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Randomised clinical trial: Psychological intervention improves work productivity and daily activity by reducing abdominal pain and fatigue in Crohn's disease

Shirley Regev[1] | Doron Schwartz[2] | Orly Sarid[1] | Ganit Goren[1] | Vered Slonim-Nevo[1] | Michael Friger[3] | Ruslan Sergienko[3] | Dan Greenberg[4] | Alon Monsonego[5] | Anna Nemirovsky[5] | Shmuel Odes[6]

[1]Department of Social Work, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[2]Department of Gastroenterology and Hepatology, Soroka Medical Center, Beer-Sheva, Israel

[3]Department of Public Health, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[4]Department of Health Systems Management, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[5]Department of Microbiology, Immunology and Genetics, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[6]Division of Clinical Medicine, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Correspondence
Shmuel Odes, Division of Clinical Medicine, Faculty of Health Sciences, Ben-Gurion University of the Negev, P.O. Box 653, Beer Sheba 8410500, Israel.
Email: odes@bgu.ac.il

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Summary

Background: Chronic abdominal pain and fatigue are characteristics of Crohn's disease (CD) and contribute to functional impairments.

Aims: To examine whether CD-tailored cognitive-behavioural and mindfulness intervention (COBMINDEX) is effective in reducing abdominal pain and fatigue in patients with CD and whether changes in abdominal pain and fatigue mediate any beneficial effects of COBMINDEX on impairments in work productivity and daily activities.

Methods: This is a secondary analysis of a parallel-group multicentre randomised controlled trial. Patients with mild-to-moderate CD (n = 142) were randomised into either intervention group receiving COBMINDEX, or control group receiving treatment-as-usual for 3 months followed by COBMINDEX. Complete data were collected from 120 patients (34.0 ± 10.7 years, 62.5% female, intervention = 60, control = 60). Analysis of covariance assessed group differences in 3-month follow-up scores, controlling for baseline scores. Multiple parallel mediation analysis assessed the proposed mechanisms for the entire sample.

Results: The intervention group demonstrated significantly lower levels of abdominal pain (F = 17.46, p < 0.001, η^2_p = 0.13), fatigue (F = 7.26, p = 0.008, η^2_p = 0.06) and impairments at work (F = 4.82, p = 0.032, η^2_p = 0.07) and daily activities (F = 6.26, p = 0.014, η^2_p = 0.05), compared with treatment-as-usual. Moreover, changes in abdominal pain and fatigue significantly mediated the beneficial effects of COBMINDEX on patients' work productivity (b = −9.90, SE = 2.86, 95% CI: −16.11 to −4.94) and daily activities (b = −9.65, SE = 1.91, 95% CI: −13.77 to 6.35), independent of changes in disease activity.

Conclusions: COBMINDEX is effective at reducing abdominal pain and fatigue in patients with CD, which in turn leads to improvement in functioning. Clinicians should incorporate screening for severe abdominal pain and fatigue and consider offering cognitive-behavioural and mindfulness training.

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1 | INTRODUCTION

Crohn's disease (CD) is a chronic, relapsing–remitting inflammatory bowel disease of largely unknown aetiology that has a typical onset in early adulthood and requires lifelong treatment.[1] The broad spectrum of clinical manifestations necessitates a multidisciplinary approach to improve prognosis and reduce disability.[1]

Fatigue is a highly prevalent and persistent symptom among patients with CD, present in 44%–86% of those with active disease and 22%–41% of those in remission.[2] A study of newly diagnosed patients with CD showed that fatigue was prevalent in 30% of the cohort.[3] Fatigue severity is higher in patients with CD than in healthy controls[4,5] and is associated with increased depression, anxiety and stress.[2,3,5,6] Fatigue is also associated with poor disease-specific quality of life.[2,3,5,6] Consistent with this, fatigue has been identified as a leading concern for patients with CD that has a significant impact on their everyday life.[7] Current evidence on the efficacy of pharmacological CD therapy in the management of fatigue is limited, and some medications for the treatment of CD may even exacerbate fatigue.[8]

Abdominal pain is another common symptom of CD, affecting approximately 70% of patients with active disease[9] and 20% of those with inactive disease.[10] In a recent study, abdominal pain was the most frequently reported symptom by patients with CD (74%).[11] Abdominal pain features prominently in patient-reported outcome measures for CD and has been associated with poor quality of life in patients with CD.[12,13] A systematic review reported that increased pain intensity was consistently associated with higher levels of stress, depression and anxiety among individuals with inflammatory bowel disease.[14] Pharmacological interventions, particularly opiates, are frequently prescribed for pain management in CD but have limited efficacy and adverse side effects.[13,15,16] In fact, taking narcotics was a predictor of increased mortality in patients with CD.[17]

In addition, patients with CD often experience a high disease burden, with symptoms affecting their ability to work and perform daily activities.[18,19] The societal cost of work disability is high. A recent Swedish population-based study found that total productivity loss in CD patients exceeded $12,000 per annum.[20] Fatigue and abdominal pain severity are particularly associated with increased loss of work productivity and activity impairment.[3,5,6,12]

A growing body of clinical data supports the presence of a bidirectional relationship between the central nervous system and the gastrointestinal system, known as the gut–brain axis.[21,22] Within this biopsychosocial framework, it has been proposed that psychological stress can contribute to relapse and exacerbation of CD symptoms. Accordingly, stress may adversely affect mucosal barrier and immune functions, leading to worsening of inflammation of the gastrointestinal tract.[22–24] Consistent with this, studies have shown that the presence and severity of fatigue and abdominal pain in patients with CD are affected by both gastrointestinal and psychological factors[6,13]; thus, highlighting the need for combining medical care with psychological treatment.

We previously reported that a specifically designed psychological intervention, consisting of cognitive-behavioural and mindfulness-based stress reduction with daily exercise (COBMINDEX) diminishes psychological stress in patients with CD.[25] Moreover, COBMINDEX related-improvement in psychological outcomes was associated with a significant reduction in inflammatory markers of CD.[23]

The present study aims to investigate whether COBMINDEX would also lead to reductions in abdominal pain and fatigue, and to determine whether any intervention-induced changes in abdominal pain and fatigue would mediate improvements in work productivity and activity impairments for patients with CD.

2 | MATERIALS AND METHODS

2.1 | Patient populations and interventions

This is a randomised parallel-design controlled trial conducted from July 2018 to July 2020; the data in the current manuscript constitute a secondary analysis not reported previously. The sample size was calculated based on $\alpha = 0.05$, power = 0.8 and SD = 14 in order to achieve a 6-point change in SIBDQ, the primary endpoint of the study (≥86 patients).[25]

Participants had to be aged 18 years or older, have proficiency in Hebrew and have a confirmed diagnosis of CD for at least a year, with mild-to-moderate disease activity (Harvey–Bradshaw Index [HBI][26] score of 5–16). Exclusion criteria were as follows: (1) planned surgery or surgery in the previous 6 months; (2) diagnosis of irritable bowel syndrome; (3) psychiatric illness; (4) alcohol or drug dependency and (5) pregnancy.

Patients deemed suitable for screening by the study coordinator underwent clinical assessment by a gastroenterologist at one of two hospitals in southern and central Israel (Soroka Medical Center and Rabin Medical Center respectively). The gastroenterologist completed the HBI and ordered calprotectin and C-reactive protein (CRP) measurements. After providing written informed consent, patients were enrolled and randomised to either COBMINDEX or waitlist control group. Randomisation was conducted by cluster random sampling with a proportionate allocation strategy, where the fractions were defined by patient sex. Medical personnel was blinded to the randomisation.

The study was registered with ClinicalTrials.gov (Identifier: NCT05085925) and with the Ministry of Health in Israel (https://my.health.gov.il/CliniTrials/Pages/MOH_2020-02-24_008721.aspx). The study was approved by the institutional review boards of the participating hospitals. All authors had access to the study data and reviewed and approved the final manuscript.

2.2 | Description of the COBMINDEX intervention

The COBMINDEX intervention consisted of seven 60-min individual-based sessions using videoconferencing over a 3-month period. A more detailed description of the intervention is provided elsewhere.[25] In brief, participants were taught cognitive-behavioural

and mindfulness techniques, such as breathing awareness, guided imagery and patterns of healthy and adaptive thinking, according to a written manual. Participants were also instructed to practice twice daily for at least 10 min and were asked to report their daily practice via an app. Podcasts related to COBMINDEX sessions were made available for participants throughout the program and beyond. The instructors of COBMINDEX were qualified social workers with at least a Master's degree and clinical experience. They also had 2 days of training on using the intervention manual written by O.S. and V.S.N. Participants in the control group received treatment as usual (TAU) for a period of 3 months and thereafter received the intervention training over the next 3 months.

2.3 | Measures and outcomes

2.3.1 | Work productivity and activity impairment

The Work Productivity and Activity Impairment Questionnaire in Crohn's disease (WPAI:CD)[27] was used to assess impairment while working (presenteeism) and during daily activities in the past 7 days due to CD. Participants are asked to rate the degree to which CD affected their productivity while working from 0 (no effect) to 10 (maximum impairment); and the degree to which CD affected their regular activities, from 0 to 10. Scores are expressed as percentage of impairment, with higher values indicating greater impairment. Only participants who were employed (full- or part-time) and had been working during the previous 7 days had data for work productivity impairment, while all participants provided data for activity impairment.

2.3.2 | Fatigue

Fatigue was evaluated using the Functional Assessment Chronic Illness Therapy–Fatigue (FACIT-F).[28] FACIT-F is a 13-item scale assessing fatigue over the past 7 days, with scores ranging from 0 to 52. Lower scores indicate greater fatigue, and a score below 30 indicates clinically severe fatigue.

2.3.3 | Abdominal pain

Abdominal pain was assessed using a composite score of three items selected from clinician-rated scales: (1) an item from the HBI[26] scale measuring the *severity* of abdominal pain experienced during the previous day on a 4-point Likert scale (0 = none, 3 = severe); (2) an item from the Short Inflammatory Bowel Disease Questionnaire (SIBDQ)[29] measuring the *frequency* of abdominal pain in the past 4 weeks on a 7-point Likert scale (0 = never, 7 = all the time); (3) an item from the Medical Outcomes Study 12-Item Short-Form Survey Instrument (SF-12)[30] measuring *functional interference* of pain in the past 2 weeks on a 5-point Likert scale (0 = not at all, 5 = very much). The three items were summed to form one measure of abdominal pain that ranged from 0 to 15. Higher scores indicated greater overall abdominal pain. Reliability and validity estimates were obtained for the abdominal pain composite scores, as examined in previous studies.[31,32] To assess reliability, Spearman's correlation coefficients were calculated among the three items and showed internal consistency. The three items were significantly correlated with each other (r_s = 0.42–0.59, p < 0.001). Additionally, test–retest reliability was estimated in the control group for abdominal pain composite scores by calculating Pearson's correlation coefficients between baseline (T1) and pre-intervention (T2). The abdominal pain composite score demonstrated good test–retest reliability over a period of 3 months (r_s = 0.77, p < 0.001).

The baseline construct validity of the abdominal pain measurement in our study was examined via cross-sectional correlations between abdominal pain composite score and a variety of physical and mental health key constructs previously found to be related to the CD illness experience.[25,33,34] Specifically, Pearson correlations were calculated at baseline between composite pain scores and measures of depression, anxiety and somatisation via three corresponding subscales of the Brief Symptom Inventory (BSI)[35] and modified measures of HBI, SF-12 and SIBDQ (excluding the relevant pain item from each scale). Correlations coefficients between abdominal pain and the three BSI subscales were statistically significant (all p < 0.001). Pearson correlation was expectedly largest for the BSI somatisation subscale (r = 0.64) that includes an item about 'Nausea or upset stomach' followed by anxiety subscale (r = 0.45) and depression subscale (r = 0.35). Abdominal pain was also associated at baseline with the modified measures of HBI (r = 0.19, p < 0.034), SF-12 (r = −0.78, p < 0.001) and SIBDQ (r = −0.64, p < 0.001). Thus, baseline levels of abdominal pain were associated with concurrently measured levels of mental health symptoms, clinical disease symptoms and indices of generic and disease-specific quality of life.

In addition, longitudinal construct validity of abdominal pain measurement was assessed using correlations between change scores in abdominal pain and change scores in the above-mentioned CD-related variables. Change scores were calculated as post-intervention scores minus pre-intervention scores. Changes in abdominal pain scores following COBMINDEX correlated significantly with changes in BSI subscales scores: somatisation (r = 0.41, p < 0.001), anxiety (r = 0.32, p < 0.001) and depression (r = 0.28, p = 0.002). Similarly, abdominal pain change scores correlated positively with changes in the modified HBI measure (r = 0.24, p = 0.009) and negatively with changes in the modified measures of SF-12 and SIBDQ (r = −0.65, p < 0.001 for both variables). Thus, decrease in abdominal pain following COBMINDEX was associated with similar decrease in overall disease symptoms and improvements in both general and disease-specific measures of health-related quality of life. Additionally, intervention-related reduction in abdominal pain was also associated with improvements in mental health symptoms that are typically elevated in patients with CD compared with healthy population.[34]

These cross-sectional and longitudinal findings suggest that the abdominal pain measure used in the current study reflects aspects of perceived pain intensity and interference with physical and psychological functioning. Importantly, the data support the reliability of this measurement in terms of internal consistency and stability over time and demonstrate its validity as a clinically relevant construct that can be used to assess responsiveness to intervention in patients with CD.

2.3.4 | Disease activity

Disease activity was measured using the HBI,[26] a well-validated scale that measures CD severity in five domains: general well-being, abdominal pain, abdominal mass, diarrheal episodes and complications. Higher scores indicate greater disease activity. HBI scores at enrolment were used for excluding participants in remission (HBI < 5) or with severe disease (HBI > 16). In addition, modified HBI scores (excluding the item on abdominal pain) at pre- and post-intervention, were included in the mediation analyses to adjust for the confounding effect of changes in disease activity.

2.4 | Statistical analysis

Per-protocol (PP) sample constituted COBMINDEX participants who completed assessments at baseline (pre-intervention) and 3-month follow-up (post-intervention), and control participants who completed assessments at baseline, 3 months (pre-intervention) and 6 months (post-intervention). All participants in the PP sample adhered to the intervention protocol in terms of session attendance. An intention-to-treat (ITT) sample was also created using the last observation carried forward. This sample comprised all participants who enrolled in the study and had baseline data, including dropouts. Participants in the ITT sample were analysed according to the group to which they were randomised. The statistical analyses presented in the current paper were based on the PP sample where each participant was analysed according to the treatment they received. In addition, analyses were also conducted on the ITT sample to examine whether they produced similar results to those in the PP sample.

The normality of data distribution for continuous variables was verified via skewness and kurtosis. Group differences at baseline measures between completers and non-completers and between the intervention and control groups were evaluated using independent-samples *t* tests and Chi-square tests. Correlations among demographic, clinical and outcome variables at baseline were evaluated using Pearson bivariate correlations.

Next, the effect of COBMINDEX on fatigue, abdominal pain, work productivity and regular activity impairments was assessed using analysis of covariance (ANCOVA). Four ANCOVA were conducted with group type (COBMINDEX versus control) as the independent variable, and scores at 3-month follow-up as the dependent variable, with baseline scores as the covariate. Effect sizes for between-group comparisons in ANCOVA were measured using Partial eta squared (η^2_p) to indicate the portion of variance in 3-month follow-up scores explained by group type, after adjusting for baseline values.

Finally, to evaluate mechanisms of change, mediation analyses for repeated measures design were conducted using the MEMORE macro (version 2.1).[36] MEMORE is a path-analytic approach that calculates the indirect effect of the intervention as the product of path coefficients. Hence, it eliminates the need for multiple hypothesis tests about individual paths in the model, thereby decreasing the probability of making Type I error. Moreover, the MEMORE technique allows for the indirect effect of each mediator to be tested, controlling for the other mediators in the model. It also allows comparison between the magnitudes of two indirect effects to determine which mediator has the strongest influence on patient outcomes.[36]

The mediation analyses in the current study were performed on a combined sample of the intervention and control patients' pre- and post-intervention assessments. For the control group, data from 3-month follow-up were used as a pre-intervention assessment. Two within-participant mediation models were performed on work impairment and activity impairment as the outcome variables. Fatigue and abdominal pain were added simultaneously to each model as parallel mediators. Standard errors and confidence intervals (CI) for the indirect, direct and total effects were generated from the bias-corrected bootstrapping method with 10,000 bootstrap samples. Statistical significance was determined at $p < 0.05$ and when the CI did not include zero. All analyses were conducted with IBM SPSS version 26 (IBM Corp).

3 | RESULTS

3.1 | Baseline patient characteristics

The study flow diagram is presented in Figure 1. Of 659 individuals who received information regarding the study, 142 individuals with Crohn's disease were eligible and randomised to COBMINDEX ($n = 72$) or Control ($n = 70$). A total of 140 participants completed baseline testing and were included in the intention-to-treat (ITT) analysis. Of these individuals, 120 participants (60 in each group) completed the intervention and post-intervention testing and were included in the per-protocol (PP) analysis. Reasons for non-completion included lack of interest ($n = 11$), time constraints ($n = 7$), other illnesses ($n = 2$) and no longer being eligible due to pregnancy ($n = 2$). The attrition rate was not significantly different between COBMINDEX and TAU groups (17% vs. 13%, $p = 0.523$). Completers and non-completers did not differ in their demographic, illness-related measures and study outcomes (all $p > 0.05$); thus, suggesting that the PP sample is representative of the original ITT sample.

In terms of outcomes in the PP sample, complete data were available on all measures, with the exception of work impairment. At each time point, only employed patients provided data on presenteeism.

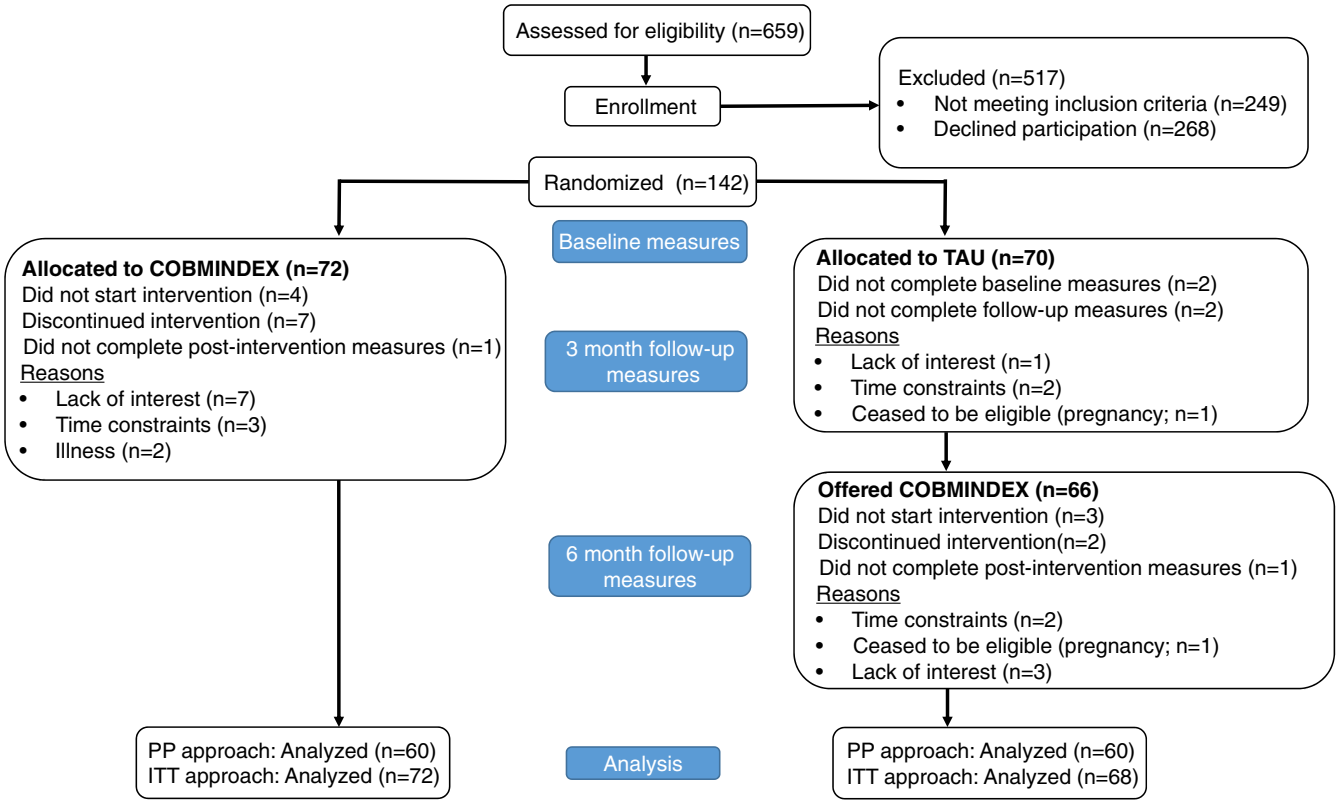

FIGURE 1 CONSORT flow diagram.

Table 1 summarises the baseline characteristics of participants in the COBMINDEX and intervention groups. There were no statistically significant differences between the two trial arms on any demographic, clinical or outcome variables at baseline (all $p > 0.05$), suggesting that randomisation was successful.

3.2 | Correlations between study variables

Pearson correlation analyses revealed that the study outcomes (work impairment, activity impairment, fatigue and abdominal pain) were not significantly correlated with demographic and clinical characteristics (sex, age, years of education and disease duration). Disease activity was significantly correlated with activity impairment ($r = 0.24$, $p = 0.009$), fatigue ($r = -0.31$, $p = 0.001$) and abdominal pain scores ($r = -0.41$, $p < 0.001$). As expected, work productivity impairment and activity impairment were strongly correlated with each other, with medium correlations among WAPI measures, fatigue and abdominal pain (all $p < 0.001$; see Table 2).

3.3 | COBMINDEX program outcomes

ANCOVAs conducted with baseline scores as the covariate revealed the COBMINDEX group to have significantly lower levels of fatigue ($p = 0.008$) and significantly lower levels of abdominal pain ($p < 0.001$), work productivity impairment ($p = 0.032$) and activity impairment ($p = 0.014$) than TAU group at 3-month follow-up. The respective ANCOVA results with scores at baseline and at 3-month follow-up are presented in Table 3.

3.4 | Mediation analysis

Based on the total sample of participants that underwent the COBMINDEX program and provided complete pre- and post-intervention assessments, we performed within-participant mediation analyses using the MEMORE macro for SPSS.[25] Changes in abdominal pain and in fatigue were the mediators and changes in impairment at work and impairment in daily life were the outcomes. As mentioned above, all participants provided data on activity impairment ($N = 120$), while only individuals who were employed at both pre- and post-intervention time points had data on work productivity impairment ($N = 64$).

3.5 | Work productivity impairment

The total effect of COBMINDEX on work productivity impairment was significant ($b = -11.87$, SE = 3.13, $p = 0.0003$, 95% CI: −18.14 to −5.61). When fatigue and abdominal pain were included as mediators in the model, the direct effect of the intervention on work productivity impairment was no longer statistically significant

TABLE 1 Baseline characteristics of completers allocated to COBMINDEX intervention or treatment as usual.

Characteristic % (*n*)	COBMINDEX (*n* = 60)	Control (*n* = 60)	*p*
Gender			
Female	67 (40)	58 (35)	
Male	33 (20)	42 (25)	0.35
Age[a]	34.4 ± 11.7	33.6 ± 9.7	0.68
Education[a]	14.9 ± 2.4	14.8 ± 2.4	0.91
Education level	14.9 ± 2.4	14.8 ± 2.4	0.91
High school	20 (12)	25 (15)	
Vocational	15 (9)	10 (6)	
Academic	65 (39)	65 (39)	0.75
Monthly income			
Below average	54 (32)	69 (41)	
Average	20 (12)	13 (8)	
Above average	26 (15)	18 (11)	0.28
Employment status			
Part-/full-time	73 (44)	73 (44)	
Unemployed	27 (16)	27 (16)	1.00
Disease duration[a]	9.4 ± 8.9	9.0 ± 8.0	0.80
Disease activity[b]			
Mild disease (HBI 5–7)	47 (28)	50 (30)	
Moderate disease (HBI 8–16)	53 (32)	50 (30)	0.71
Bowel surgery in previous year	20 (12)	20 (12)	1.00
Active smoker	11.7 (7)	10.0 (6)	0.77
Disease location[c]			
L1: ileal	63 (38)	52 (31)	
L2: colonic	5 (3)	13 (8)	
L3: ileocolonic	32 (19)	32 (19)	
L4: Isolated upper disease	0 (0)	3 (2)	

Note: The *p* value shows significance levels based on *t* tests for continuous variables and χ^2 test for categorical variables.

[a]Mean ± SD, in years.

[b]Based on scores on Harvey–Bradshaw Index (HBI); COBMINDEX: Cognitive-Behavioural and Mindfulness-based stress reduction.

[c]Disease location was defined by Montreal classification; χ^2 test could not be used to assess differences in disease location due to the low frequency of L4.

(*b* = −1.97, SE = 3.11, *p* = 0.53, 95% CI: −8.21 to 4.26). The total indirect effect of COBMINDEX on work productivity impairment through these two mediators was statistically significant (*b* = −9.90, SE = 2.86, 95% CI: −16.11 to −4.94). In addition, the specific indirect effects through fatigue (*b* = −6.54, SE = 2.20, 95% CI: −11.87 to −3.02) and abdominal pain (*b* = −3.36, SE = 1.93, 95% CI: −8.17 to −0.40) were both significant. Thus, reductions in abdominal pain significantly mediated the effect of the intervention on work productivity impairment beyond the effect of improved fatigue. Similarly, improvements in fatigue significantly mediated the effect of the intervention on work productivity impairment beyond the effect of reduced abdominal pain. Pairwise contrasts suggested that these two indirect effects did not differ in magnitude (contrast = 3.18, SE = 2.99, 95% CI: −2.50 to 9.47). These results indicate that the beneficial effect of COBMINDEX on work productivity impairment is fully mediated by both reductions in abdominal pain and fatigue. See Figure 2 for the mediation model predicting work productivity impairment.

3.6 | Activity impairment

The total effect of COBMINDEX on activity impairment was significant (*b* = −10.42, SE = 2.22, *p* < 0.0001, 95% CI: −14.82 to −6.02). When fatigue and abdominal pain were included as mediators, the direct effect of the intervention on activity impairment was no longer statistically significant (*b* = −0.76, SE = 2.24, *p* = 0.73, 95% CI: −5.20 to 3.68). The total indirect effect through these two mediators was significant (*b* = −9.65, SE = 1.91, 95% CI: −13.77 to −6.35). The specific indirect pathways through fatigue (*b* = −3.52, SE = 1.20, 95% CI: −6.47 to −1.65) and through abdominal pain (*b* = −6.13, SE = 1.51, 95% CI: −9.43 to −3.49) were both significant. Thus, reductions in abdominal pain significantly mediated the effect of COBMINDEX on improvement in activity impairment beyond the effect of reduced fatigue. Similarly, reductions in fatigue significantly mediated the effect of COBMINDEX on activity impairment beyond the effect of reduced abdominal pain. Pairwise contrasts revealed that these indirect effects did not differ from each other (contrast = −2.60, SE = 1.95, 95% CI: −6.63 to 1.13). Thus, the beneficial effect of COBMINDEX on activity impairment was fully mediated by both changes in abdominal pain and fatigue. See Figure 2B for the mediation model predicting activity impairment.

3.7 | ITT analyses

ITT analyses were conducted in which the cases that did not receive COBMINDEX and/or completed post-intervention assessments were included in the analyses (*n* = 14 for work impairment and *n* = 22 for activity impairment). Findings from the ITT analyses were similar to those found in the PP analyses (data not shown).

3.8 | Disease activity as a confounding variable

To rule out the possibility that intervention-related improvement in disease activity is responsible for the mediating effects of abdominal pain and fatigue, mediation analyses were performed using modified HBI scores (after excluding the abdominal pain item) or inflammatory markers (calprotectin and CRP) as mediators.

TABLE 2 Correlations of study variables.

Variable	(1)[a]	(2)[b]	(3)[b]
(1) Work impairment	−1.00		
(2) Activity impairment	−0.748***	−1.00	
(3) Fatigue	−0.478***	−0.518***	−1.00
(12) Abdominal pain	−0.370***	−0.482***	−0.565

[a]$N = 85$.
[b]$N = 120$.
***$p \leq 0.001$.

TABLE 3 ANCOVA of COBMINDEX ($n = 60$) versus TAU ($n = 60$) on study variables.

	COBMINDEX		TAU		ANCOVA[A]		
	Baseline	3 months	Baseline	3 months	*F*	*p*	η^2_p
FACIT-F	27.1 ± 11.0	32.6 ± 10.9	24.7 ± 10.3	26.8 ± 12.6	7.26	0.008	0.06
Pain	9.23 ± 2.7	6.98 ± 2.8	9.42 ± 2.8	8.92 ± 3.4	17.46	<0.001	0.13
WAPI: W[b]	41.0 ± 29.3	28.2 ± 24.5	44.5 ± 24.6	39.2 ± 24.8	4.82	0.032	0.07
WAPI: A	44.7 ± 25.7	32.3 ± 25.9	51.0 ± 24.2	46.7 ± 28.5	6.26	0.014	0.05

Note: Values are presented as mean ± SD.

Abbreviations: ANCOVA, analysis of covariance; COBMINDEX, cognitive-behavioural and mindfulness-based stress reduction intervention; TAU, treatment as usual; FACIT-F, functional assessment of chronic illness therapy–fatigue; Pain, abdominal pain; WPAI:W, work productivity and activity impairment questionnaire: work impairment; WPAI:A, work productivity and activity impairment questionnaire: activity impairment.

[a]The ANCOVA results are for group effect comparing COBMINDEX versus control on 3-month follow-up scores, controlling for baseline scores.

[b]Based on $N = 85$ employed participants.

With regard to modified HBI scores, the indirect effect of COBMINDEX through disease activity was not significant for work productivity impairment ($b = -1.02$, SE = 3.13, 95% CI: −7.30 to 5.12) and for activity impairment ($b = -3.35$, SE = 2.39, 95% CI: −8.38 to 0.94). Similar results were found when the modified HBI scores were included together with either fatigue or abdominal pain in parallel multiple mediation models; moreover, the individual indirect effects of fatigue and abdominal pain in these multiple mediation models remained significant after controlling for changes in disease symptoms (see Table S1).

With regard to inflammatory biomarkers, because CRP and calprotectin levels were not normally distributed, the two-step approach for transforming continuous variables was applied.[37] The indirect effect of COBMINDEX through CRP was not significant for work productivity impairment ($b = -0.02$, SE = 0.38, 95% CI: −0.51 to 1.11) and for activity impairment ($b = -0.03$, SE = 0.30, 95% CI: −0.77 to 0.49). Similarly, no indirect effects were found via calprotectin for work productivity impairment ($b = 0.35$, SE = 0.8195% CI: −1.20 to 2.20) or activity impairment ($b = -0.20$, SE = 0.76, 95% CI: −1.76 to 1.58). When CRP or calprotectin was included with either fatigue or abdominal pain in parallel multiple mediation models, the individual indirect effects of fatigue and abdominal pain in these models remained significant after controlling for changes in inflammatory biomarkers (data not shown).

These results indicate that neither general clinical disease symptoms nor inflammatory biomarkers mediate the effect of COBMINDEX on work impairment and activity impairment, thus ruling out disease activity as a confounding factor.

4 | DISCUSSION

Crohn's disease is characterised by abdominal pain and fatigue that may negatively affect the work and activity productivity of patients and as such presents substantial economic burdens on the individual and society. In addressing these issues, our aim was two-fold. First, we examined the effectiveness of COBMINDEX as an adjunct to usual care for patients with CD compared to treatment as usual care alone. Both PP and ITT analyses yielded statistically significant results, with intervention having a positive impact on fatigue and abdominal pain severity as well as on patients' productivity during work and regular activities. Second, we tested whether reductions in fatigue and abdominal pain might mediate the efficacy of COBMINDEX in improving CD-related productivity at work and in daily life. Results showed that both fatigue and abdominal pain served as significant mediators of intervention effects.

These findings are consistent with cross-sectional studies linking abdominal pain and fatigue to work and activity impairments in CD.[3,5,6,12] To our knowledge, the current research is the first to provide experimental evidence of the interplay between abdominal pain and fatigue in explaining functional disability among patients with CD. As such, our findings provide initial support for the notion that abdominal pain and fatigue may represent distinct pathophysiological mechanisms of CD-related disability. Specifically, abdominal pain and fatigue seem to contribute independently and in combination to impairments at work and daily life in patients with active CD.

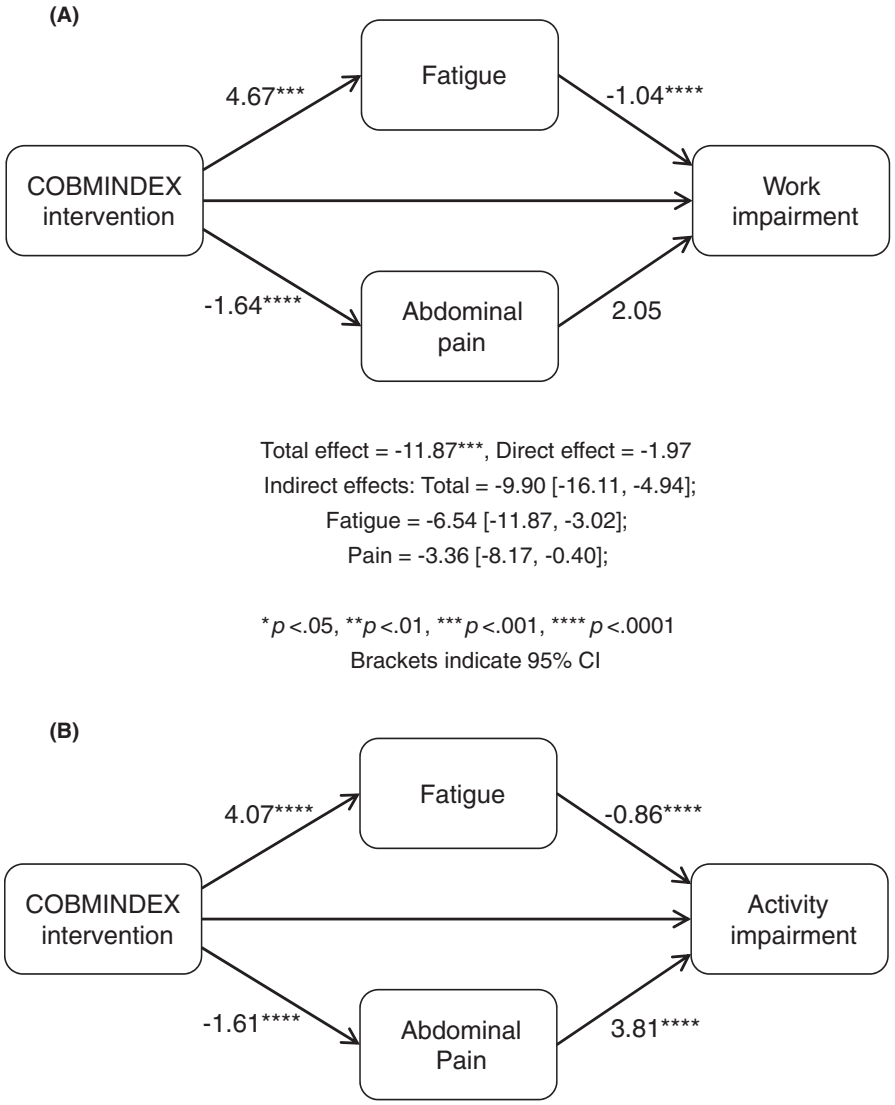

FIGURE 2 (A) Parallel multiple mediator model predicting a reduction in work impairment following COBMINDEX intervention through improvements in abdominal pain and fatigue among patients with Crohn's disease ($N = 64$). (B) Parallel multiple mediator model predicting a reduction in activity impairment following COBMINDEX intervention through improvements in abdominal pain and fatigue among patients with Crohn's disease ($N = 120$).

Moreover, although our intervention successfully reduced disease activity, as reported previously,[25] improvements in work and activity impairments following COBMINDEX were not attributable to changes in general disease symptoms, but rather to improvements specifically in patients' fatigue and abdominal pain; thus, further highlighting the importance of targeting these key symptoms in psychological and pharmacological treatments for CD.

This study is also the first to demonstrate the benefits of a non-pharmacologic intervention in terms of improving CD-related productivity at work and in daily activities. Given the considerable levels of work and activity impairments observed in the present study and in other studies among patients with CD,[18,19] there is a critical need to implement effective strategies to reduce CD-related functional impairments.

Previous studies in patients with gastrointestinal disorders evaluated abdominal pain using a single item, typically derived from an existing clinical scale.[31,32] While this practice may offer reduced response burden, it does not capture the complexity and multifaceted nature of abdominal pain in gastrointestinal diseases.[38] By combing three items from routinely used clinical scales, we were able to employ a reliable and valid multi-item measurement of abdominal pain that reflects clinically relevant data with minimal response burden.

Future intervention studies in CD assessing abdominal pain outcomes should take into account the frequency and severity of abdominal pain and its impact on the patient's life.

Overall, our findings lend experimental support to the biopsychosocial model of CD,[14,22,24,39] suggesting that psychological factors, such as emotional stress and maladaptive coping, contribute to the pathogenesis of disease symptoms of fatigue and abdominal pain. In recent years, there has been a growing interest in the efficacy of psychological interventions for the management of fatigue and abdominal pain in patients with CD. However, current clinical evidence is inconclusive and limited by high attrition rates, lack of a randomised control group and small cohorts of patients, most of whom were in clinical remission.[40,41] This work addresses this gap by providing strong evidence that online cognitive-behavioural and mindfulness intervention can be a safe and effective adjunct in alleviating CD-related fatigue and abdominal pain.

Strengths of the present study include the randomised controlled trial design, the fairly large size of the cohort and the relatively low rate of attrition. Another advantage is reliance on clinician examination for medical confirmation of CD diagnosis. Limitations included the use of self-report measures that can be susceptible to response bias. In addition, the study population consisted of patients with mild to moderate active disease; thus, results might not generalise to severely affected patients or those with inactive disease.

In conclusion, our findings suggest that a short-term cognitive-behavioural and mindfulness intervention has the capacity to reduce abdominal pain and fatigue as well as improve functioning in patients with mild-to-moderate CD. Practitioners should consider evidence-based psychosocial interventions, such as COBMINDEX, as an adjunct treatment for CD.

AUTHOR CONTRIBUTIONS

Shirley Regev: Formal analysis (lead); writing – original draft (lead). **Doron Schwartz:** Conceptualization (equal); supervision (equal). **Orly Sarid:** Conceptualization (equal); methodology (lead); writing – review and editing (supporting). **Ganit Goren:** Investigation (lead); project administration (lead); writing – review and editing (supporting). **Vered Slonim-Nevo:** Conceptualization (equal); methodology (lead). **Michael Friger:** Conceptualization (equal). **Ruslan Sergienko:** Data curation (lead); software (lead). **Dan Greenberg:** Conceptualization (equal); writing – review and editing (supporting). **Alon Monsonego:** Conceptualization (equal); writing – review and editing (supporting). **Anna Nemirovsky:** Writing – review and editing (supporting). **Selwyn Odes:** Conceptualization (equal); funding acquisition (lead); supervision (lead); writing – review and editing (lead).

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AUTHORSHIP

Guarantor of the article: Shirley Regev.

CONFLICT OF INTEREST STATEMENT

SR, OS, VSN, MF, SR, DG, AM, AN and SO: no conflict of interest identified. DS has served as a speaker, a consultant and/or an advisory board member for Takeda Pharmaceutical Co Ltd, AbbVie Inc, Pfizer Inc, Janssen Pharmaceuticals Inc, Ferring Pharmaceuticals Inc and Neopharm Labs Inc. GG has served as a speaker for Ferring Pharmaceuticals Inc.

ORCID

Shirley Regev https://orcid.org/0000-0001-8920-7857
Doron Schwartz https://orcid.org/0000-0002-4316-3243
Orly Sarid https://orcid.org/0000-0002-6967-8755
Ganit Goren https://orcid.org/0000-0001-8377-6258
Vered Slonim-Nevo https://orcid.org/0000-0003-3220-9039
Michael Friger https://orcid.org/0000-0001-7234-6607
Ruslan Sergienko https://orcid.org/0000-0001-9583-008X
Dan Greenberg https://orcid.org/0000-0002-6759-3985
Alon Monsonego https://orcid.org/0000-0002-4888-7865
Anna Nemirovsky https://orcid.org/0000-0002-8250-9112
Shmuel Odes https://orcid.org/0000-0002-8452-9926

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SUPPORTING INFORMATION

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