Effect of cognitive behavioral therapy on clinical disease course in adolescents and young adults with inflammatory bowel disease and subclinical anxiety and/or depression: results of a randomized trial

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ABSTRACT

Background Anxiety and depressive symptoms are prevalent in patients with inflammatory bowel disease (IBD) and may negatively influence disease course. Alternatively, disease activity could be affected positively by treatment of psychological symptoms. We investigated the effect of cognitive behavioral therapy (CBT) on clinical disease course in 10-25-year-old IBD patients experiencing subclinical anxiety and/or depression.

Methods In this multicenter parallel group randomized controlled trial, IBD patients were randomized to disease-specific CBT in addition to standard medical care (CBT + care-as-usual [CAU]) or CAU only. The primary outcome was time to first relapse in the first 12 months. Secondary outcomes were clinical disease activity, fecal calprotectin and C-reactive protein (CRP). Survival analyses and linear mixed models were performed to compare groups.

Results Seventy patients were randomized (CBT+CAU=37, CAU=33), with a mean age of 18.3 years (±50% < 18 y) (31.4% male, 51.4% Crohn's disease, 93% in remission). Time to first relapse did not differ between patients in the CBT+CAU vs CAU group (n=65, p=0.915). Furthermore, clinical disease activity, fecal calprotectin and CRP did not significantly change over time between/within both groups. Exploratory analyses in 10-18-year-old patients showed a 9% increase/month of fecal calprotectin as well as a 7% increase/month of serum CRP in the CAU group, which was not seen in the CAU+CBT group.

Conclusions CBT did not influence time to relapse in young IBD patients with subclinical anxiety and/or depression. However, exploratory analyses may suggest a beneficial effect of CBT on inflammatory markers in children.

INTRODUCTION

Inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis [UC]) is a chronic inflammatory disorder of the intestine, and is often accompanied by embarrassing, invalidating and unpredictable intestinal and systemic symptoms [1].

Having IBD in adolescence impacts the lives of young IBD patients and is a threat to a healthy psychosocial development. Patients may suffer from an altered self-image [2], the unpredictability of the disease, social isolation[3], family and school dysfunction, and school problems [4, 5]. Consequently, having IBD challenges a smooth transition to adulthood [6]. Studies show that adolescent and adult IBD patients are at risk for anxiety and depression [7, 8] Recent meta-analyses in children and adults have shown pooled prevalence rates ranging from 16.4-35.1% for anxiety symptoms, and 15.0-21.6% for depressive symptoms [9, 10].

The bidirectional relationship between IBD and psychological problems can be explained in terms of the 'brain-gut'-axis [11], meaning that the presence of anxiety and/or depressive symptoms or disorders can increase intestinal inflammation and may contribute to disease relapse, and conversely, intestinal inflammation can negatively influence mood [11, 12]. Several cross-sectional studies support this hypothesis by showing an association between clinical disease activity and symptoms of anxiety [9, 12-14] or depression [9, 12, 13]. In addition, this association has also been studied longitudinally. In a recent systematic review 5 out of 11 studies reported an association between depressive symptoms and worsening of disease course [15]. Similarly, for anxiety symptoms some studies did report this association [12, 16], while others did not [17, 18]. Besides the influence of anxiety and/or depressive symptoms on disease activity and disease course, IBD patients with psychological symptoms are at risk for school or work absenteeism [19, 20], lower therapy adherence [8], higher health care utilization [8, 14], all leading to high societal costs [21]. Therefore, studies on the effect of psychological treatment on disease course and these other aspects are warranted.

At present, cognitive behavioral therapy (CBT) is the most effective evidence based psychological treatment for anxiety and depressive symptoms and disorders in patients of all ages [22, 23] and has been found to be effective in reducing anxiety and depressive symptoms in both pediatric [24, 25] and adult [26] IBD patients.

Studies investigating the effect of CBT on disease activity or disease course in patients with both anxiety and/or depressive symptoms or disorders are scarce. A randomized trial by Szigethy et al. studied two psychotherapies (CBT and supportive nondirective therapy) in adolescents with IBD with both minor and major depression. The authors report an improvement in clinical disease activity scores (raw increase of ±10 points on both the Pediatric Ulcerative Colitis Activity Index [PUCAI] and the Pediatric Crohn's Disease Activity Index [PCDAI]) in the first 3 months in both groups,

favoring CBT [25]. In addition, a pilot study including 9 patients investigated the effect of CBT on clinical disease activity (PCDAI, PUCAI) in adolescent IBD patients suffering from an anxiety disorder, and showed that clinical disease activity improved from mild to inactive in half of the patients after 3 months [24].

Therefore, we performed a randomized controlled trial (RCT) in IBD patients aged between 10 and 25 with subclinical anxiety and/or depression and evaluated the effect of CBT on the course of anxiety, depression, disease course and inflammatory markers. The current study focused on the effect of 3 months of CBT on disease course in the following year. The primary outcome was time to first relapse, secondary outcome measures were clinical disease activity, C-Reactive Protein (CRP) and fecal calprotectin. We hypothesized that CBT would promote sustained remission, prolong the time until the first relapse and reduce clinical disease activity and inflammatory markers.

MATERIALS AND METHOD

Design

This multicenter parallel group RCT was designed according to the CONSORT guidelines for trials of non-pharmacologic treatments [27] and was registered at ClinicalTrials.gov with study number NCT02265588. Participants were recruited from two university and four community hospitals in the South-West of The Netherlands from September 2014 until October 2016. Initially, only adolescents aged 10-20 years were included in the study, a few months after start of recruitment patients aged 21-25 years were also recruited. We chose to include adolescent and young adult patients because the impacts and challenges of a chronic disease in this unique life phase are different compared with what pediatric or adult patients are facing.

Eligible patients were screened for anxiety and/or depressive symptoms. Patients with symptoms of anxiety or depression or both were included, because anxiety and depressive symptoms often occur together and can both impact disease activity in IBD [16, 28]. Patients with subclinical/elevated symptoms, who did not meet the criteria of a psychiatric disorder, were randomized to either a 3-month course of disease-specific CBT (CBT+CAU) in addition to care-as-usual or to the control condition, Care as Usual (CAU). After randomization, medical and psychological data were collected at baseline, and at 3, 6, and 12 months. Nine-month medical data was only collected if in routine medical care patients had scheduled appointments every 3 month. For more information regarding the study design, see van den Brink & Stapersma et al. [29].

Measurements

Demographic characteristics Age and gender were collected at baseline. Socioeconomic status was classified using the occupational level from parents or, if patients lived on their own, patients [30]. Ethnicity was derived from the Rotterdam's Quality of Life Interview [31].

Clinical characteristics At baseline, disease type, age at diagnosis, disease duration, disease phenotype at diagnosis (Paris or Montreal classification) [32], previous and current therapy, previous bowel surgery and previous relapses were collected.

Anxiety and depressive symptoms For anxiety the Screen for Child Anxiety Related Emotional Disorders [33] (SCARED; 10-20 years; cutoff ≥26 for boys and ≥30 for girls) and the Hospital Anxiety and Depression Scale – Anxiety Scale [34] (HADS-A; 21-25 years; cutoff ≥8) were used. For depression the Child Depression Inventory [35] (CDI; 10-17 years; cutoff ≥13) and the Beck Depression Inventory – second edition [36] (BDI-II; 18-25 years; cutoff ≥14) were used.

Clinical disease activity Clinical disease activity was assessed by four validated, physician-reported, age appropriate instruments, with higher scores indicating more active disease.

In UC patients the Pediatric Ulcerative Colitis Activity Index [37] (PUCAI; 10-20 years; score 0-85) and the partial Mayo [38] (pMayo; 21-25 years; score 0-9) were used. In CD patients, the Pediatric Crohn's Disease Activity Index [39] (PCDAI; 10-20 years; total score 0-100) and the Crohn's Disease Activity Index [40] (CDAI; 21-25 years; score 0-600) were used.

Relapse The presence of a relapse at any time point during follow-up was determined by the treating physician. For UC, relapse was defined as follows: (a) clinical disease activity score above cutoff (PUCAI >34 or an increase of ≥20 points or pMayo ≥3 [41, 42]) or (b) fecal calprotectin above 250 µg/g [43] or (c) inflammation at endoscopy and (d) intensification of treatment. For CD, relapse was defined as: (a) clinical disease activity score above cutoff (PCDAI >30 or an increase of ≥15 points or CDAI score >150 [40, 44]) or (b) fecal calprotectin above 250 µg/g [43] or (c) inflammation at endoscopy and (d) intensification of treatment. In addition, perianal disease requiring intervention in CD patients was also considered a relapse. If patients experienced a relapse at baseline, this relapse was not taken into account and monitoring for relapse started after remission was achieved.

Inflammatory markers C-reactive protein (CRP) and fecal calprotectin were obtained during visits to the outpatient clinic as part of routine clinical care.

Recruitment and procedure

Step 1: Screening

Eligible patients (and parents, for patients age 10-20 years) were informed about the study by their treating (pediatric) gastroenterologist. Preferably, patients were recruited when they were in clinical remission, considering the impact of the intervention. The following in- and exclusion criteria were used: (1) a diagnosis of IBD conform current diagnostic criteria [45-47] (2) age 10-25 years and (3) informed consent provided by patients and (if necessary) parents. Exclusion criteria were: (1) (parental report of) intellectual disability, (2) current treatment for mental health problems (pharmacological and/or psychological), (3) insufficient mastery of the Dutch language, (4) CBT in the past year (for at least 8 sessions), (5) a diagnosis of selective mutism, bipolar disorder, schizophrenia, autism spectrum disorder, obsessive-compulsive disorder, posttraumatic or acute stress-disorder, (6) participation in another interventional study and (7) anxiety/depressive disorder. After written informed consent, an email with a link to the online questionnaires was sent to the patients (and parents). Anxiety and depressive symptoms were assessed using age-appropriate self-report instruments (see "measurements"). For more information regarding step 1, see van den Brink et al. [13].

Step 2: Inclusion RCT

If patients scored above the cutoff of the anxiety and/or depression questionnaire, a trained psychologist performed a diagnostic psychiatric interview (Anxiety Disorders Interview Schedule - Child and Parent Versions (ADIS-C/P) [48]) by telephone to determine the severity of the symptoms using age appropriate severity rating scales. The Pediatric Anxiety Rating Scale [49] (PARS; 10-20 years; cutoff ≥18) and the Hamilton Anxiety rating scale [50, 51] (HAM-A; 21-25 years; cutoff ≥15) were used for anxiety symptoms. Depression was rated using the Child Depression Rating Scale Revised [52] (CDRS-R; 10-12 years; cutoff ≥40), the Adolescent Depression Rating Scale Revised [53] (ADRS-R; 13-20 years; cutoff ≥20) and the Hamilton Depression Rating Scale [54, 55] (HAM-D; 21-25 years; cutoff ≥17). A psychiatric disorder was defined as meeting criteria for an anxiety or depressive disorder on the ADIS-C/P and a score equal to or above the clinical cutoff on the rating scale. Patients with subclinical anxiety/depression (elevated symptoms of anxiety and/or depression not meeting the criteria for a psychiatric disorder) were eligible for randomization. Patients with an anxiety/depressive disorder were directly referred for psychological treatment and were excluded from the RCT since it would be unethical to randomize patients to the CAU condition.

Randomization

Patients with subclinical anxiety and/or depression were randomized to CBT+CAU or CAU with a 1:1 ratio. 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. After randomization, treatment in the CBT+CAU group started within a maximum of 4 weeks. The physicians assessing the disease activity and the psychologist conducting the diagnostic interviews were blinded for outcome of randomization. As patients could not be blinded, they were explicitly asked not to discuss the outcome of randomization with their treating physician.

Intervention

The Primary and Secondary Control Enhancement Therapy (PASCET) is a manual-based CBT protocol, originally designed to treat depression [56]. In this study the PASCET-Physical Illness (PASCET-PI) was used, an IBD-specific modification which encompasses the illness narrative (i.e. perceptions and experiences of having IBD), disease-specific psychoeducation, techniques for coping with pain, social skills training and emphasis on IBD-related cognitions and behaviors [57]. The protocol was modified to treat anxiety as well, and adjustments were made to make it age appropriate for patients aged 21-25 years. Participants received ten weekly sessions in a timespan of twelve weeks (6 face-to-face, 4 by telephone), three additional family sessions (for patients <18 years and voluntary for patients >18 years living with their parents) and after the first 12 weeks three-monthly booster sessions. Patients were considered treatment completers if they had followed at least 8 sessions. The therapy was provided by all licensed (healthcare/CBT) psychologists, who received onsite training from the developer (E.M. Szigethy) of the PASCET-PI and executed the therapy in their own hospital or center.

CAU consisted of regular medical appointments with the (pediatric) gastroenterologist every 3 months, involving a 15-30 minute consultation discussing overall wellbeing, disease activity, results of diagnostics tests, medication use, and future diagnostic/treatment plans, but no psychological intervention.

Sample Size and Power

In our previously published study protocol, the primary outcome was defined as relapse rate per group in the first year after randomization [29]. As the study continued and inclusion appeared challenging, we decided to also include 21-25 year old patients and re-estimate the sample size [58]. Adapting the primary outcome to time to first relapse reduced the required sample size.

Literature shows that in general, approximately 40% of IBD patients have at least one relapse per year [59, 60]. Based on expert opinion and previous studies [61, 62] a 30% difference was expected between the 2 groups (survival rate 0.6 CBT; 0.9 CAU). To detect a difference of 0.3 in survival rate after 52 weeks of follow up, with a 2-sided

significance level of 5% and 80% power, 37 patients were need in each group. With 65 patients in remission at baseline, the study had a power of 77%.

Statistical Analysis

Descriptive statistics were computed for demographic and clinical characteristics for the entire cohort and each treatment group. T, Chi^2/Fisher exact and Mann-Whitney-U tests were used, where appropriate, to assess baseline differences between treatment groups.

For the primary outcome time to first relapse, survival analyses were performed. Kaplan-Meier curves were tested with a two-sided log rank test. For this analysis, patients with a relapse at baseline were excluded. For the longitudinally measured secondary outcomes clinical disease activity, CRP and calprotectin, differences between the groups were assessed using linear mixed effects models to account for the correlations in the repeated measurements. All 4 clinical disease activity scores were converted to a 0-1 score (Supplementary Table 1, step 1). This pooled disease activity score enabled us to include all patients in one analysis. As all three secondary outcomes had a non-normal distribution, transformations were done to assure normality. CRP and calprotectin were transformed using the natural logarithm. For pooled clinical disease activity, a two-step logistic transformation was performed (Supplementary Table 1, Step 2 and 3). In all three linear mixed models, treatment condition (result of randomization), time in months and the interaction between time*treatment were added in the specification of the fixed effects. A likelihood ratio test (LRT) was used to specify the random effects. With the LRT the model with a random intercept only (covariance structure: identity) was compared with the model with both a random intercept and random slope (covariance structure: unstructured). Restricted maximum likelihood (REML) was applied as the estimation method. Assumptions of the models were checked using residual plots. Considering the previous findings in pediatric patients [25], exploratory analyses were performed in patients 10-18 years of age.

All analyses were performed based on the intention-to-treat (ITT) principle. For patients with missing and/or incomplete assessments, only available data were used. A p-value of <0.05 was considered statistically significant. Data analyses were performed using SPSS version 24.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA).

Ethical considerations

This study conformed to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Erasmus Medical Center and of each participating center.

RESULTS

Patient characteristics

A total of 552 patients were eligible to participate, of which 374 patients completed the anxiety and depression questionnaires at baseline. Of the 371 patients who completed both questionnaires, 47.4% experienced elevated symptoms of anxiety and/or depression. Of the 134 patients who participated in the diagnostic psychiatric interview, 46 patients (34%) met the criteria for a psychiatric disorder and 88 patients (66%) experienced subclinical symptoms of anxiety and/or depression [13]. Of these 88, 70 patients (80%) gave consent for randomization (CBT+CAU [n=37] CAU [n=33]) (Figure 1).

Of all randomized patients, 68.6% were female, ± 50% was <18 years of age (median age [interquartile range] 18.27 [14,5 – 22,37] years. 51.4% had a diagnosis of CD, 80.9% had a Western ethnicity and socioeconomic status was respectively low, middle and high in 17.1%, 36.8% and 45.6% (data not shown). Patients were included based on anxiety symptoms (71.4%), depressive symptoms (4.3%) or both (24.3%). Five patients experienced a relapse of IBD at baseline.

There were no baseline differences between the CBT+CAU versus the CAU group for demographic and disease characteristics, except for disease duration ($p = 0.03$) and corticosteroid dependency the past 3 months ($p = 0.03$) (Table 1).

Protocol adherence

Thirty-four out of 37 (92%) patients allocated to CBT+CAU completed ≥8 CBT-sessions (treatment completers). The other 3 patients followed 5, 3 and 1 sessions respectively. The mean number of treatment sessions followed was 9.38.

During follow-up, 2 patients in the CAU group (at 6 and 9 months) and one patient in the CBT+CAU group (at 3 months) developed severe symptoms meeting the criteria for a psychiatric disorder (2 patients with anxiety disorders, and 1 with anxiety and depressive disorder) and were directly referred for psychiatric/psychological help, whereas follow-up data was collected for the ITT analysis. Of these patients, all follow up assessments were completed. Furthermore, on persistent parental request 1 patient switched from the CAU to the CBT+CAU group after 3 months, follow up data was collected, and analyses were performed according to the intention to treat principle (CAU group). Three patients missed one or more follow-up assessments (1 CAU group, 2 CBT+CAU group): 2 patients missed the 6-month visit and 1 patient missed all visits after baseline. Nine-month medical data were collected for 26 patients.

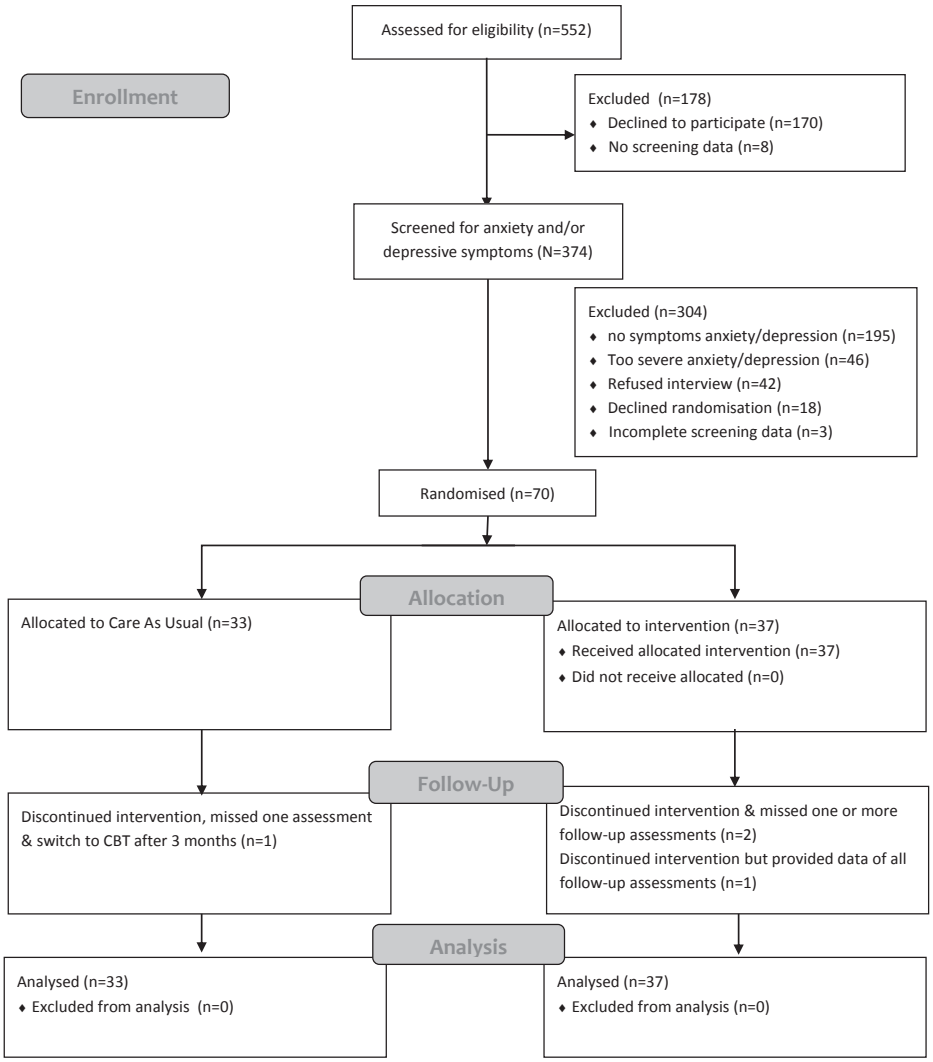

Figure 1 | CONSORT study flow chart
Abbreviations: CBT= cognitive behavioral therapy

Primary outcome: time to first relapse

During 52 weeks of follow up, 16 patients (43.2%) in the CBT+CAU group and 16 patients (48.5%) in the CAU group experienced one or more relapse. For the 65 patients in remission at baseline, no difference in time-to-relapse between groups was found (p 0.915) (Figure 2).

Table 1 | *Patient characteristics*

		CBT (n=37) *Median (IQR) or n (%)*	CAU (n=33) *Median (IQR) or n (%)*	*p*-value
Gender, Male		10 (27%)	12 (36.4%)	0.40
Age (years) (% <18 years)		18.5 (16.1-23.0)(48%)	18.0 (13.7-21.8) (51%)	0.37
Age at diagnosis (years)		15.7 (12.8-17.8)	14.9 (11.2-19.6)	0.90
Duration of disease (years)		2.6 (1.8-5.3)	1.3 (0.7-3.3)	***0.03***
Disease Type	CD	18 (48.6%)	18 (54.5%)	0.84
	UC	14 (37.8%)	12 (36.4%)	
	IBD-U	5 (13.5%)	3 (9.1%)	
Paris classification at diagnosis*:	*CD: location*† (N = 36)			0.83
	L1	4 (22.2%)	5 (27.8%)	
	L2	6 (33.3%)	4 (22.2%)	
	L3	8 (44.4%)	9 (50.0%)	
	+ L4a/L4b	4 (22.2%)	4 (22.2%)	1.00
	CD: behavior			1.00
	Nonstricturing, nonpenetrating	18 (100%)	18 (100%)	
	structuring, penetrating or both	0 (0%)	2 (11.1%)	
	perianal disease	4 (22.2%)	4 (22.2%)	1.00
	UC: extent (N = 34)‡			0.07
	limited: E1 + E2	11 (57.9%)	4 (26.7%)	
	extensive: E3 + E4	8 (42.1%)	11 (73.3%)	
	UC: severity, ever severe	1 (5.3%)	4 (26.7%)	0.15
Clinical Disease activity¥	Remission	29 (78.4%)	26 (78.8%)	0.55
	Mild	6 (16.2%)	7 (21.2%)	
	Moderate	2 (5.4%)	0 (0%)	
	Severe	0 (0%)	0 (0%)	
CRP (mg/L)		2.0 (1.0-5.0)	1 (0.3-4.4)	0.19
Fecal calprotectin (µg/g)		67.5 (24.8-318.5)	169 (19.5-563.0)	0.73
Current medication use	Aminosalicylates	18 (48.6%)	12 (36.4%)	0.30
	Immunomodulators	17 (45.9%)	16 (48.5%)	0.17
	Biologicals	8 (21.6%)	12 (36.4%)	0.66
	Corticosteroids¶	2 (5.4%)	3 (9.1%)	0.83
	Enemas§	4 (10.8%)	0 (0%)	0.12
	No medication	2 (5.4%)	1 (3%)	1.00
Steroid dependence past 3 months		3 (8.1%)	9 (27.3%)	***0.03***
Baseline relapse		4 (10.0%)	1 (3.0%)	0.36

Table 1 | *Patient characteristics (continued)*

		CBT (n=37) *Median (IQR) or n (%)*	CAU (n=33) *Median (IQR) or n (%)*	*p*-value
Relapse preceding year		15 (40.5%)	10 (30.3%)	0.39
Bowel resection in history		3 (8.1%)	2 (6.1%)	1.00
EIM [II]		7 (18.9%)	4 (12.1%)	0.44
Hospital type	University Hospital	16 (43.2%)	15 (45.5%)	0.85
Anxiety and/ or depressive symptoms	Anxiety symptoms	30 (81.1%)	20 (60.6%)	0.08
	Depressive symptoms	0 (0.0%)	3 (9.1%)	
	Both	7 (18.9%)	10 (30.3%)	

Abbreviations: IQR= interquartile range, CD= Crohn's Disease, UC= ulcerative colitis, IBD-U= IBD Unclassified, CRP= C-reactive protein; CBT= cognitive behavioral therapy + care-as-usual, CAU= care-as-usual.

Notes: *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 [¥]Based on clinical disease activity scores (pMayo, PCDAI, PUCAI, CDAI) ¶prednisone (oral and intravenous) and budesonide (oral) [§]aminosalicylate or corticosteroid enemas [||]EIM: involving skin (31.5%), eyes (1.75%), liver and biliary tracts (10.5%), joints (33.3%) and bones (28.1%).

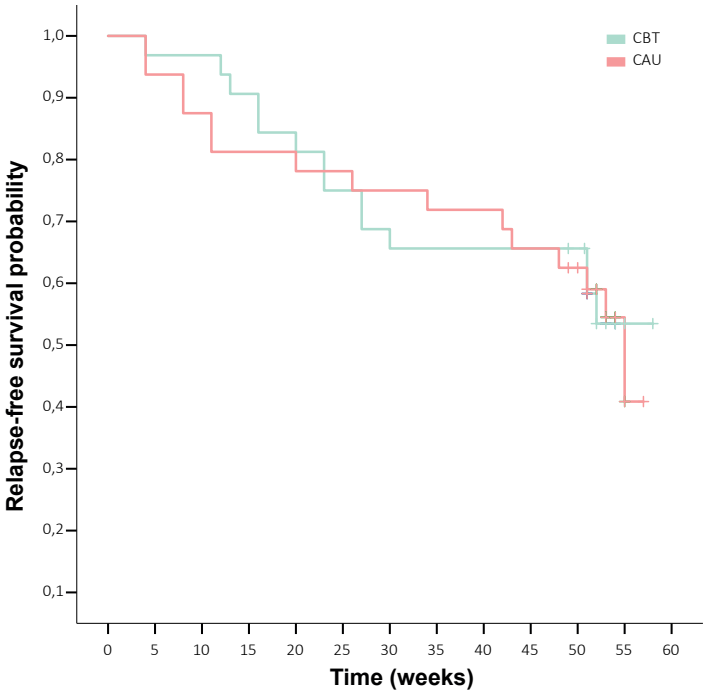

Figure 2 | Survival curve time to first flare
Abbreviations: CBT= cognitive behavioral therapy + care-as-usual; CAU= care-as-usual

Secondary outcomes

Clinical disease activity

Linear mixed model analysis showed no difference in the course of (pooled) clinical disease activity over time between both groups (interaction time*treatment not significant) (Table 2). In addition, no significant changes were found within either the CBT+CAU or the CAU group (Table 2). Raw means of the 4 clinical disease activity scores over time are displayed in Figure 3.

Similarly, exploratory analysis in patients <18 years (n=35) showed no significant difference between both groups (p = 0.20), or within the CBT+CAU (p = 0.92) or the CAU (p = 0.085) group (data not shown). In addition, there was no difference in CD versus UC patients (data not shown).

Table 2 | *Results Linear mixed models (n=70)*

		Time			Interaction time*treatment		
		β	*95% CI*	*p-value*	β	*95% CI*	*p-value*
Clinical disease activity							
Within group	CBT	-0.006	-0.052 - 0.040	0.80			
	CAU	0.012	-0.036 - 0.061	0.61			
Between groups					-0.019	-0.085 - 0.048	0.59
C-reactive protein (mg/dL)							
Within group	CBT	-0.015	-0.050 - 0.020	0.41			
	CAU	0.021	-0.015 - 0.057	0.24			
Between groups					-0.036	-0.086 – 0.014	0.158
Fecal calprotectin (µg/g)							
Within group	CBT	-0.019	-0.075 - 0.037	0.50			
	CAU	0.005	-0.052 - 0.063	0.851			
Between groups					-0.025	-0.11 - 0.056	0.543

Abbreviations: CI= confidence interval, CBT= cognitive behavioral therapy+ care-as-usual, CAU= care-as-usual; β= Beta-coefficient

Note: "Within group" displays whether there is a significant (p-value <0.05) change over time within either the CBT or the CAU group. "Between group" reflects whether the course over time is significantly different between the CAU and CBT group (p-value interaction time*treatment < 0.05)

Inflammatory markers: Fecal calprotectin and C-reactive protein

For CRP and fecal calprotectin, no significant differences were found between the CAU and CBT+CAU group (interaction term not significant). In addition, no significant change was found over time within each group (Table 2, raw means displayed in Supplementary Figure 1).

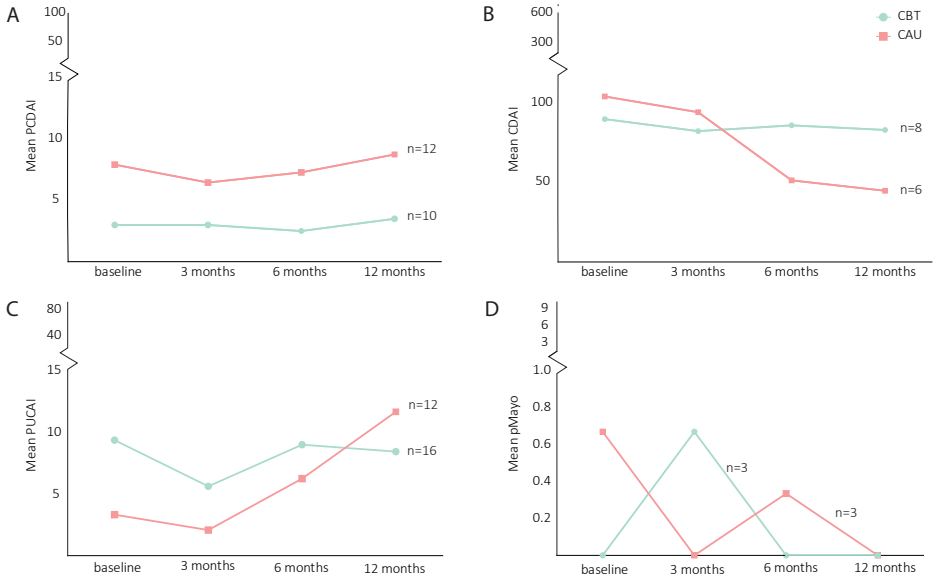

Figure 3 | Raw means of clinical disease activity scores over time
Abbreviations: PUCAI= Pediatric Ulcerative Colitis Activity Index; pMayo= partial Mayo; PCDAI= Pediatric Crohn's Disease Activity Index; CDAI= Crohn's Disease Activity Index; CBT= cognitive behavioral therapy; CAU= care-as-usual

Exploratory analysis in 10-18-year-old patients (n=35) showed that for calprotectin, the interaction between time*treatment was significant (Beta-coefficient (β) -0.11, 95% CI [-0.195 - -0.031], p = 0.008). A statistically significant increase was seen in the CAU group over time (β 0.085, 95% CI [0.028-0.143], p = 0.004), whereas no change was found in the CBT+CAU group (β -0.028, 95% CI [-0.087 - 0.031], p = 0.35). Reverse transformation to the original scale revealed a 9% increase per month in the CAU group (data not shown). For CRP, no change was observed within the CBT+CAU group over time (β -0.012, 95% CI [-0.070 – 0.046], p = 0.68), whereas a significant increase in the CAU group was observed (β 0.069, 95% CI [0.011 – 0.13], p = 0.022). Reverse transformation to the original scale revealed a 7% increase per month in the CAU group. The interaction between time*treatment approached significance (β -0.081, 95% CI [-0.164 – 0.001], p = 0.054) (data not shown). For both CRP and calprotectin, there was no difference between CD and UC patients (data not shown).

DISCUSSION

This study was the first to investigate the effect of CBT versus CAU only on subsequent disease course in young IBD patients with subclinical anxiety and/or depression. We showed that time to first relapse in the first year after randomization did not significantly differ between patients in the CBT+CAU versus the CAU group. Furthermore, (pooled) clinical disease activity, CRP and fecal calprotectin also did not significantly change over time between the CBT+CAU and the CAU group, or within both groups. Exploratory analyses in 10-18-year-old patients suggested a significantly different course of fecal calprotectin between groups, with an increase in the CAU group. In addition, the difference in the course of CRP between the CAU and CBT+CAU group approached significance, with an increase in the CAU group. These results could suggest a possible positive effect of CBT on fecal calprotectin and CRP levels in 10-18-year old patients, with perhaps a positive influence on intestinal inflammation in the longer term. However, this should be replicated in larger patient cohorts.

Within the 'brain-gut-axis' it is hypothesized that a decrease in anxiety/depressive symptoms is accompanied by a decrease in (intestinal) inflammation and vice versa and that it may promote sustained remission. In the current trial both groups equally improved in anxiety/depressive symptoms and HRQOL after 3 [63] and 6-12 months (Stapersma et al. in revision). Therefore, it is not surprising that we did not find a difference in clinical outcomes. As an improvement in anxiety and depressive symptoms within the CBT+CAU and CAU group over time was observed [63], improvement in clinical outcomes within both groups could have been expected. Low baseline clinical disease activity and low baseline inflammatory activity could also explain why we did not find an improvement in clinical disease activity scores, CRP or calprotectin in the whole sample.

Several studies reported on the effect of CBT on clinical disease course, specifically relapse rate, clinical disease activity and CRP. Time-to-relapse has not been studied before. Three studies included adolescent [24, 25, 64], and three included adult [65-68] IBD patients. Only 2 pediatric studies selected patients based on anxiety [24] or depression [25]. In all these studies, mostly patients in clinical remission or with mildly active disease were included. At first, Levy et al. tested the effectiveness of a brief (3 session) CBT (versus education support condition) in 185 adolescent IBD patients unselected for anxiety and depression and mainly in disease remission (63%). In line with our results, they reported no difference in relapse rate between the 2 conditions. An exploratory analysis in patients who experienced ≥2 or more flares in the year prior to the study, showed a decrease in relapse rate following CBT (CBT 16.7%, CAU 52.9% $p = 0.04$) [64]. However, this sub-analysis was limited by the liberal definition of relapse, without considering objective items such as treatment intensification.

Second, Szigethy et al. studied the effect of two psychotherapies (CBT versus supportive nondirective therapy) in 217 adolescents with IBD and minor/major depression. Although it is not reported in the article, looking at the mean PCDAI and PUCAI scores, it can be assumed that most patients were in remission or had mildly active disease. An improvement in depressive symptoms, HRQOL and pooled clinical disease activity after 3 months was found in both groups. However, it should be noted that this improvement corresponded with a rather small, not clinically relevant, decrease in raw disease activity scores of ±10 points on the PCDAI /PUCAI that was reported to be larger in the CBT group [25]. A third study of interest was performed by Mikocka-Walus et al.: it investigated whether adding 10 sessions (face-2-face or online) CBT to standard medical care influenced clinical disease activity in 176 unselected adult IBD patients. Approximately 75% of patients had quiescent disease at baseline. No difference in remission rates after 12 months (73.2% CBT vs 71.7% CAU) or in clinical disease activity scores or CRP levels after 12 and 24 months were reported [66, 67].

In conclusion, studies reporting on the effect of CBT or other psychotherapies on disease course in IBD patients with (sub)clinical anxiety and/or depression are scarce. [69] Only 1 trial in pediatric IBD patients in remission or with mildly active disease reported a small improvement in clinical disease activity after CBT (and supportive non directive therapy) [25]. As far as we know, no studies are available investigating the effect of psychotherapy on disease course in IBD patients with at least moderately active disease and suffering from (sub)clinical anxiety/depression .

Our finding that CBT did not influence time to relapse, relapse rates or clinical disease activity is in accordance with the 2 previous studies in patients unselected for anxiety/depression [64, 66]. In contrast, Szigethy et al. did find a small improvement in disease activity over time in both psychotherapy groups, favoring CBT [25]. In addition, due to the short follow up, it is unclear how this improvement would evolve in the longer term. It should be noted Szigethy et al. is the only RCT to date performed in patients selected for emotional symptoms (minor/major depression).

It is possible that CBT is more effective in improving disease course (reducing inflammation) in patients with more severe anxiety/depression, as more improvement in psychological symptoms can be gained. This could be supported by Szigethy et al. who also included patients with major depression (±60%). In studies that did not select patients on anxiety/depression [64, 66, 67], no improvement in clinical disease activity was found and only one study [68] found a decrease in anxiety/depressive symptoms.

Considering we did not find an effect of CBT on clinical disease course, it is possible that CBT has an effect on other measures of disease course, such as disability, healthcare use (e.g. visits to the Emergency Room) and school absenteeism. This is supported by a study by Keerthy et al., reporting a significant reduction in IBD-related healthcare use following CBT [70]. We attempted to analyze school absenteeism in

our sample, but could only collect data from patients 10-18 years because in The Netherlands only elementary and high schools register (reasons for) absenteeism. For 18 out of 35 children data was available (CBT: n=6, CAU: n=12), unfortunately, due to high heterogeneity of the registration methods used and missing data, analysis was not possible.

It is not likely that baseline differences influenced our results. First, the longer disease duration in the CBT+CAU group could be accompanied by better coping strategies, providing an advantage in learning certain CBT-specific skills. As the improvement of psychological symptoms was similar in both groups [63] (Stapersma et al., in revision) and disease course did not change over time, any influence of disease duration is unlikely. Second, baseline corticosteroid dependency in the past three months was higher in the CAU than in the CBT+CAU group (27.3% vs. 8.1%). This could indicate higher disease activity in the CAU group. However, considering there were no differences in other markers of disease activity (baseline clinical disease activity scores, relapse rates, CRP, fecal calprotectin and current steroid use) between both groups (see Table 1), it is plausible that this baseline difference was attributable to a type-I-error.

Strengths and limitations

Major strengths of this study are its multicenter RCT-design and the unique study population: pediatric and young adult IBD patients from regional as well as tertiary medical centers, which increases generalizability. In addition, and contrary to other studies [24, 25], we included patients based on subclinical anxiety and/or depression as these symptoms often occur together. Moreover, because CBT has previously been found to have a significant effect over and above placebo in previous studies [71], CAU was chosen as a control condition because it resembles current clinical care best. These 2 aspects combined provided us with the opportunity to determine whether CBT prevents the development of subclinical into clinical disorders. Additionally, we included all IBD-types, and pooling of clinical disease activity scores enabled us to study disease activity for all patients simultaneously. To investigate the course of disease, we followed patients for 1 year after randomization, which is longer than in previous studies [25, 65, 68]. Furthermore, the use of an IBD-specific CBT protocol and the low attrition, especially when compared to other studies [25, 64, 66, 67], strengthen our study. Lastly, we were the first to incorporate fecal calprotectin levels and assess the effect of CBT on CRP levels in children.

Inevitably, our trial has some limitations. First of all, the study was relatively underpowered, as not all eligible patients were willing to participate in our trial with a time-consuming psychological intervention. This is a well-known problem in RCTs with a psychological intervention [25, 66]. Another limitation is the relatively unequal result

of randomization (37 vs 33), most likely due to randomization with random block sizes. Furthermore, the large number of patients with a Western ethnicity (80.9%), reduce the generalizability of our findings. Additionally, considering the majority of included patients were in clinical remission at baseline, we could not investigate whether the effect of CBT on disease activity would be greater in a population with active disease. Moreover, it would have been interesting to have included factors such as treatment adherence or IBS symptoms because they can both impact disease outcomes but are also affected by psychological symptoms. As previously mentioned, the effectiveness of CBT on psychological outcomes is published in separate publications [63] (Stapersma et al., in revision). It is known that parental behavior and psychopathology are important determinants for children's behavior. Therefore, a questionnaire measuring parental anxiety and depression was incorporated in the study design, which will be part of future analyses. Lastly, impact of disease was evaluated using the disease specific health related quality of life questionnaires, questionnaires that partly assess impact of disease. Unfortunately, validated patient reported outcomes of for example disease burden (symptom burden or disability) are not available for pediatric IBD. If available, they would have provided additional insight regarding experienced disease burden. Similarly, we did not include a validated measure of fatigue in our design, although this is a common invalidating complaint in IBD patients, possibly responsive to psychological interventions.

Directions for future research

The variation in study design, and mixed results from the available studies investigating the effect of CBT on disease course, force us to be careful drawing conclusions. Large, sufficiently powered studies, that factor in high attrition rates in sample size calculation, are necessary. In addition, several subgroups of patients (e.g. severe anxiety/depression, patients with at least moderately active IBD) need to be studied to determine whether there are certain patient groups in which CBT does influence disease course. Furthermore, other formats of psychotherapeutic interventions ánd other treatment modalities (e.g. group or e-therapy) with varying intensity should also be investigated in patients with (sub) clinical anxiety/depression, as most studies have been performed in patients unselected for psychological problems.

Conclusions

In conclusion, CBT added to CAU does not influence subsequent clinical disease course in young IBD patients with subclinical anxiety and/or depression. However, the findings suggest that CBT may have a positive effect on inflammatory markers in pediatric patients.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1 | Stepwise transformation clinical disease activity scores

Step 1: S'

S': transformation to a [0,1] scale by dividing each individual score by the maximum score for that instrument (PCDAI 100, CDAI 600, PUCAI 85, pMayo 9).

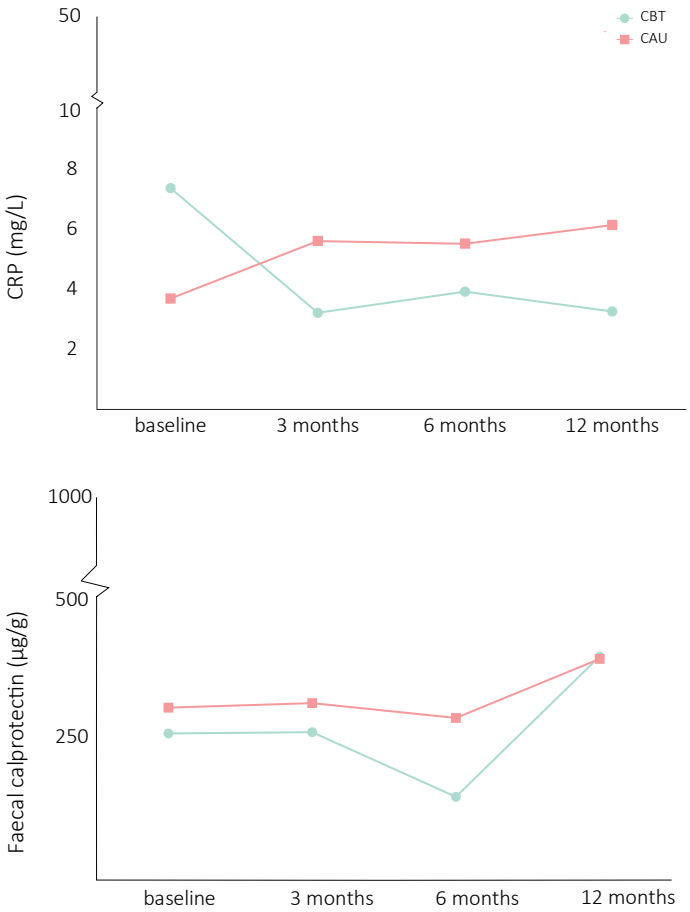
Step 2: S''

S'' = [S' * (n-1) + 0.5]/n

(n=number of patients included in RCT: 70)

Step 3: S'''

S''' = Ln (S''/1-S'')



Supplementary Figure 1 | Raw means of CRP and Calprotectin levels over time