Psychological outcomes of a cognitive behavioral therapy for youth with inflammatory bowel disease: results of the HAPPY-IBD randomized controlled trial at 6 and 12 months follow-up

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In revision (Journal of Clinical Psychology in Medical Settings)

ABSTRACT

Youth with inflammatory bowel disease (IBD) often experience psychological difficulties, such as anxiety and depression. This random controlled study tested whether a 3 month disease-specific cognitive behavioral therapy (CBT) in addition to standard medical care versus standard medical care only was effective in improving these youth's psychological outcomes. As this was a preventive study, we included 70 patients (10-25 years) with subclinical anxiety and/or depression, and measured psychological outcomes at 6 and 12 months' follow-up. In general, patients in both groups showed improvements in anxiety, depression, health-related quality of life, social functioning, coping, and illness perceptions, sustained until 12 months follow-up. Overall, we found no differences between those receiving additional CBT and those receiving standard medical care only. We assume that this can be explained by the perceived low burden (both somatically and psychologically) or heightened awareness regarding psychological difficulties and IBD. ClinicalTrials.gov: NCT02265588.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract characterized by periods of active inflammation (with increased clinical symptoms) followed by periods of clinical remission. The two main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Symptoms are abdominal pain, bloody diarrhea, fatigue, fever, and weight loss [1, 2]. Pediatric patients may also suffer from anorexia/loss of appetite, malnutrition, and experience delayed growth and puberty onset – especially those with CD [3, 4].

Adolescents and young adults (hereafter referred to as youth) with IBD may experience various psychological problems related to the disease and its treatment. Firstly, they are at risk for anxiety and depression [5, 6]. More specifically, a large cohort study found that these patients have a higher risk for anxiety or depressive disorders [7]. Secondly, they are at risk for a lower health-related quality of life (HRQOL) compared to healthy peers [8], likely on account of more maladaptive avoidant coping [9, 10]. In addition, negative illness perceptions (i.e. negative cognitions on for example the consequences of the disease or personal control) are associated with more negative outcomes in these patients [11, 12]. Thirdly, youth with IBD also experience sleep problems [13], related to anxiety and depression [14]. Lastly, they their social functioning is worse than that of healthy controls [6]. In conclusion, youth with IBD are likely to experience psychological problems as described above and the interrelationships between these problems makes treating this patients somatically and psychologically even more complex.

Importantly, psychological problems of youth with IBD can influence medical outcomes, creating a vicious circle of problems [e.g. 15-17]. There seems to be a reciprocal relationship between these psychological difficulties and clinical symptoms due to gut inflammation [18]. It has been hypothesized that psychological interventions may positively influence the inflammatory disease course [19]. Psychological treatment should be focused on decreasing anxiety and depression and addressing other psychological problems, such as coping or negative illness perceptions, and on improving HRQOL and daily functioning. A recent randomized controlled trial (RCT) of Levy et al. [20] in pediatric patients with IBD tested the effect of a 3-session social learning and cognitive behavioral therapy (SLCBT) versus educational support (ES; focusing on the gastrointestinal system, food labels, and nutrition) on a large set of psychological outcomes. SLCBT outperformed educational support in improving IBD-related quality of life 1 week after treatment and coping and school attendance over the course of 12 months, but had no effect on anxiety, depression, and functional disability. However, patients were not selected on either somatic of psychological symptoms, and therefore, many of them did not have psychological problems. Mikocka-Walus et al. [21]

have suggested that targeted psychological treatment may be more useful to tackle psychological problems such as elevated anxiety and/or depression. Furthermore, Levy et al. [20] used an intervention of only 3 sessions, whereas in IBD it has been shown that a full 12-session protocol of disease-specific CBT improved depressive symptoms and HRQOL [22, 23].

HAPPY-IBD aimed to test the extent to which disease-specific CBT in youth with subclinical anxiety and depression is effective to decrease the negative impact of the disease and these subclinical psychological symptoms. By providing CBT for these specifically subclinical symptoms, we aimed to improve the disease course and to prevent the development of clinical anxiety and depressive disorders. So the study had a perspective of secondary prevention. To cover the important life phase of transition from adolescence to adulthood, we included youth aged 10-25 years. In this adolescent life phase, IBD can affect the psychological development, such as becoming independent from parents, developing long-term friendships, and forming an own (sexual) identity. For teenagers, important changes are starting secondary education, making new friends at a new school, becoming more independent from parents, and spending more time with peers. For late adolescents these processes continue and graduating, experimenting with alcohol or drugs, finding a (side) job and earning money, and forming an identity will take place as well. Lastly, young adults face developmental challenges such as finding a job, leaving home, having long lasting romantic relationships, and becoming financially independent [24]. A diagnosis of IBD can involve a sense of loss in for example body image, future plans, self-confidence, sense of control, and roles inside and outside the family context [25]. These changes and challenges should be considered in the treatment of youth with IBD.

Earlier we have reported the immediate post-treatment assessment of this RCT, three months after baseline: patients in both the CBT and the standard medical care group improved on anxiety, depression, and HRQOL, but the level of improvement did not differ between groups [26]. Considering that IBD has a fluctuating disease course, we re-assessed psychological outcomes at 6 and 12 months. We expected that patients who had received CBT would be better able to deal with possible flares and be better equipped with skills to prevent worsening of their subclinical psychological problems. Since CBT in general aims to improve anxiety and depression, these were chosen as primary outcomes. In addition, in this study we extended and innovated the range of our outcomes and also measured HRQOL, social functioning, coping [27], illness perceptions [28], and sleep problems.

In summary, the present study aims to test the effectiveness of a full disease-specific CBT protocol in addition to standard medical care), 6 and 12 months after the baseline assessment, to improve anxiety and depressive symptoms, and other psychological outcomes, in youth with IBD (10-25 years old) and subclinical symptoms of anxiety and

depression, compared to standard medical care only. We hypothesized that patients who had received CBT would have more sustained improvement on all psychological outcomes than those in the standard medical care group.

METHODS

For details of this RCT and the 3-month outcomes, see Van den Brink & Stapersma et al. [29] and Stapersma et al. [26]. This study is a two-armed multi-center parallel group RCT, comparing a disease-specific CBT (Primary and Secondary Control Enhancement Training for Physical Illness; PASCET-PI) [30] in addition to standard medical care to standard medical care only (care-as-usual, CAU). The latter represents the current usual care for youth with IBD in the Netherlands, and was therefore chosen as control condition. Patients were consecutively recruited between October 2014 and October 2016 in two academic and four community hospitals in urban and rural regions. The trial design adheres to the CONSORT guidelines for non-pharmacological treatments [31]. The research protocol was approved by the Medical Ethics Committee of the Erasmus MC (approval number NL49147.078.14) and confirmed by the ethics boards of all participating hospitals. The study was registered with ClinicalTrials.gov as study number NCT02265588.

Participants and Assessment procedure

After patients and/or their parents had provided written informed consent, they were included in two steps. Patients from the age of 12 years provided informed consent themselves as well, patients of 10 or 11 years provided assent. All patients received a small financial reward (25 EUR voucher) for participating.

Step 1 involved baseline screening of anxiety and depression symptoms, for which all consecutive youth (aged 10-25 years) with a confirmed diagnosis of IBD (CD, UC or inflammatory bowel disease unclassified) recruited in the abovementioned period were eligible.

Step 2, the actual RCT, included only youth with subclinical anxiety or depression established in step 1, as we aimed to examine whether the disease specific CBT could prevent clinical anxiety and/or depression. In addition, it is unethical to withhold treatment to patients with clinical anxiety and/or depression.

Subclinical anxiety or depressive symptoms were defined as a score equal or above the cutoff of age-appropriate questionnaires, but not meeting criteria for clinical anxiety and depression (see below). Subclinical anxiety symptoms were measured with the Screen for Child Anxiety Related Emotional Disorders (SCARED; 10-20 years; cutoff ≥26 for boys and ≥30 for girls) [32] and the Hospital Anxiety and Depression Scale –

Anxiety Scale (HADS-A; 21-25 years; cutoff ≥8) [33]. Subclinical depressive symptoms were measured with the Child Depression Inventory (CDI; 10-17 years; cutoff ≥13) [34] and the Beck Depression Inventory – second edition (BDI-II; 18-25 years; cutoff ≥14) [35].

Patients were assumed to suffer from clinical anxiety or depression if they met DSM-5 criteria for an anxiety or depressive disorder, as assessed a psychiatric interview (Anxiety Disorders Interview Schedule for Children; ADIS-C) [36], and scored equal to or above the clinical cutoff on age-specific severity rating scales: the Pediatric Anxiety Rating Scale (PARS; 10-20 years; cutoff ≥18) [37] or the Hamilton Anxiety Rating Scale (HAM-A; 21-25 years; cutoff ≥15) [38, 39] for anxiety; the Child Depression Rating Scale Revised (CDRS-R; 10-12 years; cutoff ≥40) [40], the Adolescent Depression Rating Scale (ADRS; 13-20 years; cutoff ≥20) [41], or the Hamilton Depression Rating Scale (HAM-D; 21-25 years; cutoff ≥17) [42, 43] for depression. All above-mentioned cutoffs only served for inclusion of patients and not for analysis purposes.

Patients with clinical anxiety or depression were referred to mental health care. Patients with subclinical anxiety or depressive symptoms (but not clinical anxiety or depression) were randomized at a ratio 1:1 to receive either PASCET-PI in addition to CAU or CAU only.

Randomization

An independent biostatistician provided a computer-generated blocked randomization list with randomly chosen block sizes (with a maximum of 6) and stratification by center using the blockrand package in the R software package, thereby providing numbered envelopes per center. Patients were enrolled by a single investigator (GB). The interviewer (LS) and treating physicians had no access to the files in which the randomization result was described. We requested patients and parents not to reveal the trial arm assignment to the interviewer and treating physicians. Patients and parents received a link to web-based questionnaires, to be completed at home. They completed the same set of questionnaires at baseline (no longer than 2 weeks before the start of the PASCET-PI), and at the post-assessments (3, 6 and 12 months after baseline). For both groups, assessments were performed at comparable time points (i.e. between 11-13 weeks, 25-27 weeks and 51-53 weeks after randomization).

Intervention

The PASCET-PI is a disease-specific CBT protocol for youth with IBD [30], consisting of ten weekly individual sessions, delivered in three months. It was provided in a 'blended format': six sessions were face-to-face with a psychologist (in the patient's own hospital), four sessions by telephone. In addition, parents of patients ≤20 years were invited for three face-to-face family sessions. Booster sessions were delivered

by telephone 4,5 and 6 months after baseline. The authorized Dutch translation of the PASCET-PI was used, developed by the research team. Originally, the PASCET-PI is targeted at depression. For this study, the treatment content was adjusted to also target aspects of anxiety such as anxiety hierarchy, exposure, cognitive restructuring, and to also target young adults (with more age-appropriate exercises and lay-out). A more detailed description is provided in Appendix 1 or Van den Brink & Stapersma et al. [29]. In short, sessions are focused on discussing, in an age-attuned manner, the patient's illness narrative and the link between behavior and feelings, on relaxation, on discussing negative thoughts and cognitive restructuring, and on personalizing the taught skills. The therapists provided age-appropriate information and exercises. In this way, the protocol took into account the patient's psychological, cognitive and social development.

The therapy was provided by licensed (healthcare/CBT) psychologists with ample experience working with youth, who had all been trained by the developer (EMS) and received monthly supervision by EMWJU (clinical psychologist/professor). Treatment integrity was ensured by supervision of the therapists and by rating of audiotaped sessions. For details, see Stapersma et al. [26]. CAU consisted of regular medical consultations of 15-30 minutes with the (pediatric) gastroenterologist and/or IBD nurse every three months, in which overall wellbeing, disease activity, and future diagnostic/treatment plans were discussed.

Outcome measures (online questionnaires)

Demographic data were obtained from a semi-structured questionnaire [44]. Socioeconomic status was based on parents' occupational level or, for patients living on their own, the own occupational level. We classified socioeconomic status into low, middle, and high [45]. Ethnicity was based on the mother's country of birth or if the mother was born in the Netherlands, the father's country of birth [46]. Disease characteristics were extracted from the electronic medical charts.

Symptoms of anxiety were assessed with the SCARED (for 10-20 years), and the anxiety scale of the HADS (for 21-25 years). Both are self-report questionnaires. The SCARED has 69-items with 3 response categories (0-2; total score 0-138) [47]. The anxiety scale of the HADS has 7-items with 4 response categories (0-3, total score 0-21) [33]. Internal consistency at baseline and the three follow-up assessments was .86, .92, .94, respectively, and .94 for the SCARED, and .54, .77, .81, .80, respectively, for the HADS-A. Clinical anxiety was defined using a psychiatric interview and severity rating scales (as described above in the assessment procedure).

Symptoms of depression were assessed using the CDI (for 10-17 years) and the BDI-II (for 18-25 years) self-report symptoms scales. The CDI has 27-items with 3 response categories (0-2, total score 0-54) [34]. The BDI-II has 21-items with 4 response categories

(0-3, total score 0-63) [35]. Internal consistency at baseline and the three follow-up assessments was .70, .77, .79, and .81, respectively, for the CDI, and .54, .83, .81, and .84, respectively, for the BDI-II. Clinical depression was defined using a psychiatric interview and severity rating scales (as described above in the assessment procedure).

Health-related quality of life (including social functioning) was assessed with the self-report questionnaires IMPACT-III (10-20 years) and the Inflammatory Bowel Disease Questionnaire (IBDQ; 21-25 years). The IMPACT-III has 35 items, scored 1-5 (total score 35-175) [48]. The IBDQ contains 32 items, scored 1-5 (total score 32-160) [49]. For both instruments a higher score indicates better HRQOL. We included in the analyses the total scores and the individual subscale scores for social functioning of both instruments. For the total score, internal consistency at baseline and the three follow-up assessments was .71, .92, .90, and .90, respectively, for the IMPACT-III, and .71, .92, .85, and .88, respectively, for the IBDQ. For the social functioning subscale score, internal consistency at baseline and the three follow-up assessments was .67, .54, .59, and .49, respectively, for the IMPACT-III subscale, and .69, .85, .48, and .51, respectively, for the IBDQ subscale.

Coping was assessed using the Cognitive Emotion Regulation Questionnaire (CERQ). The CERQ contains 36 items, scored 1-5, subdivided into 9 subscales. These scales are divided in two domains: adaptive coping (e.g. positive reappraisal) and maladaptive coping (e.g. self-blame and catastrophizing). A higher score indicates more use of a particular coping style [50]. Internal consistency at baseline and the three follow-up assessments was .89, .91, .94, and .94, respectively, for the adaptive coping domain, and .87, .88, .87, and .86, respectively, for the maladaptive coping domain.

Illness perceptions were assessed with the Brief Illness Perceptions Questionnaire (B-IPQ) [51, 52]. It contains 9 self-report items on cognitive and emotional representations of illness. Eight dimensions (e.g. consequences of illness, personal control, concerns, and understanding) are scored from 0-10. A higher score represents more negative illness perceptions. Internal consistency at baseline and the three follow-up assessments was .74, .79, .78, and .75.

Sleep problems were assessed using the sleep problem items of the Youth Self-Report (YSR; for ages 10-17) [53] and the Adult Self-Report (ASR; for ages 18-25) [54]. These questionnaires contain three comparable items on sleep problems (scored 0, 1 or 2), of which the scores were added up: 'I sleep more than most other people during day and/or night.' and 'I have trouble sleeping.'

Clinical disease activity was assessed with four validated clinical disease activity measures around the moments that patients filled out the online questionnaires on psychological symptoms. For patients of 10-20 years with CD, the short Pediatric Crohn's Disease Activity Index (sPCDAI) [55] was used; for patients with UC and IBD-U the Pediatric Ulcerative Colitis Activity Index (PUCAI) [56]. For patients of 21-25 years

with CD, the Crohn's Disease Activity Index (CDAI) [57] was used; for patients with UC and IBD-U the partial Mayo score [58]. All are physician rated forms (not online), that provide four categories of clinical disease activity: remission, mild, moderate, and severe.

Statistical analysis

We tested differences in demographic and disease characteristics between the two groups at baseline using t-tests, Mann-Whitney tests and chi-square tests.

To be able to combine all participants in one analysis (thereby maximizing power), despite the use of age-appropriate instruments, we calculated a Reliable Change Index (RCI) [59] value separately for anxiety and depression (primary outcomes) for each participant, at each assessment. The RCI of an instrument is calculated from the standard error of measurement (SEM) of the pretest reliability and the test-retest reliability. The RCI can have three possible values; reliably improved; no reliable change; and reliably deteriorated (see Appendix 2 for RCI details). Chi-square tests were used to test for differences in RCI values between the two groups. These analyses included only patients for whom pre- and posttest data were available (see Table 1 for the details on sample sizes for each chi-square test). The proportions of patients who developed clinical anxiety and/or depression were compared between groups using a separate chi-square test.

For exploratory analyses, we used linear mixed models (taking into account missing data) to compare the change on full-range scores from baseline to 6 and 12 months follow-up between groups. The outcomes were anxiety (SCARED or HADS-A), depression (CDI or BDI-II), HRQOL (IMPACT-III or IBDQ), social functioning (subscale of IMPACT-III or IBDQ), coping (CERQ), illness perceptions (B-IPQ), and sleep problems (YSR or ASR). The starting model for all outcomes included a random intercept and fixed factors for time, group, and the interaction between time and group. Next, we examined with the use of likelihood-ratio tests whether adding a random slope of time and a quadratic term of time and the interaction between the quadratic term of time with group improved the model. The restricted maximum likelihood method was applied, as this is preferred for relatively small sample sizes [60, 61]. Because we had no expectations about the relationship between the random intercept and slope, we used an unstructured covariance structure was selected, which is the most flexible structure.

Follow-up data were analyzed based on the intention-to-treat principle, unless otherwise specified. For the chi-square analyses (with the primary dichotomous outcomes) this implied inclusion of only those randomized for whom follow-up data were available (since follow-up data were required to calculate the RCI). For the exploratory analyses (secondary continuous outcomes), the intention-to-treat principle implied in-

clusion of all randomized patients, also those without follow-up data (since the linear mixed models take into account missing data and follow-up data were not required). A *p*-value of <.05 was considered statistically significant. Data were analyzed using SPSS version 24.

Sample size and power

Sample size and power were based on anxiety and depressive symptoms as primary outcomes. Meta-analytic studies in youth without a somatic disease have shown medium-to-large effect sizes for anxiety symptoms [62] and medium effect sizes for depressive symptoms [63]. These correspond with φ >0.40 and φ >0.30, for anxiety and depressive symptoms respectively. For the main chi-square analyses this means that a sample size of 70 patients would give us enough power for the anxiety outcomes (>85%, β = 0.14) and medium power for the depression outcomes (>60%, β = 0.39).

RESULTS

Demographic data

In total, 70 patients were randomized; 37 to the PASCET-PI group and 33 to the CAU group (see Figure 1). Attrition was very low; only two patients dropped out of the PASCET-PI, and only three patients (6 months) and two patients (12 months) did not complete follow-up assessments. Demographic variables did not significantly differ between the groups (see Appendix 3): percentage males (27.0% vs. 36.4%, *p* = .401), mean age (18.62 vs. 17.69, *p* = .393), socioeconomic status (*p* = .348), and ethnicity (*p* = .749). The number of patients included at baseline based on anxiety, depression or both did not differ between groups as well (*p* = .070). The patients' disease characteristics did not differ between the groups: IBD subtype (% CD 48.6% vs. 54.5%), Paris classification at diagnosis (CD location; *p* = .808, CD behavior; *p* = .243, UC extent; *p* = .069, UC severity; *p* = .104), percentage of patients in clinical remission (73.0% vs. 78.8%, *p* = .571), and use of IBD medication (% immunomodulators 43.2% vs. 48.5% and % biologicals 21.6% vs. 36.4%). However, the median disease duration was longer in the PASCET-PI group than in the CAU group (2.59 vs. 1.17 years, *p* = .039). In the PASCET-PI group, 18 patients were aged 10-17 years and 19 patients 18-25 years. In the CAU group, 17 patients were aged 10-17 years and 16 patients 18-25 years.

With respect to treatment integrity, adherence to the protocol was good. The mean number of sessions followed in the PASCET-PI group was 9.38 (out of 10). The mean number of family sessions followed was 2.57 (out of 3), and the mean number of booster sessions followed was 2.59 (out of 3). In all sessions, at least 75% of the topics were discussed.

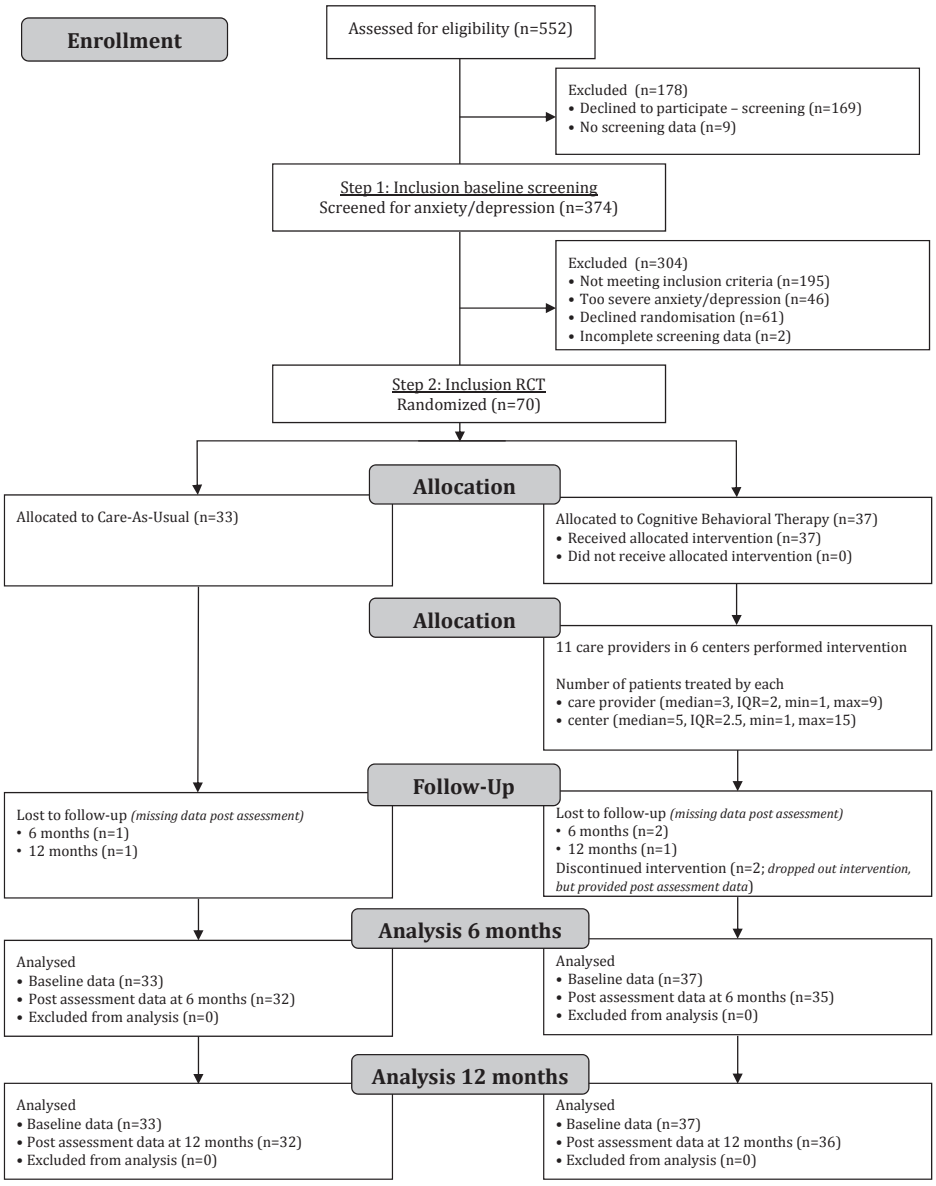

Figure 1 | CONSORT study flow chart
Abbreviations: RCT= randomized controlled trial; IQR= inter quartile range

Effect of disease-specific CBT on symptoms of depression and anxiety

In the chi-square tests, some cells in the cross-tabulation were smaller than 5. Only few patients (0-4) were in the 'Reliable increase of score / deterioration' category (i.e. deteriorated in anxiety or depression). Therefore, we combined this category with the

'No reliable change' category, to test if the PASCET-PI and CAU groups differed with respect to the proportions of patients who had improved on anxiety or depression. In these main analyses, RCI values for anxiety (χ^2 (1) = .226, p = .801) and depression (χ^2 (1) = 2.680, p = .141) after 6 months did not differ between the groups, and neither did the RCI values for anxiety (χ^2 (1) = .337, p = .626) after 12 months. This indicates that in both groups a similar proportion of patients improved. For depression after 12 months, the RCI values differed significantly between the groups, indicating that a higher proportion of patients in the CAU group improved than in the PASCET-PI group (χ^2 (1) = 5.460, p = .026), see Table 1. In the PASCET-PI group, two patients developed clinical anxiety and/or depression during follow-up, versus one patient in the CAU group, which was not significantly different (χ^2 (1) = .240, p = .543).

To provide more insight into age differences, we also performed the chi-square analyses separately for the 10-17-year-olds and the 18-25-year-olds. The results were

Table 1 | *Crosstabulation of 6 & 12 month RCI of symptoms of anxiety and depression vs. group*

6 months			
	Reliable increase of score / deterioration or no reliable change	Reliable decrease of score / improvement	Total
	RCI categories anxiety (SCARED or HADS-A)		
CAU	11 (34.4%)	21 (65.6%)	32
CBT	14 (40.0%)	21 (60.0%)	35
χ^2 = .226, p = .801, ϕ = -.058 (95%BI .000-.293). Numbers in parentheses indicate row percentages			
	RCI categories depression (CDI or BDI-II)		
CAU	11 (34.4%)	21 (65.6%)	32
CBT	19 (54.3%)	16 (45.7%)	35
χ^2= 2.680, p = .141, ϕ = .200 (95%BI .000-.439). Numbers in parentheses indicate row percentages			
12 months			
	Reliable increase of score / deterioration or no reliable change	Reliable decrease of score / improvement	Total
	RCI categories anxiety (SCARED or HADS-A)		
CAU	12 (37.5%)	20 (62.5%)	32
CBT	16 (44.4%)	20 (55.6%)	36
χ^2= .337, p = .626, ϕ = .070 (95%BI .000-.306). Numbers in parentheses indicate row percentages			
	RCI categories depression (CDI or BDI-II)		
CAU	8 (25.0%)	24 (75%)	32
CBT	19 (52.8%)	17 (47.2%)	36
χ^2= 5.460, p = .026, ϕ = .283 (95%BI .036- .521). Numbers in parentheses indicate row percentages			

almost completely similar to the chi-square analyses in the total group (data not shown). However, a higher proportion of 18-25-year-olds in the CAU group improved on depression after 12 months than in the PASCET-PI group (χ^2 (1) = 6.349, p = .019).

The exploratory analyses gave similar results as the chi-square analyses. For all outcomes, the residuals of the models were approximately normally distributed. For the SCARED and the IMPACT-III, the final model included a fixed factor for time and group, a random intercept, and a random slope for time, since the likelihood-ratio test indicated that adding a random slope for time improved the model significantly. Because this was not the case for all the other outcomes, the respective models did not include a random slope for time. For the BDI-II, the final model included fixed factors for time group, and for the interaction between time and group, and a random intercept. For all the other outcomes, however, including a fixed factor for the interaction between time and group did not improve the model. Therefore, for all other outcomes the final model included fixed factors for time and group, and a random intercept. For the SCARED, HADS-A, and BDI-II, adding a quadratic term of time significantly improved the model. Then adding the interaction between the quadratic term of time and group did not improved the model for these outcomes.

sNo significant time-group (PASCET-PI versus CAU group) interaction effect was found for anxiety (SCARED: p = .798; HADS-A: p = .997), depression (CDI: p = .693), HRQOL (IMPACT-III Total score: p = .117; IBDQ Total score: p = .247), social functioning (IMPACT-III Social functioning: p = .407; IBDQ Social functioning; p = .879), coping (CERQ Adaptive coping: p = .506; CERQ Maladaptive coping: p = .592), illness perceptions (B-IPQ: p = .474) and sleep problems (YSR/ASR: p = .858). The only significant time and group interaction was found on the BDI-II (p = .025, favoring the CAU group over the course of 12 months). Therefore, for all outcomes except the BDI-II, the effect of time was similar for both groups. Table 2 presents the coefficients for time presented for the model without the interaction of time and group; only for the BDI-II the estimate is presented for the model with the interaction of time and group included. For all outcomes (except sleep problems; p = .070), the average effect of time was significant, indicating that over the course of 12 months, patients improved on their psychological outcomes (anxiety, depression, HRQOL, social functioning, coping, and illness perceptions). For the SCARED, HADS-A, and BDI-II, the quadratic effect was significant. This indicates that for these outcomes the model follows a quadratic trajectory over the course of 12 months.

Table 2 | *Results of linear mixed models: time effects for outcome variables with overall Estimated Marginal Means*

Variable	β (SE) (time effect)[a]	*p* (time effect)	β (SE) (time² effect)[a]	*p* (time² effect)	Baseline Mean (SE)	6 Months Mean (SE)	12 Months Mean (SE)
SCARED [b,c] (anxiety; 10-20 years, n=50)	-1.065 (.103)	**<.001**	.013 (.002)	**<.001**	37.8 (1.9)	18.9 (1.9)	18.6 (2.3)
HADS-A[c] (anxiety; 21-25 years, n=20)	-.216 (.037)	**<.001**	.003 (.001)	**<.001**	9.5 (0.6)	5.9 (0.6)	6.3 (0.6)
CDI (depression; 10-17 years, n=35)	-.078 (.013)	**<.001**	NA	NA	9.0 (0.8)	6.9 (0.7)	4.9 (0.8)
BDI-II[c] (depression; 18-25 years, n=35)	-.360 (.057)[d]	**<.001**	.005 (.001)	**<.001**	13.9 (1.2)	5.8 (1.1)	5.2 (1.2)
IMPACT-III Total score [b] (HRQOL; 10-20 years, n=50)	.223 (.035)	**<.001**	NA	NA	140.1 (2.0)	146.1 (1.8)	151.9 (2.1)
IMPACT-III Social functioning (10-20 years, n=50)	.055 (.013)	**<.001**	NA	NA	49.5 (0.8)	51.0 (0.7)	52.4 (0.8)
IBDQ Total score (HRQOL; 21-25 years, n=20)	.292 (.094)	**.003**	NA	NA	168.1 (3.8)	176.0 (3.1)	183.5 (4.2)
IBDQ Social functioning (21-25 years, n=20)	.060 (.029)	**.006**	NA	NA	29.7 (0.9)	31.3 (0.8)	32.9 (1.0)
CERQ Adaptive coping (10-25 years, n=70)	-.086 (.037)	**.024**	NA	NA	59.1 (1.8)	56.8 (1.7)	54.6 (2.1)
CERQ Maladaptive coping (10-25 years, n=70)	-.092 (.020)	**<.001**	NA	NA	27.8 (0.9)	25.3 (0.8)	22.9 (1.1)
B-IPQ (illness perceptions; 10-25 years, n=70)	-.149 (.022)	**<.001**	NA	NA	39.9 (1.3)	35.9 (1.2)	32.0 (1.4)
YSR/ASR (sleep problems; 10-25 years, n=70)	-.004 (.003)	.070	NA	NA	0.8 (0.1)	0.7 (0.1)	0.6 (0.1)

Notes. NA= not applicable. [a] For the SCARED, HADS-A, CDI, BDI-II, CERQ Adaptive coping, B-IPQ, and YSR/ASR, a negative beta indicates improvement of problems. For the IMPACT-III, IMPACT-III Social functioning, IBDQ, IBDQ Social functioning, and CERQ Maladaptive coping, a positive beta indicates improvement of problems. For all outcomes the beta is the time effect for both groups, unless otherwise specified. [b] For these outcomes the linear mixed model also included a random slope for time, whereas for all the other outcomes the model included only fixed factors and a random intercept. [c] For these outcomes the linear mixed model also included a quadratic term of time. [d] Since the interaction of time and group is significant for the BDI-II, this beta is the time effect for the control group.

DISCUSSION

In the current RCT we examined the long-term effects of a disease-specific CBT on psychological outcomes of youth with IBD. The results showed that, overall, both groups improved on anxiety and depressive symptoms, HRQOL, social functioning, coping, and illness perceptions and that these improvements sustained until the final follow-up assessment at 12 months. In both groups a similar proportion of patients improved in anxiety and/or depression (main analyses) and the groups did not differ in the proportion of patients that developed clinical anxiety and/or depression. However, in general, no differences between the CBT and CAU groups were found.

Our results are partly in line with results of earlier similar trials. Levy et al. [20] found that three sessions of social learning and cognitive behavioral therapy (SLCBT) outperformed educational support, but only in improving HRQOL (after 1 week of follow-up), coping and school attendance (after 12 months of follow-up), and in parent- and child-reported distract/ignore coping of the child. In line with our results, no beneficial effect of SLCBT was found on anxiety, depression, or coping or functional disability. Szigethy et al. [22] compared CBT with supportive nondirective therapy and found that CBT outperformed supportive nondirective therapy in improving disease activity after three months, with a difference of 10 points in raw disease activity scores from pre- to post-intervention. When only data of patients with active CD were analyzed, CBT was more effective than supportive nondirective therapy in improving disease activity and somatic depressive symptoms after three months of treatment [64].

Explanations for the lack of an effect of the disease-specific CBT in our trial may be the following. Firstly, most patients in our study experienced no or only mild somatic symptoms at baseline, reflected by low IBD disease activity scores. Receiving the full protocol of CBT may have been "over-treatment" in patients with a rather low burden of disease, somatically as well as psychologically. Many patients remarked that the acquired skills would be useful and necessary in times of disease exacerbations. Thus, we hypothesize that CBT may be more useful for patients with severe anxiety/depression and/or those with active disease.

Secondly, patients in the control group may have received more than just standard medical care, because they participated in the trial. Via the informed consent form and the invitation by the medical staff, they were informed about psychological problems in IBD. Then, they were systematically screened with questionnaires and diagnostic interviews. This provided them with the opportunity to express their emotions and concerns, which may have evoked feelings of reassurance and safety. The created awareness may have benefitted all patients, and may have been enough to improve

the subclinical anxiety and depression. This also may be an explanation for the fact that so few patients in both groups developed clinical anxiety and/or depression.

It is unexpected and counter-intuitive that at 12 months of follow-up the proportion of patients that had improved on depressive symptoms was the highest in the CAU group, albeit this was only the case for the 18-25-year old patients. Youth in this age range have a more advanced cognitive development than younger peers. Those receiving CBT may find themselves confronted with the life-long impact of IBD (on for example long-lasting romantic relationships, work, and career prospects. This may maintain the depressive symptoms. Still, this unexpected finding, may have been a chance finding, considering the number of statistical tests. and also considering that at 3 and 6 months no difference in depression was found between the CBT and CAU groups.

Furthermore, at baseline the disease duration in the CBT group was significantly longer than that in the CAU group (2.59 vs. 1.17 years). This may have had an effect on the outcomes, since several studies showed that a shorter disease duration is associated with lower HRQOL or more emotional/behavioral problems [65, 66]. Patients in the CBT group may have had fewer psychological problems, and, therefore, less room to improve. This is not likely, however, considering the fact that both the RCI analysis and the exploratory linear mixed models took into account the baseline psychological outcomes scores.

In addition, since the PASCET-PI was originally developed and found effective for improving mainly depression [22], it was unexpected that we found no differences on depressive symptoms. Furthermore, we found no additional effect on anxiety symptoms, although we adapted the PASCET-PI to also target anxiety. Szigethy et al. [64] only found an additional effect of CBT on somatic depressive symptoms and disease activity in patients with active CD. In our study approximately three-quarters of the patients were in clinical remission, which may explain differences in results.

We also did not find differences between the groups in improvement in coping and negative illness perceptions. For coping or illness perceptions to change after psychological treatment, these should explicitly have been made the focus of treatment. The PASCET-PI contains components that may influence coping (e.g. practicing with positive thinking) and illness perceptions (e.g. discussing the illness narrative of the patient). Perhaps, there was too little focus on challenging coping styles in the current protocol. An alternative explanation may be that the patients experienced little negative illness perceptions, due to the low levels of disease activity [e.g. 67, 68]. However, the secondary analyses were exploratory (and conducted in subgroups of patients based on age). As a consequence, this study may have not been the most suitable to investigate coping and illness perceptions. Future studies should therefore

investigate how coping and illness perceptions can be the focus of psychological treatment to improve anxiety and depression.

Clinical and future directions

Considering the results of the current study and that of earlier studies into CBT for youth with IBD [20, 22, 64], it remains unclear which patients with IBD will benefit the most from CBT, how the intervention should be delivered, and which outcomes improve the most.

Based on our findings, providing a full protocol of disease-specific CBT seems not necessary for preventive purposes. We assume that that patients with more clinical anxiety and/or depression likely will benefit more from CBT, as was found in both youth [22] and adults with IBD [69]. Moreover, although this is not clear yet, a full protocol of CBT may be more helpful for improving their psychological as well as somatic symptoms of IBD patients who suffer from active disease. However, since these patients are often hospitalized or need intensive pharmacological treatment, it is important to find out how the CBT can be delivered best to them (e.g. via telephone or Internet). Group interventions in the hospital have been shown to be promising in youth with IBD [70] and effective in youth with chronic illnesses (including IBD) [71]. Furthermore, apart from anxiety, depression and HRQOL, other clinically relevant psychological outcomes such as social functioning, school attendance, or treatment adherence may be important to target as well. Psychological interventions aiming at these outcomes have been shown to be effective in youth with either IBD or other chronic illnesses [72, 73].

Strengths and limitations

One of the strengths of the current study is the randomized and prospective design, in which the interviewer and the treating physicians were blinded to the group assignment. In addition, we included patients with a broad and clinical relevant age range and our findings have external validity since patients came from both rural and urban centers (including different therapists). Furthermore, the study had very low attrition and we investigated several psychological outcomes. An important limitation is that we did not control for attention placebo effects. We chose to use standard medical care as control condition, because it was already known that CBT as state-of-the-art psychotherapy performs better than placebo for anxiety and depression. Therefore, we deemed this as the most clinical relevant comparison, considering that this resembles our current care best. Furthermore, the relatively small sample size is a limitation, although the study was sufficiently powered. In addition, to cover the whole age-range, we had to use several different age-specific instruments, making it

difficult to combine all patients in one analysis. Consequently, the exploratory linear mixed models could only be performed on subgroups.

Conclusion

The current RCT showed that, in general, patients in both the CBT and the control group remained stable, improved or deteriorated on their psychological outcomes 6 and 12 months after baseline. CBT did not have an additional effect in improving anxiety, depression, HRQOL, social functioning, coping, illness perceptions, and sleep problems, when compared to CAU. We think that a full protocol of CBT was not necessary in patients with relatively low somatic and psychological burden and that the awareness created by participating in an RCT had a positive effect on the psychological outcomes of patients in both groups.

Acknowledgements

We thank our financial supporters *Stichting Crohn en Colitis Ulcerosa Fonds Nederland | Maag Lever Darm Stichting, Fonds NutsOhra*, *Stichting Theia*, and *Stichting Vrienden van het Sophia*. Furthermore, we are very grateful to the patients and their parents that consented, and to the participating hospitals and their professionals that included patients: Erasmus Medical Center (coordinating center), Albert Schweitzer Hospital, Maasstad Hospital, Haga Hospital, Amphia Hospital, Leiden University Medical Center. We also thank the psychologists that provided the therapy.

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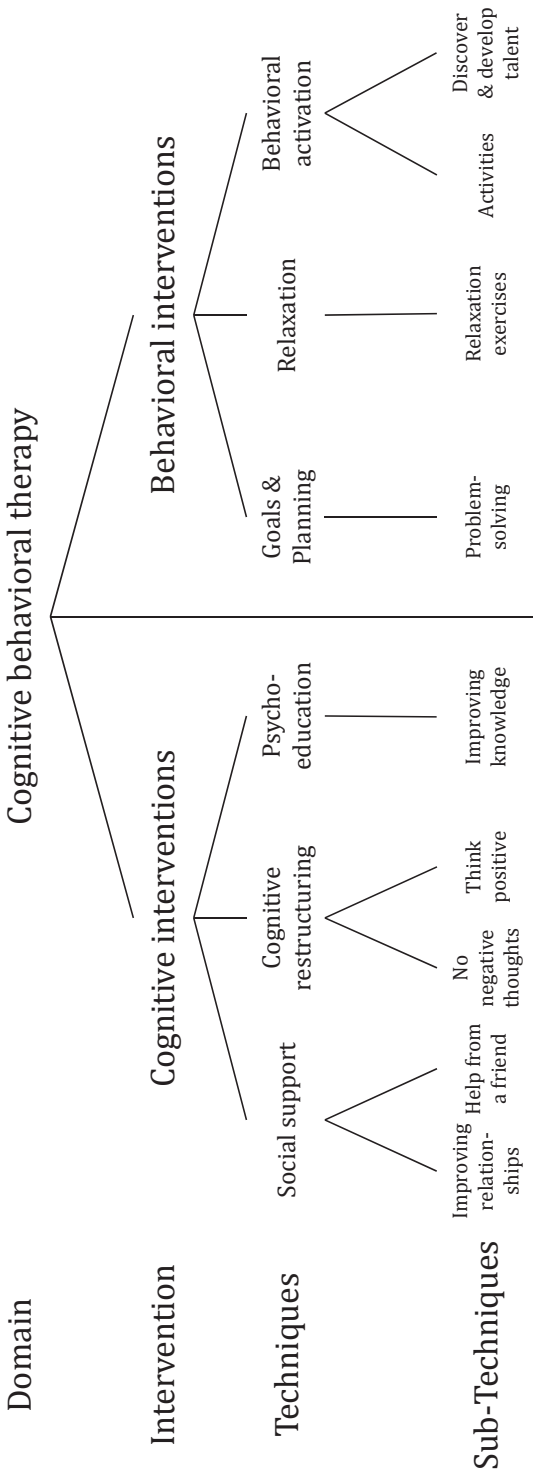
APPENDIX 1. OUTLINE OF THE PASCET-PI [29, 30] AND TREE DIAGRAM

APPENDIX 1 | Outline of the PASCET-PI [29, 30] and tree diagram

Session number	Content of session
Session 1 *Live (60 min)*	Introduction of **ACT** & **THINK** model and PASCET-PI, building work alliance, psycho-education about IBD and depression or anxiety, illness narrative
Session 2 *Live (60 min)*	Mood monitoring, explaining link between feelings, thoughts and behaviors, discussing feeling good and feeling bad, problem-solving
Session 3 *By telephone (30 min)*	Link between behavior and feelings: **A**ctivities to feel better
Session 4 *Live (60 min)*	Be **C**alm and Confident: relaxation exercises
Session 5 *Live (60 min)*	Be Calm and **C**onfident: positive self versus negative self, training social skills
Session 6 *By telephone (30 min)*	**T**alents: developing talents and skills makes you feel better
Session 7 *Live (60 min)*	Social problem solving, discussing the **ACT** skills and introduction of the **THINK** skills with discussing negative thoughts (**T**hink positive)
Session 8 *By telephone (30 min)*	**H**elp from a friend, **I**dentify the 'Silver Lining', and **N**o replaying bad thoughts
Session 9 *By telephone (30 min)*	**K**eep trying – Don't give up, making several plans to use the **ACT** & **THINK** skills
Session 10 *Live (60 min)*	Quiz on **ACT** & **THINK** model, discussing use of **ACT** & **THINK** skills in the future, updating illness narrative
Booster 1 *By telephone (30 min)*	Several plans to use the **ACT** & **THINK** skills, updating illness narrative, personalizing **ACT** & **THINK** skills
Booster 2 *By telephone (30 min)*	Several plans to use the **ACT** & **THINK** skills, updating illness narrative, personalizing **ACT** & **THINK** skills
Booster 3 *By telephone (30 min)*	Several plans to use the **ACT** & **THINK** skills, updating illness narrative, personalizing **ACT** & **THINK** skills
Family 1 *Live (60 min)*	Parental view on IBD, family situation, psycho-education about IBD and depression or anxiety, introduction of **ACT** & **THINK** model and PASCET-PI
Family 2 *Live (60 min)*	Parental view on progress, the **ACT** & **THINK** skills that are most effective for the patient, expressing emotions within family, family communication, family stress game
Family 3 *Live (60 min)*	Parental view on progress, family communication, parental depression or anxiety

Abbreviations: IBD= Inflammatory Bowel Disease; PASCET-PI= Primary and Secondary Control Enhancement Training for Physical Illness.


Domain
Intervention
Techniques
Sub-Techniques
Cognitive behavioral therapy
Cognitive interventions
Social support
Improving relation-ships
Help from a friend
Cognitive restructuring
No negative thoughts
Think positive
Psycho-education
Improving knowledge
Behavioral interventions
Goals & Planning
Problem-solving
Relaxation
Relaxation exercises
Behavioral activation
Activities
Discover & develop talent
Parental involvement
Parental depression & anxiety
Parental psycho-education
Family communication
Expressing emotions in familiy

APPENDIX 2. CALCULATION OF RELIABLE CHANGE INDEX (RCI) VARIABLES

Step 1. Calculating the standard error of difference for each participant, separately for anxiety and depression:

$$RC = \frac{x_2 - x_1}{S_{diff}} \qquad S_{diff} = \sqrt{2(S_E)^2} \qquad S_E = S_1\sqrt{1 - r_{xx}}$$

In which x_1 and x_2 are the individual's scores on baseline and at follow up, respectively. S_1 is the pre-test variance for that instrument. r_{xx} is the test-retest reliability of the instrument as reported in the manual.

- SCARED (10-20 years): r_{xx} = .81 [47] | S_1 = 13.389| S_{diff} = 8.253
- HADS-A (21-25 years): r_{xx} = .89 [74] | S_1 = 2.373| S_{diff} = 1.113
- CDI (10-17 years): r_{xx} = .86 [34]| S_1 = 4.648| S_{diff} = 2.459
- BDI-II (18-25 years): r_{xx} = .93 [35] | S_1 = 4.38| S_{diff} = 1.639

Step 2. Calculating the difference between the follow up and the baseline for each participant, separately for anxiety and depression.

Step 3. Calculating the RC value for each participant, separately for anxiety and depression.

Step 4. Determining the RCI value for each participant, separately for anxiety and depression. Both for anxiety and depression this leads to a variable with three possible values: no reliable change, reliable deterioration, and reliable improvement. An RC value of between -1.96 and 1.96 indicates no reliable change ($p < .05$). When RC is higher than 1.96, this indicates a reliable increase in the score ($p < .05$), i.e. reliable deterioration (as for all the instruments applies that a higher score represents more symptoms). When RC is lower than -1.96, this indicates a reliable decrease in the score ($p < .05$), i.e. reliable improvement.

APPENDIX 3. BASELINE DEMOGRAPHIC AND DISEASE CHARACTERISTICS

	PASCET-PI group (n=37)	CAU group (n=33)	*p-value*
Demographic status			
Male, n (%)	10 (27.0)	12 (36.4)	.401[a]
Age, mean (SD), years	18.62 (4.27)	17.69 (4.82)	.393[b]
SES, n (%)			
Low	8 (21.6)	4 (12.9)	
Middle	15 (40.5)	10 (32.3)	.348[a]
High	14 (37.8)	17 (54.8)	
Ethnicity, n (%) (n = 64)			
Dutch / Western	30 (81.1)	25 (80.6)	.749[a]
Other	7 (18.9)	6 (19.4)	
Included on, n (%)			
Anxiety	30 (81.1)	20 (60.6)	
Depression	0 (0.0)	3 (9.1)	.070[a]
Both	7 (18.9)	10 (30.3)	
IBD subtype, n (%)			
Crohn's disease	18 (48.6)	18 (54.5)	
Ulcerative colitis	14 (37.8)	12 (36.4)	.808[a]
IBD-U	5 (13.5)	3 (9.1)	
Paris classification at diagnosis, n (%)			
CD: location[†] (n = 36)			
L1	4 (22.2)	2 (11.1)	
L2	4 (22.2)	4 (22.2)	.813[a]
L3	6 (33.3)	8 (44.4)	
+ L4a/L4b	4 (22.2)	4 (22.2)	
CD: behavior (n = 36)			
Nonstricturing, nonpenetrating	18 (100.0)	16 (88.9)	.243[c]
Stricturing, penetrating, or both	0 (0.0)	2 (11.1)	
UC: extent[‡] (n = 34)			
Limited: E1 + E2	11 (57.9)	4 (26.7)	.069[a]
Extensive: E3 + E4	8 (42.1)	11 (73.3)	
UC: severity			
Never severe	18 (94.7)	11 (73.3)	.104[c]
Ever severe	1 (5.3)	4 (26.7)	
Clinical disease activity, n (%)			
Remission	27 (73.0)	26 (78.8)	.571[a]
Mild	10 (27.0)	7 (21.2)	

	PASCET-PI group (n=37)	CAU group (n=33)	*p-value*
Disease duration, median, years	2.59	1.17	.039[d]
IBD Medications, n (%)			
Aminosalicylates	18 (48.6)	12 (36.4)	.300[a]
Immunomodulators	16 (43.2)	16 (48.5)	.660[a]
Biologicals	8 (21.6)	12 (36.4)	.173[a]
Corticosteroids[§]	2 (5.4)	5 (15.2)	.170[c]
Enemas	3 (8.1)	1 (3.0)	.352[c]
No medication	2 (5.4)	1 (3.0)	.543[c]

Abbreviations: PASCET-PI= Primary and Secondary Control Enhancement Training for Physical Illness; CAU= care-as-usual; SD= Standard Deviation; IBD= Inflammatory Bowel Disease; IBD-U= Inflammatory Bowel Disease Unclassified; SES= Socioeconomic Status.
Notes: [a] chi-square, [b] ANOVA, [c] Fisher's Exact test, [d] Mann-Whitney test | * UC includes IBD-U patients, [†] L1: ileocecal, L2: colonic, L3: ileocolonic, L4a: upper gastrointestinal tract proximal, and L4b distal from Treitz ligament [‡] E1: proctitis, E2: left sided colitis distal of splenic flexure, E3: extensive colitis distal of hepatic flexure, E4: pancolitis [§] prednisone (oral and intravenous) and budesonide (oral)