	–0.13 (0.31)	–0.07 (0.52)	–0.10 (0.16)	–0.06 (0.47)	–0.02 (0.81)
8	HBI	COBMINDEX	0.00 (1.00)	0.02 (0.51)	0.01 (0.67)	0.02 (0.30)	0.01 (0.75)
		Waitlist	**–0.07 (0.003)**	**–0.06 (0.005)**	–0.02 (0.13)	0.00 (0.93)	0.00 (0.81)
	FACIT-F	COBMINDEX	**0.01 (0.01)**	**0.02 (0.02)**	0.00 (0.45)	0.00 (0.58)	0.00 (0.70)
		Waitlist	**–0.02 (0.01)**	–0.01 (0.18)	–0.01 (0.17)	–0.01 (0.07)	–0.01 (0.07)
	Depression	COBMINDEX	**–0.30 (<0.001)**	**–0.28 (0.001)**	–0.16 (0.06)	–0.08 (0.19)	–0.05 (0.47)
		Waitlist	**–0.28 (0.003)**	**–0.19 (0.03)**	**–0.15 (0.01)**	**–0.13 (0.04)**	–0.14 (0.06)
9	HBI	COBMINDEX	0.00 (0.97)	–0.01 (0.80)	0.02 (0.39)	0.02 (0.33)	0.01 (0.50)
		Waitlist	**–0.07 (0.003)**	–0.02 (0.35)	–0.01 (0.44)	0.00 (0.77)	–0.02 (0.37)
	FACIT-F	COBMINDEX	0.03 (0.08)	0.01 (0.11)	0.01 (0.15)	0.00 (0.55)	0.00 (0.87)
		Waitlist	0.00 (0.90)	–0.01 (0.16)	–0.01 (0.09)	–0.01 (0.11)	–0.01 (0.26)
	Phobic anxiety	COBMINDEX	–0.20 (0.44)	**–0.37 (0.008)**	**–0.23 (0.03)**	–0.10 (0.21)	–0.08 (0.29)
		Waitlist	–0.17 (0.12)	–0.18 (0.16)	–0.15 (0.07)	**–0.18 (0.04)**	0.01 (0.90)
Systemic							
1	HBI	COBMINDEX	0.12 (0.77)	0.08 (0.22)	0.05 (0.10)	**0.08 (0.04)**	0.03 (0.31)
		Waitlist	0.00 (0.98)	0.00 (0.94)	–0.01 (0.50)	–0.01 (0.67)	**0.04 (0.005)**
	FMI	COBMINDEX	–0.03 (0.85)	0.00 (0.89)	0.00 (0.67)	0.00 (0.83)	**0.02 (0.04)**
		Waitlist	–0.01 (0.64)	0.00 (0.86)	0.00 (0.70)	0.00 (0.60)	–0.01 (0.07)
	FACIT-F	COBMINDEX	0.02 (0.84)	0.01 (0.32)	0.00 (0.51)	0.01 (0.27)	0.00 (0.84)
		Waitlist	0.02 (0.16)	0.00 (0.88)	0.00 (0.59)	0.00 (0.86)	0.00 (0.80)
2	HBI	COBMINDEX	0.13 (0.75)	0.07 (0.27)	0.04 (0.27)	0.06 (0.14)	0.03 (0.28)
		Waitlist	0.02 (0.80)	–0.03 (0.38)	–0.02 (0.36)	0.01 (0.71)	**0.05 (<0.001)**
	FMI	COBMINDEX	–0.02 (0.87)	0.01 (0.68)	0.01 (0.54)	0.00 (0.95)	0.02 (0.05)
		Waitlist	0.00 (0.92)	0.00 (0.75)	0.00 (0.83)	–0.01 (0.15)	**–0.01 (0.01)**
	GSI	COBMINDEX	–0.21 (0.91)	–0.12 (0.64)	0.04 (0.77)	–0.17 (0.38)	0.00 (0.99)
		Waitlist	–0.27 (0.42)	0.08 (0.54)	–0.06 (0.52)	–0.09 (0.24)	–0.10 (0.05)
3	HBI	COBMINDEX	0.05 (0.90)	**0.10 (0.03)**	0.06 (0.10)	0.06 (0.10)	0.01 (0.83)
		Waitlist	–0.01 (0.94)	–0.02 (0.50)	–0.02 (0.27)	–0.01 (0.64)	**0.05 (<0.001)**
	FMI	COBMINDEX	–0.05 (0.70)	0.01 (0.40)	0.01 (0.31)	0.00 (0.81)	0.02 (0.16)
		Waitlist	–0.01 (0.86)	–0.01 (0.39)	0.00 (0.57)	0.00 (0.60)	**–0.01 (0.02)**
	Somatization	COBMINDEX	–0.42 (0.76)	–0.18 (0.28)	–0.19 (0.14)	**–0.33 (0.01)**	–0.19 (0.24)
		Waitlist	–0.18 (0.47)	0.11 (0.30)	0.13 (0.05)	–0.01 (0.89)	–0.05 (0.16)
4	HBI	COBMINDEX	0.04 (0.92)	0.06 (0.35)	0.05 (0.19)	0.07 (0.08)	0.03 (0.28)
		Waitlist	0.05 (0.44)	0.02 (0.64)	–0.02 (0.31)	0.00 (1.00)	**0.06 (<0.001)**
	FMI	COBMINDEX	0.00 (0.98)	0.01 (0.53)	0.01 (0.69)	0.00 (0.96)	**0.02 (0.04)**
		Waitlist	0.00 (0.87)	–0.01 (0.51)	–0.01 (0.21)	–0.02 (0.07)	**–0.02 (0.003)**
	Depression	COBMINDEX	0.29 (0.82)	–0.04 (0.82)	0.03 (0.76)	–0.09 (0.47)	0.00 (0.99)
		Waitlist	-0.36 (0.11)	-0.15 (0.24)	**-0.14 (0.03)**	**-0.19 (0.02)**	**-0.09 (0.03)**
5	HBI	COBMINDEX	0.00 (0.99)	0.05 (0.33)	0.04 (0.14)	0.05 (0.09)	0.03 (0.40)
		Waitlist	0.03 (0.68)	–0.02 (0.42)	–0.03 (0.12)	–0.01 (0.60)	**0.05 (0.001)**
	FMI	COBMINDEX	–0.03 (0.82)	0.01 (0.64)	0.00 (0.77)	**0.03 (0.01)**	**0.03 (0.009)**
		Waitlist	0.00 (0.88)	0.00 (0.77)	0.00 (0.90)	0.00 (0.67)	**–0.01 (0.04)**
	Phobic anxiety	COBMINDEX	–0.01 (0.99)	–0.16 (0.51)	–0.06 (0.63)	0.12 (0.35)	0.16 (0.23)
		Waitlist	–0.30 (0.31)	0.14 (0.21)	0.08 (0.28)	0.00 (0.98)	0.01 (0.90)

Table 5. Continued

Model	Independent Variables at Baseline	Group	Regression Coefficient (*P*)				
			10%	25%	50%	75%	90%
Systemic							
6	HBI	COBMINDEX	0.05 (0.91)	0.06 (0.30)	0.06 (0.09)	0.08 (0.05)	0.03 (0.55)
		Waitlist	–0.01 (0.92)	–0.01 (0.70)	–0.01 (0.57)	–0.01 (0.57)	**0.04 (0.04)**
	FACIT-F	COBMINDEX	0.01 (0.93)	0.02 (0.25)	0.01 (0.41)	0.01 (0.45)	0.00 (0.82)
		Waitlist	0.01 (0.78)	0.00 (0.89)	0.00 (0.73)	–0.01 (0.15)	–0.01 (0.05)
	GSI	COBMINDEX	0.25 (0.93)	0.09 (0.74)	0.06 (0.66)	–0.07 (0.69)	–0.11 (0.58)
		Waitlist	–0.13 (0.74)	0.07 (0.70)	0.03 (0.80)	–0.12 (0.31)	–0.21 (0.05)
7	HBI	COBMINDEX	0.16 (0.72)	0.09 (0.12)	**0.06 (0.04)**	0.00 (0.11)	–0.02 (0.60)
		Waitlist	–0.03 (0.58)	–0.02 (0.52)	–0.01 (0.49)	–0.01 (0.55)	0.03 (0.07)
	FACIT-F	COBMINDEX	0.00 (0.99)	0.01 (0.63)	0.01 (0.41)	0.00 (0.86)	–0.01 (0.43)
		Waitlist	0.01 (0.40)	0.00 (0.93)	0.00 (0.58)	–0.01 (0.40)	–0.01 (0.06)
	Somatization	COBMINDEX	–0.33 (0.85)	–0.15 (0.49)	–0.09 (0.41)	–0.29 (0.07)	**–0.41 (0.01)**
		Waitlist	0.01 (0.98)	0.09 (0.47)	0.12 (0.17)	–0.04 (0.57)	–0.11 (0.10)
8	HBI	COBMINDEX	0.07 (0.87)	0.07 (0.28)	0.06 (0.08)	0.08 (0.05)	0.02 (0.59)
		Waitlist	**0.09 (0.03)**	0.00 (0.92)	–0.01 (0.65)	0.01 (0.76)	0.03 (0.20)
	FACIT-F	COBMINDEX	0.02 (0.80)	0.02 (0.25)	0.01 (0.42)	0.01 (0.37)	0.00 (0.89)
		Waitlist	–0.02 (0.13)	–0.01 (0.37)	0.00 (0.76)	–0.01 (0.22)	–0.01 (0.05)
	Depression	COBMINDEX	0.37 (0.76)	0.06 (0.73)	0.04 (0.68)	–0.03 (0.79)	–0.09 (0.52)
		Waitlist	**–0.62 (0.001)**	–0.24 (0.08)	–0.09 (0.30)	**–0.17 (0.03)**	**–0.25 (0.004)**
9	HBI	COBMINDEX	0.06 (0.89)	0.07 (0.23)	0.05 (0.10)	0.06 (0.13)	0.05 (0.45)
		Waitlist	–0.03 (0.45)	–0.01 (0.82)	–0.03 (0.23)	0.00 (0.85)	0.01 (0.84)
	FACIT-F	COBMINDEX	–0.02 (0.87)	0.01 (0.32)	0.01 (0.46)	0.01 (0.39)	0.01 (0.69)
		Waitlist	0.02 (0.22)	0.01 (0.26)	0.01 (0.33)	0.00 (0.70)	0.00 (0.73)
	Phobic anxiety	COBMINDEX	–0.03 (0.99)	0.00 (1.00)	0.04 (0.77)	0.20 (0.18)	0.07 (0.76)
		Waitlist	0.19 (0.36)	0.23 (0.11)	0.17 (0.14)	0.05 (0.59)	0.00 (0.99)
Bowel							
1	HBI	COBMINDEX	–0.04 (0.16)	0.01 (0.82)	0.00 (0.78)	0.01 (0.75)	0.01 (0.79)
		Waitlist	–0.04 (0.25)	–0.01 (0.60)	–0.02 (0.16)	–0.01 (0.68)	0.02 (0.28)
	FMI	COBMINDEX	0.01 (0.14)	0.01 (0.23)	0.01 (0.07)	0.01 (0.19)	0.02 (0.08)
		Waitlist	–0.01 (0.64)	0.00 (0.90)	0.00 (0.42)	0.00 (0.53)	–0.01 (0.50)
	FACIT-F	COBMINDEX	–0.01 (0.42)	–0.01 (0.11)	0.00 (0.80)	0.00 (0.92)	0.00 (0.74)
		Waitlist	0.00 (0.63)	0.00 (0.62)	0.00 (0.96)	0.00 (0.52)	0.00 (0.86)
2	HBI	COBMINDEX	–0.02 (0.36)	–0.02 (0.54)	0.00 (0.86)	0.01 (0.70)	0.02 (0.52)
		Waitlist	–0.04 (0.23)	–0.02 (0.36)	–0.02 (0.16)	0.00 (0.81)	0.03 (0.11)
	FMI	COBMINDEX	0.01 (0.29)	0.01 (0.41)	**0.01 (0.02)**	0.02 (0.13)	**0.03 (0.02)**
		Waitlist	–0.01 (0.50)	0.00 (0.88)	0.00 (0.40)	0.00 (0.59)	–0.01 (0.30)
	GSI	COBMINDEX	–0.07 (0.55)	0.08 (0.54)	0.08 (0.25)	0.05 (0.71)	0.15 (0.32)
		Waitlist	–0.15 (0.25)	–0.02 (0.82)	0.01 (0.82)	0.04 (0.50)	–0.07 (0.38)
3	HBI	COBMINDEX	–0.03 (0.23)	–0.01 (0.72)	0.00 (0.94)	0.01 (0.71)	0.02 (0.61)
		Waitlist	–0.02 (0.34)	–0.02 (0.34)	–0.02 (0.21)	–0.01 (0.67)	0.03 (0.18)
	FMI	COBMINDEX	0.01 (0.29)	0.00 (0.73)	0.01 (0.08)	0.01 (0.15)	0.02 (0.08)
		Waitlist	0.00 (0.77)	0.00 (0.86)	0.00 (0.97)	0.00 (0.39)	–0.01 (0.39)
	Somatization	COBMINDEX	–0.10 (0.25)	–0.07 (0.53)	0.03 (0.66)	0.01 (0.92)	0.11 (0.46)
		Waitlist	–0.10 (0.24)	–0.01 (0.82)	–0.04 (0.35)	0.03 (0.50)	–0.04 (0.55)
4	HBI	COBMINDEX	–0.03 (0.43)	–0.01 (0.62)	0.00 (0.88)	0.01 (0.62)	0.03 (0.28)
		Waitlist	–0.04 (0.08)	–0.01 (0.47)	–0.02 (0.17)	–0.01 (0.72)	0.03 (0.08)
	FMI	COBMINDEX	0.01 (0.31)	0.01 (0.29)	0.01 (0.07)	0.01 (0.18)	**0.03 (0.001)**
		Waitlist	–0.02 (0.16)	0.00 (0.95)	0.00 (0.43)	0.00 (0.55)	–0.01 (0.29)
	Depression	COBMINDEX	0.02 (0.88)	0.06 (0.52)	0.03 (0.53)	0.01 (0.93)	0.12 (0.10)
		Waitlist	–0.15 (0.08)	–0.02 (0.73)	0.01 (0.79)	0.03 (0.57)	–0.04 (0.45)

Table 5. Continued

Model	Independent Variables at Baseline	Group	Regression Coefficient (*P*)				
			10%	25%	50%	75%	90%
Bowel							
5	HBI	COBMINDEX	–0.05 (0.10)	0.02 (0.55)	0.00 (0.91)	0.01 (0.77)	0.01 (0.82)
		Waitlist	–0.01 (0.48)	–0.02 (0.31)	–0.02 (0.17)	0.00 (0.80)	0.03 (0.11)
	FMI	COBMINDEX	0.00 (0.78)	0.01 (0.39)	0.01 (0.07)	0.01 (0.15)	0.02 (0.12)
		Waitlist	0.00 (0.93)	0.00 (0.84)	0.00 (0.42)	–0.01 (0.30)	–0.01 (0.29)
	Phobic anxiety	COBMINDEX	–0.13 (0.31)	–0.16 (0.18)	0.07 (0.32)	0.05 (0.68)	0.02 (0.93)
		Waitlist	–0.12 (0.07)	–0.01 (0.83)	0.01 (0.83)	0.03 (0.64)	–0.06 (0.41)
6	HBI	COBMINDEX	**–0.05 (0.04)**	0.03 (0.38)	0.00 (0.87)	0.01 (0.69)	0.02 (0.72)
		Waitlist	–0.04 (0.11)	–0.02 (0.45)	–0.01 (0.25)	0.00 (0.79)	0.02 (0.31)
	FACIT-F	COBMINDEX	–0.01 (0.32)	–0.01 (0.31)	0.00 (0.99)	0.00 (0.70)	–0.01 (0.74)
		Waitlist	–0.01 (0.60)	0.00 (0.65)	0.00 (0.58)	–0.01 (0.17)	–0.01 (0.32)
	GSI	COBMINDEX	–0.18 (0.09)	–0.13 (0.29)	–0.01 (0.89)	–0.10 (0.41)	–0.23 (0.44)
		Waitlist	–0.18 (0.26)	0.01 (0.91)	0.01 (0.88)	–0.07 (0.37)	–0.10 (0.38)
7	HBI	COBMINDEX	–0.04 (0.11)	0.02 (0.42)	0.00 (0.87)	0.02 (0.49)	0.04 (0.37)
		Waitlist	–0.03 (0.31)	–0.01 (0.47)	–0.01 (0.27)	0.00 (0.74)	0.02 (0.52)
	FACIT-F	COBMINDEX	–0.01 (0.36)	–0.01 (0.41)	0.00 (0.89)	0.00 (0.94)	0.00 (0.99)
		Waitlist	0.00 (0.81)	0.00 (0.71)	0.00 (0.64)	**–0.01 (0.01)**	–0.01 (0.26)
	Somatization	COBMINDEX	–0.11 (0.28)	–0.12 (0.31)	0.00 (0.96)	–0.09 (0.42)	0.17 (0.39)
		Waitlist	–0.10 (0.34)	–0.01 (0.95)	–0.07 (0.21)	**–0.13 (0.02)**	–0.14 (0.23)
8	HBI	COBMINDEX	–0.02 (0.52)	–0.02 (0.60)	0.00 (0.88)	0.02 (0.46)	0.03 (0.62)
		Waitlist	–0.04 (0.06)	–0.01 (0.54)	–0.01 (0.26)	–0.01 (0.73)	0.02 (0.22)
	FACIT-F	COBMINDEX	0.00 (0.96)	0.00 (0.63)	0.00 (0.98)	0.00 (0.84)	–0.01 (0.56)
		Waitlist	0.00 (0.73)	0.00 (0.77)	0.00 (0.49)	0.00 (0.56)	–0.01 (0.30)
	Depression	COBMINDEX	–0.07 (0.51)	0.03 (0.70)	–0.01 (0.89)	–0.03 (0.72)	–0.10 (0.51)
		Waitlist	–0.12 (0.19)	–0.02 (0.82)	0.01 (0.79)	0.01 (0.92)	–0.09 (0.23)
9	HBI	COBMINDEX	**–0.07 (0.01)**	0.02 (0.33)	0.01 (0.62)	0.02 (0.39)	0.04 (0.52)
		Waitlist	0.00 (0.74)	–0.01 (0.46)	–0.01 (0.33)	–0.01 (0.52)	0.03 (0.21)
	FACIT-F	COBMINDEX	–0.01 (0.41)	**–0.01 (0.03)**	0.00 (0.91)	0.00 (0.86)	0.00 (0.76)
		Waitlist	0.00 (0.35)	0.00 (0.72)	0.00 (0.42)	–0.01 (0.19)	–0.01 (0.36)
	Phobic anxiety	COBMINDEX	–0.18 (0.10)	**–0.23 (0.006)**	–0.08 (0.37)	–0.05 (0.64)	–0.02 (0.91)
		Waitlist	**–0.20 (0.008)**	–0.01 (0.95)	0.01 (0.81)	–0.04 (0.55)	–0.12 (0.24)
Social							
1	HBI	COBMINDEX	0.07 (0.59)	–0.01 (0.91)	0.00 (0.98)	0.04 (0.11)	0.01 (0.87)
		Waitlist	–0.05 (0.62)	–0.02 (0.62)	0.00 (0.89)	–0.02 (0.43)	0.01 (0.54)
	FMI	COBMINDEX	0.04 (0.38)	0.01 (0.75)	**0.02 (0.02)**	0.01 (0.28)	0.02 (0.17)
		Waitlist	0.01 (0.74)	–0.01 (0.57)	–0.01 (0.59)	0.00 (0.86)	0.01 (0.50)
	FACIT-F	COBMINDEX	**0.06 (0.04)**	0.02 (0.53)	0.00 (0.53)	0.01 (0.24)	0.00 (0.87)
		Waitlist	0.01 (0.62)	0.01 (0.67)	0.00 (0.74)	–0.01 (0.24)	–0.01 (0.11)
2	HBI	COBMINDEX	0.05 (0.59)	–0.02 (0.84)	–0.03 (0.32)	0.03 (0.10)	0.00 (0.96)
		Waitlist	–0.11 (0.26)	–0.04 (0.39)	0.00 (0.91)	0.02 (0.35)	0.01 (0.76)
	FMI	COBMINDEX	0.01 (0.77)	0.01 (0.84)	0.02 (0.05)	0.01 (0.44)	0.02 (0.24)
		Waitlist	0.00 (0.91)	–0.01 (0.69)	–0.01 (0.61)	–0.01 (0.16)	–0.01 (0.54)
	GSI	COBMINDEX	**–1.48 (0.001)**	–0.24 (0.65)	–0.02 (0.85)	–0.11 (0.22)	0.01 (0.96)
		Waitlist	0.25 (0.53)	–0.02 (0.92)	–0.07 (0.48)	–0.14 (0.10)	–0.01 (0.94)
3	HBI	COBMINDEX	0.02 (0.93)	–0.04 (0.58)	–0.02 (0.49)	0.04 (0.06)	0.00 (0.95)
		Waitlist	–0.07 (0.32)	–0.04 (0.39)	0.00 (0.97)	0.01 (0.71)	0.01 (0.74)
	FMI	COBMINDEX	0.02 (0.78)	0.01 (0.71)	**0.02 (0.03)**	0.00 (0.52)	0.02 (0.17)
		Waitlist	0.02 (0.61)	–0.01 (0.67)	0.00 (0.68)	–0.01 (0.51)	–0.01 (0.53)
	Somatization	COBMINDEX	–0.71 (0.32)	–0.44 (0.13)	–0.05 (0.66)	–0.13 (0.09)	0.01 (0.95)
		Waitlist	0.20 (0.41)	–0.01 (0.92)	–0.06 (0.41)	–0.12 (0.14)	–0.01 (0.95)

Table 5. Continued

Social							
Model	Independent Variables at Baseline	Group	Regression Coefficient (*P*)				
			10%	25%	50%	75%	90%
4	HBI	COBMINDEX	0.05 (0.69)	–0.02 (0.82)	–0.02 (0.47)	0.03 (0.15)	0.01 (0.86)
		Waitlist	–0.07 (0.44)	–0.05 (0.20)	0.00 (0.96)	0.01 (0.71)	0.01 (0.73)
	FMI	COBMINDEX	0.02 (0.68)	0.01 (0.83)	0.02 (0.06)	0.00 (0.47)	0.02 (0.19)
		Waitlist	0.00 (0.96)	–0.01 (0.76)	–0.01 (0.55)	–0.02 (0.06)	–0.01 (0.34)
	Depression	COBMINDEX	**–0.99 (0.02)**	–0.18 (0.59)	–0.05 (0.61)	–0.09 (0.14)	0.01 (0.94)
		Waitlist	–0.15 (0.62)	0.05 (0.75)	–0.03 (0.74)	–0.09 (0.23)	–0.13 (0.18)
5	HBI	COBMINDEX	–0.07 (0.68)	–0.04 (0.65)	–0.01 (0.68)	0.02 (0.43)	0.00 (1.00)
		Waitlist	–0.11 (0.14)	–0.04 (0.42)	0.00 (0.97)	0.01 (0.86)	0.02 (0.58)
	FMI	COBMINDEX	0.00 (0.98)	0.00 (0.96)	0.01 (0.22)	0.01 (0.17)	0.02 (0.25)
		Waitlist	0.01 (0.87)	–0.01 (0.69)	–0.01 (0.57)	0.00 (0.96)	–0.01 (0.51)
	Phobic anxiety	COBMINDEX	–1.06 (0.15)	–0.40 (0.30)	–0.15 (0.19)	–0.20 (0.05)	–0.22 (0.23)
		Waitlist	0.16 (0.59)	–0.02 (0.92)	–0.08 (0.35)	–0.06 (0.59)	–0.07 (0.60)
6	HBI	COBMINDEX	0.05 (0.63)	–0.05 (0.64)	0.00 (0.96)	0.03 (0.09)	0.02 (0.74)
		Waitlist	–0.07 (0.35)	0.00 (0.96)	0.00 (0.99)	0.00 (0.95)	–0.01 (0.75)
	FACIT-F	COBMINDEX	0.00 (0.88)	0.01 (0.70)	0.01 (0.29)	0.00 (0.64)	0.00 (0.86)
		Waitlist	0.02 (0.53)	0.02 (0.41)	0.00 (0.77)	**–0.02 (0.03)**	–0.02 (0.14)
	GSI	COBMINDEX	**–1.50 (0.001)**	–0.31 (0.54)	–0.14 (0.29)	–0.12 (0.20)	–0.13 (0.67)
		Waitlist	0.30 (0.50)	0.18 (0.51)	–0.07 (0.60)	–0.19 (0.07)	–0.30 (0.11)
7	HBI	COBMINDEX	–0.05 (0.78)	–0.03 (0.67)	0.01 (0.75)	0.04 (0.07)	0.03 (0.73)
		Waitlist	–0.00 (0.96)	–0.00 (0.95)	–0.00 (0.94)	0.01 (0.54)	0.01 (0.85)
	FACIT-F	COBMINDEX	0.02 (0.55)	0.01 (0.66)	0.01 (0.30)	0.00 (0.72)	0.00 (0.92)
		Waitlist	0.03 (0.21)	0.02 (0.20)	–0.01 (0.40)	**–0.01 (0.04)**	–0.01 (0.32)
	Somatization	COBMINDEX	–0.66 (0.33)	–0.45 (0.15)	–0.17 (0.14)	–0.13 (0.12)	–0.12 (0.71)
		Waitlist	0.19 (0.56)	0.20 (0.27)	–0.12 (0.27)	–0.16 (0.06)	–0.05 (0.64)
8	HBI	COBMINDEX	0.07 (0.54)	–0.01 (0.89)	–0.01 (0.82)	0.03 (0.12)	0.02 (0.79)
		Waitlist	–0.05 (0.59)	–0.03 (0.49)	0.00 (1.00)	–0.01 (0.60)	–0.01 (0.71)
	FACIT-F	COBMINDEX	0.01 (0.62)	0.01 (0.53)	0.01 (0.27)	0.00 (0.53)	0.00 (0.82)
		Waitlist	0.01 (0.84)	0.01 (0.39)	0.00 (1.00)	–0.01 (0.09)	–0.01 (0.14)
	Depression	COBMINDEX	**–1.01 (0.003)**	–0.27 (0.35)	–0.06 (0.47)	–0.09 (0.14)	–0.08 (0.67)
		Waitlist	–0.12 (0.77)	0.11 (0.48)	0.00 (1.00)	–0.10 (0.16)	–0.13 (0.24)
9	HBI	COBMINDEX	0.00 (0.97)	–0.06 (0.49)	0.02 (0.59)	0.03 (0.12)	0.02 (0.75)
		Waitlist	–0.07 (0.24)	–0.01 (0.73)	0.00 (0.98)	–0.01 (0.50)	0.02 (0.50)
	FACIT-F	COBMINDEX	0.03 (0.30)	0.01 (0.58)	0.00 (0.48)	0.01 (0.28)	0.00 (0.77)
		Waitlist	**0.04 (0.03)**	0.02 (0.14)	–0.01 (0.52)	**–0.02 (0.008)**	–0.01 (0.18)
	Phobic anxiety	COBMINDEX	**–1.07 (0.03)**	–0.30 (0.38)	–0.22 (0.07)	**–0.18 (0.04)**	–0.16 (0.53)
		Waitlist	0.45 (0.12)	0.25 (0.23)	–0.14 (0.23)	**–0.25 (0.009)**	–0.14 (0.26)

The bold-face values are statistically significant.
*Percentage change from baseline to 3 months.

3-point reduction of the HBI in COBMINDEX patients was facilitated by the psychological intervention. Notably, responses to 4 of the HBI questions (extraintestinal complications excluded) are indeed partially subjective and may be affected by the patient's psychological condition. Unlike the HBI, the CRP and calprotectin measures decreased significantly in COBMINDEX patients but not in waitlist patients. It is tempting to speculate whether these measures, like the HBI, could be affected by the psychological state of the patient. It has been shown that psychological distress in children and adults is associated with elevated CRP levels.[42] However, we are not aware of any study showing a relationship between calprotectin levels and psychological distress. Note that there is an increasing body of evidence showing the complex interaction between the hypothalamic-pituitary axis and the autonomic nervous system, and bowel permeability, the microbiome, and immune regulation in CD that can significantly impact the disease process.[43, 44] Data from our patients regarding these factors will be reported elsewhere.

We performed quantile regression analysis to determine whether baseline variables could be predictors of relative change of the SIBDQ and its 4 domains. This analysis resulted in the important finding that patients exhibiting a lower quality of life, more psychological symptoms, and more fatigue at

enrollment would experience a greater increase in quality of life after COBMINDEX. Rather astonishingly, the HBI disease activity score was seldom a predictor of relative change in the SIBDQ in either COBMINDEX or waitlist patients, and then usually with a coefficient of –0.04. Baseline mindfulness disposition (FMI) was a strong predictor of relative change in the SIBDQ, particularly in COBMINDEX patients. The psychological distress scales GSI, somatization, and phobic anxiety were all predictors of relative change in the SIBDQ in COBMINDEX patients in the 75% and 90% quantiles (coefficients ranging from 0.32 to 0.53). Depression was a significant predictor in the 75% quantile in COBMINDEX patients. Notably, fatigue was not a predictor in COBMINDEX patients, despite the large increase in the FACIT-F score observed over the study period and the significant negative correlation with the relative change in the SIBDQ. This result was unexpected. In a cohort of largely remittent patients with CD, the FACIT-F score was inversely related to quality of life but did not predict quality of life on multiple regression analysis, echoing our findings.[45] This relationship needs more investigation.

Mindfulness is a core psychological disposition that enables patients to be aware of stressful moment-to-moment events without panicking and reacting ineffectively. Mindfulness-based practice has been applied to several medical conditions, but its use in CD is limited. Our perusal of the literature has yielded a mixed impression of its success and prompted the present study. But mindfulness-based stress reduction alone is insufficient, and we combined it with cognitive-behavioral techniques to achieve maximum distress reduction and to enhance patients' mindfulness disposition. This factor likely explains why the psychological outcomes were so different between the COBMINDEX and waitlist groups. Previous studies of cognitive-behavioral and/or mindfulness intervention on quality of life in patients with CD (and ulcerative colitis) had reported mixed outcomes, as noted previously.[22-30] Surprisingly, baseline anxiety, unlike phobic anxiety, did not predict the relative change of the SIBDQ after COBMINDEX. Phobic anxiety is a condition characterized by excessive fear of a specific threatening situation, whereas anxiety is a feeling of unease about an event of uncertain outcome. A recent mental health study of patients with CD found similar scores for anxiety and phobia.[46] Further investigation is needed.

Important strengths of our study include the use of online psychological teaching, which afforded patients flexibility in scheduling appointments with the social worker without interrupting work and social pursuits. We safeguarded patients' privacy in 2 ways: by conducting all sessions with the same social worker and by obviating the need to attend multipatient sessions. The requirement of self-reported, twice-daily home performance of learned skills is a unique strength. Moreover, patients were recruited at several hospitals and via social media, making for a community-based cohort rather than one that was referral hospital–based.

A further important strength of our study is the generalization of the method. Online communication has become increasingly important as more people worldwide develop basic skills in communication technology. In the current COVID-19 pandemic, where social distancing is an essential policy in many countries to decrease the spread of the disease, online interventions have become increasingly common, including even consultations with physicians and other professionals. Our intervention has external validity as a model that can be adopted by social workers and psychologists who are teaching psychological distress reduction in a variety of medical and nonmedical conditions and brings their skills to people who may be living at great distances from tertiary medical centers where these therapeutic methods are developed. Intuitively, we would also expect that COBMINDEX is cost-saving for providers and patients, but this hypothesis would have to be determined in an appropriately designed study.

We note several limitations. First, our cohort was derived from 1 ethnic group in 1 country, with a preponderance of well-educated, working, nonsmoking patients of moderate economic status. This designation may not be representative of other populations. Second, the number of variables in the regression models was restricted by the moderate size of the cohort. For this reason, we did not enter COBMINDEX (yes/no) as an independent variable. Third, of 139 patients entering the trial, 15 COBMINDEX and 8 waitlist patients dropped out. Some patients found attendance at all sessions too demanding; others had difficulty completing daily practice. Other investigators too have reported large dropout rates or noncompliance with psychological interventions.[28, 47] Fourth, there may have been some element of placebo effect on the study outcome measures in the waitlist group, resulting from periodic telephone contact with the study workers over 3 months. However, an equal placebo effect would likely have occurred in the COBMINDEX patients from their contacts with the study team. We believe that the results of the study were not materially affected by any placebo effect.

Conclusions

Our method of cognitive-behavioral and mindfulness-based stress reduction was shown to increase the quality of life in patients with CD and decrease their psychological symptoms and fatigue. Patients with the poorest quality of life and greatest psychological symptoms and fatigue at enrollment actually had the best response to COBMINDEX. Longer follow-up will show whether these benefits are sustained. We recommend performing a trial of COBMINDEX instruction in other chronic diseases with similar psychological symptoms because we believe that this method is not specific to CD but would address psychological distress in a variety of medical conditions. Furthermore, we intend to investigate a variety of hormones and cytokines in blood samples from patients before and after COBMINDEX instruction to determine the mechanisms the improvements in CRP and calprotectin.

Acknowledgments

We acknowledge the social workers Noa Szulc, MSW; Adi Vilensky, MSW; Milca Hanukoglu, MSW; Helen Israel, MSW; Shahar Michael, MSW; Naama Peled-Ironi, MSW; Zohar Zigner-Peled, MSW; Oneg Kabizon-Perry, MSW; Shem Tsruya, MSW; Paula Perpinial, MSW; Meital Simchi, PhD; May Bujanover, MSW; Zehavit Shpitzer, MSW; Rebeka Sindresky, MSW; Amital Cohen, MA; and Roi Zur, MA; and the psychologist Noa Geva, MA, who all taught COBMINDEX to the patients. We acknowledge the non-

Israeli IBD Research Nucleus gastroenterologists Eyal Hirsch, MD; Timna Naftali, MD; Anat Nevo, MD; Naim Abu-Freha, MD; Arik Segal, MD; and David Yardeni, MD, who referred patients to the study. Trial registration: Ministry of Health, Israel (https://my.health.gov.il/CliniTrials/Pages/MOH_2020-02-24_008721.aspx).

References

1. Cosnes J, Gower-Rousseau C, Seksik P, *et al.* Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology.* 2011;140:1785–1794.e4.
2. Kaplan GG. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol.* 2015;12:720–727.
3. Bernstein CN, Eliakim A, Fedail S, *et al.*; Review Team. World Gastroenterology Organisation global guidelines inflammatory bowel disease: update August 2015. *J Clin Gastroenterol.* 2016;50:803–818.
4. Ghosh S, Shand A, Ferguson A. Ulcerative colitis. *BMJ.* 2000;320:1119–1123.
5. Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut.* 2017;66:2179–2187.
6. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, *et al.* The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol.* 2010;105:289–297.
7. Lichtenstein GR, Feagan BG, Cohen RD, *et al.* Infliximab for Crohn's disease: more than 13 years of real-world experience. *Inflamm Bowel Dis.* 2018;24:490–501.
8. Quezada SM, McLean LP, Cross RK. Adverse events in IBD therapy: the 2018 update. *Expert Rev Gastroenterol Hepatol.* 2018;12:1183–1191.
9. Chhibba T, Walker JR, Sexton K, *et al.* Workplace accommodation for persons with IBD: what is needed and what is accessed. *Clin Gastroenterol Hepatol.* 2017;15:1589–1595.e4.
10. Kemp K, Griffiths J, Lovell K. Understanding the health and social care needs of people living with IBD: a meta-synthesis of the evidence. *World J Gastroenterol.* 2012;18:6240–6249.
11. Graff LA, Vincent N, Walker JR, *et al.* A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflamm Bowel Dis.* 2011;17:1882–1889.
12. Neuendorf R, Harding A, Stello N, *et al.* Depression and anxiety in patients with inflammatory bowel disease: a systematic review. *J Psychosom Res.* 2016;87:70–80.
13. Regev S, Odes S, Slonim-Nevo V, *et al.* Differential relationships of somatization, depression, and anxiety to severity of Crohn's disease. *J Health Psychol.* Published online April 3, 2020. doi: 10.1177. 1359105320909879.
14. Sarid O, Slonim-Nevo V, Schwartz D, *et al.*; Israel IBD Research Nucleus (IIRN). Differing relationship of psycho-social variables with active ulcerative colitis or Crohn's disease. *Int J Behav Med.* 2018;25:341–350.
15. Mikocka-Walus A, Pittet V, Rossel JB, *et al.* Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2016:14:829–835.e1.
16. Walker JR, Ediger JP, Graff LA, *et al.* The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *Am J Gastroenterol.* 2008;103:1989–1997.
17. Iglesias-Rey M, Barreiro-de Acosta M, Caamaño-Isorna F, *et al.* Psychological factors are associated with changes in the health-related quality of life in inflammatory bowel disease. *Inflamm Bowel Dis.* 2014;20:92–102.
18. McCombie AM, Mulder RT, Gearry RB. Coping strategies and psychological outcomes of patients with inflammatory bowel disease in the first 6 months after diagnosis. *Inflamm Bowel Dis.* 2015;21:2272–2280.
19. van der Zaag-Loonen HJ, Grootenhuis MA, Last BF, *et al.* Coping strategies and quality of life of adolescents with inflammatory bowel disease. *Qual Life Res.* 2004;13:1011–1019.
20. Jelsness-Jørgensen LP, Bernklev T, Henriksen M, *et al.* Chronic fatigue is associated with impaired health-related quality of life in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2011;33:106–114.
21. Alexakis C, Kumar S, Saxena S, Pollok R. Systematic review with meta-analysis: the impact of a depressive state on disease course in adult inflammatory bowel disease. *Aliment Pharmacol Ther.* 2017;46:225–235.
22. Boye B, Lundin KE, Jantschek G, *et al.* INSPIRE study: does stress management improve the course of inflammatory bowel disease and disease-specific quality of life in distressed patients with ulcerative colitis or Crohn's disease? A randomized controlled trial. *Inflamm Bowel Dis.* 2011;17:1863–1873.
23. Goodhand JR, Wahed M, Rampton DS. Management of stress in inflammatory bowel disease: a therapeutic option? *Expert Rev Gastroenterol Hepatol.* 2009;3:661–679.
24. Ballou S, Keefer L. Psychological interventions for irritable bowel syndrome and inflammatory bowel diseases. *Clin Transl Gastroenterol.* 2017;8:e214.
25. Knowles SR, Monshat K, Castle DJ. The efficacy and methodological challenges of psychotherapy for adults with inflammatory bowel disease: a review. *Inflamm Bowel Dis.* 2013;19:2704–2715.
26. Vogelaar L, van't Spijker A, van Tilburg AJ, *et al.* Determinants of fatigue in Crohn's disease patients. *Eur J Gastroenterol Hepatol.* 2013;25:246–251.
27. Neilson K, Ftanou M, Monshat K, *et al.* A controlled study of a group mindfulness intervention for individuals living with inflammatory bowel disease. *Inflamm Bowel Dis.* 2016;22:694–701.
28. Schoultz M, Atherton I, Watson A. Mindfulness-based cognitive therapy for inflammatory bowel disease patients: findings from an exploratory pilot randomised controlled trial. *Trials.* 2015;16:379.
29. Berrill JW, Sadlier M, Hood K, *et al.* Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels. *J Crohns Colitis.* 2014;8:945–955.
30. Timmer A, Preiss JC, Motschall E, *et al.* Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database Syst Rev.* 2011;2:CD006913.
31. Spiller R, Major G. IBS and IBD—separate entities or on a spectrum? *Nat Rev Gastroenterol Hepatol.* 2016;13:613–621.
32. Vivinus-Nébot M, Frin-Mathy G, Bzioueche H, *et al.* Functional bowel symptoms in quiescent inflammatory bowel diseases: role of epithelial barrier disruption and low-grade inflammation. *Gut.* 2014;63:744–752.
33. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet.* 1980;1:514.
34. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983;13:595–605.
35. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. *Am J Gastroenterol.* 1996;91:1571–1578.
36. Ware JE, Keller SD, Kosinski M. *SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales.* 2nd ed. Boston, MA: Health Institute, New England Medical Center; 1995.
37. Euroqol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16:199–208.
38. Advocat J, Enticott J, Vandenberg B, *et al.* The effects of a mindfulness-based lifestyle program for adults with Parkinson's disease: a mixed methods, wait list controlled randomised control study. *BMC Neurol.* 2016;16:166.
39. Walach H, Buchheld N, Buttenmuller V, *et al.* Measuring mindfulness—the Freiburg Mindfulness Inventory (FMI). *Pers Individ Differ.* 2006;40:1543–1555.

40. Tinsley EA, Macklin JR, Korzenik JR, *et al*. Validation of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2011;34:1328–1336.
41. Burisch J, Weimers P, Pedersen N, *et al.* Health-related quality of life improves during one year of medical and surgical treatment in a European population-based inception cohort of patients with inflammatory bowel disease—an ECCO-EpiCom study. *J Crohns Colitis*. 2014;8:1030–1042.
42. Lina JE, Neylanb TC, Epel E, *et al*. Associations of childhood adversity and adulthood trauma with C-reactive protein: a cross-sectional population-based study. *Brain Behav Immun*. 2016;53:105–112.
43. Pellissier S, Dantzer C, Mondillon L, *et al*. Relationship between vagal tone, cortisol, TNF-alpha, epinephrine and negative affects in Crohn's disease and irritable bowel syndrome. *PLoS One*. 2014;9:e105328.
44. Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology.* 2013;144:36–49.
45. Villoria A, García V, Dosal A, *et al*. Fatigue in out-patients with inflammatory bowel disease: prevalence and predictive factors. *PLoS One*. 2017;12:e0181435.
46. Nazarinasab M, Nematpour S, Seyedian SS, *et al*. Assessing mental health and the relation with variables of demographic and clinical in Crohn's disease patients. *J Family Med Prim Care*. 2019;8:728–732.
47. Bartels-Velthuis AA, Schroevers MJ, van der Ploeg K, *et al*. A mindfulness-based compassionate living training in a heterogeneous sample of psychiatric outpatients: a feasibility study. *Mindfulness (N Y)*. 2016;7:809–818.