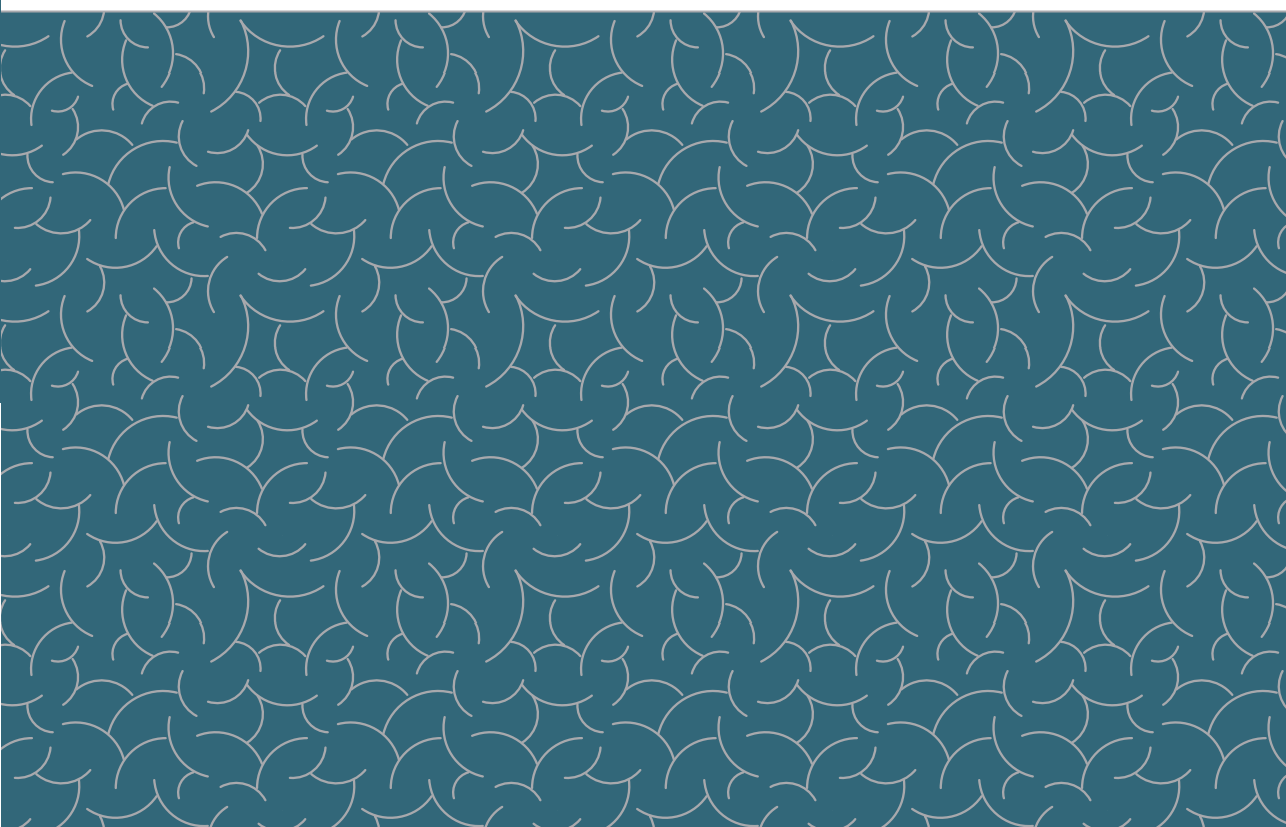
# HAPPY-IBD: A Study into Anxiety and Depression in Youth with Inflammatory Bowel Disease

*Screening and the effect of a cognitive behavioral therapy*

Luuk Stapersma



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# HAPPY-IBD: A Study into Anxiety and Depression in Youth with Inflammatory Bowel Disease
# Screening and the effect of a cognitive behavioral therapy

HAPPY-IBD: een onderzoek naar angst en depressie bij jongeren met een inflammatoire darmziekte
Screening en het effect van een cognitieve gedragstherapie

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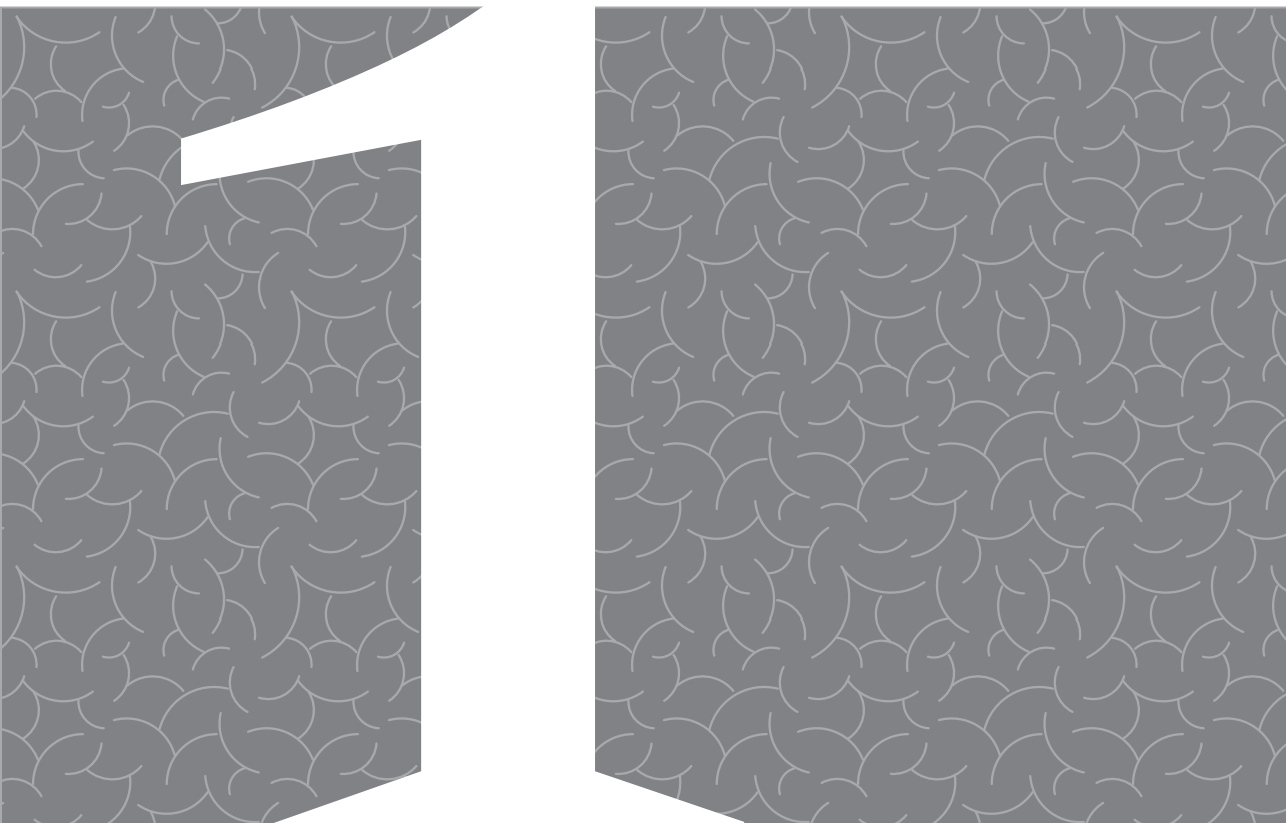
# General introduction



# GENERAL INTRODUCTION

## Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic debilitating disease, with inflammation of the gastrointestinal tract as main characteristic. IBD has two main types; Crohn's disease (CD) and ulcerative colitis (UC). In patients who have IBD colitis that cannot (yet) be classified into CD or UC, the term IBD-unclassified (IBD-U) is used. IBD is characterized by periods of active disease (relapses, with increased symptoms) and periods of clinical remission (no symptoms present). Both CD and UC share common symptoms such as abdominal pain, bloody diarrhea, anemia, and systemic symptoms such as fatigue, lack of appetite and weight loss [1, 2]. CD usually has an insidious onset and can affect any part of the gastrointestinal tract from mouth to anus. In CD, inflammation presents itself often in 'skip lesions', in which some parts of the intestines are affected whereas other parts may be not. CD can be complicated by strictures and/or fistulas between parts of the intestinal tract or from intestine to the (perianal) skin. UC often has a more explicit onset, with frequent bloody diarrhea accompanied by abdominal cramping [3, 4]. Suspicion of IBD is present in case of typical symptoms and laboratory abnormalities in blood and stool. A confirmed diagnosis of IBD can only be made after extensive endoscopy of both upper and lower part of the intestinal tract with multiple mucosal biopsies. With respect to the complex etiology, several factors have been implicated. It has been shown that a genetic susceptibility in combination with a dysregulated immunological response to the bacterial gut flora is present. Environmental factors such as infection, certain foods, smoking and psychological stress can further trigger this dysregulation [1, 3].

## IBD in children and adolescents

Approximately 10-25% of all patients receives the diagnosis of IBD before they are 18 years of age, and for patients up to 25 years of age this is approximately 35% [2, 5, 6]. Children and adolescents (hereafter referred to as youth) with IBD often present with malnutrition, growth failure, or delayed puberty [4]. In Europe, the incidence rate for pediatric IBD ranges from 3.11 – 12.00 per 100.000 persons, with somewhat higher incidence rates for CD (2.71 – 13.90 per 100.000 cases) than for UC (1.61 – 5.70 per 100.000 persons). These incidence rates are rising, which can be attributed to the rising incidence rates of CD [5]. In the Netherlands over 80.000 patients suffer from IBD, of whom 2500 to 3000 are younger than 18 years.

## Medical treatment

Since IBD cannot be cured, its medical treatment is focused on the suppression of the inflammation, aimed at the induction and maintenance of clinical remission

and preferably also healing of the inflamed mucosa [7]. For children with active CD, the first-line treatment is exclusive enteral nutrition. This is less invasive than pharmacological therapy but requires adherence to a liquid formula diet for 8 weeks. Corticosteroids are often used for induction of remission in moderate to severe UC and CD (if enteral nutrition fails). After remission is induced, immunomodulators are used to maintain remission [8, 9]. In case of refractory disease, biologicals such as infliximab or adalimumab (anti-TNF treatments) of vedolizumab (anti-integrin) can be used. Surgery is indicated when non-inflammatory strictures are present in CD, or in UC when all treatments fail.

## Psychological aspects of IBD

### Psychological problems

The biopsychosocial model implies that psychological and social factors are likely to influence disease symptoms and functional outcomes, in addition to disease mechanisms such as inflammation in IBD [10]. Due to the unpredictable course of the disease and the chronic nature of IBD adolescents frequently experience psychological and social problems [11]. Several studies have shown that youth with IBD have a lower health-related quality of life (HRQOL) compared to healthy youth [12]. Youth with IBD also can experience problems with their self-esteem or social functioning [13, 14].

The psychological problems most studied in IBD patients are anxiety and depression. In adults, a meta-analysis of Neuendorf et al. [15] showed that patients with IBD have a high risk for having anxiety and/or depression, consisting of either subclinical anxiety/depression or clinical anxiety or depressive disorders. In youth, no meta-analysis is performed yet. However, original and review studies showed that youth with IBD also have a high risk for anxiety and/or depression [11, 16-18].

### Bidirectional relationship inflammation and anxiety/depression in IBD

In IBD, the relationship between inflammation and anxiety/depression seems bidirectional. Evidence for this bidirectionality mainly comes from studies in adults. On one hand, anxiety and depression are associated with clinical relapse during follow-up [19-21]. More specifically, depression has a negative impact on the disease course [22] and is related to a shorter time to relapse when compared to anxiety [23]. In youth with IBD, Van Tilburg et al. [24] showed that psychological factors (anxiety, depression, coping and pain beliefs) impacted self-reported somatic symptoms and disability. On the other hand, evidence was found for the impact of clinical disease activity on anxiety and depression [25, 26]. In youth, clinical disease activity was associated with more symptoms of anxiety [27] and depression [28], and was a risk factor for having anxiety and depressive disorders [29]. Recently, two studies in adults with IBD provided even more evidence for the bidirectionality of the relationship between inflammation and

anxiety/depression. Sexton et al. [30] reported that clinical disease activity predicted change in perceived stress, where perceived stress predicted change in clinical disease activity. Furthermore, Gracie et al. [31] reported that clinical disease activity gave a 6-fold risk on anxiety 2 years later, and that baseline anxiety and depression were associated with several indicators of increased clinical disease activity.

**Brain-gut axis**

The brain-gut axis provides an hypothesized explanation for the common combination of IBD inflammation and psychological problems, such as anxiety, depression and stress. This axis involves interactions between the autonomic nervous system, the central nervous system, the stress system (hypothalamic-pituitary-adrenal [HPA] axis), the corticotropin-releasing factor system, and the intestinal response, that make the brain and the gut communicate. This communication seems bidirectional [32]. Increased production of pro-inflammatory cytokines (e.g. tumor necrosis factor α; TNF-α) is known to directly and indirectly affect the brain, with increased symptoms of anxiety and depression as result [33, 34]. On the other hand increased anxiety and/or depression can increase inflammation. In this way a vicious circle arises in which inflammation and anxiety/depression negatively influence each other, to an increasing extent. More inflammation can lead to more anxiety/depression, and vice versa more anxiety/depression can lead to more inflammation [32]. Evidence for the brain-gut hypothesis comes from animal studies showing that stress induces reactive inflammation in colitis models [35]. In addition, studies in humans showed elevated levels of inflammatory markers in otherwise healthy patients with depression [36-39] and anxiety [40-42]. The last decades more evidence has become available for this psychoneuroimmunological approach to mental health problems, such as anxiety and depression [43, 44].

**Other psychological factors**

Apart from the above described psychological problems, other psychological aspects of IBD also need to be considered. Earlier studies have shown that several psychological factors – often tested separately – were related to negative outcomes in IBD, e.g. functional disability or anxiety and depression. Coping and illness perceptions are two factors that are important in youth with IBD.

*Coping*. Coping refers to the cognitive and behavioral strategies one uses to deal with negative experiences, such as having a chronic illness [45]. Often a distinction is made between coping styles that are associated with favorable psychological outcomes (adaptive coping), or those associated with unfavorable psychological outcomes (maladaptive coping). Although it is still unclear whether youth with IBD cope differently than healthy controls, it appears that coping impacts psychological outcomes in these

patients [46, 47]. For example, maladaptive or passive coping was associated with more anxiety and depression [48], and adaptive coping (i.e. positive strategies) was associated with better HRQOL [49].

*Illness perceptions*. Illness perceptions are representations someone has about the illness, its treatment, and consequences of the illness [50]. There are several dimensions of representations: identity (the label that the persons uses to describe the illness), consequences (expected effects of the illness), cause (personal ideas about the cause of the illness), timeline (how long the patient believes the illness will last), and cure (the extent to which the patient believes treatment cures or controls the illness). In patients with IBD, illness perceptions have been shown to affect outcomes and adjustment [47, 51-53], with unfavorable perceptions being related to unfavorable adjustment. Illness perceptions have been less studied in children and adolescents than in adults. However, the few studies conducted suggest that also in youth with IBD, illness perceptions are associated with psychological problems [29].

To describe the potential relationships between illness, illness perceptions, coping, and illness outcomes, Diefenbach & Leventhal developed the Common Sense Model (CSM) [54]. In this model, illness characteristics (such as clinical disease activity) lead to certain thoughts about the illness, the so-called illness perceptions of a patient. These illness perceptions influence the type of coping the patient uses to deal with his/her symptoms. These factors lead to positive or negative illness outcomes, for example anxiety, depression, HRQOL, or adjustment. In turn, via a feedback loop illness outcomes can influence disease factors, coping, and illness perceptions [54, 55]. In adults with IBD, evidence was found for the CSM. That is, illness perceptions and coping were important mediators between clinical disease activity and anxiety and depression [56]. In youth with IBD these interrelationships have not been tested directly. Some evidence exists for separate pathways for different factors. For example, independent from the impact of disease factors on HRQOL, anxiety and depression (separately tested) have a negative impact on HRQOL as well [57-59]. However, the precise pathways between the factors included in the CSM are still unknown.

**Cognitive behavioral therapy for youth with IBD**

Considering the possible negative impact of anxiety and depression on the mental and somatic health status of children and adolescents with IBD, from a health care perspective it is important to treat not only the somatic symptoms, but also the psychological problems. The bidirectionality of the relationship between inflammation, and anxiety/depression implies that treating the psychological problems may also improve disease course. The most evidence based psychological treatment for anxiety and depression in children and adolescents is cognitive behavioral therapy (CBT) [60,

61]. In children with other chronic illnesses, such as diabetes and asthma, CBT has been shown effective in improving psychological problems [62, 63].

Only a few, and mostly small, studies have been conducted in youth with IBD. In 2007, Szigethy et al. performed a randomized controlled trial (RCT; n=41) and published preliminary, but promising results of cognitive behavioral therapy (CBT) in IBD patients aged 11-17 years with *subclinical depression* [64]. The CBT protocol used was the Primary and Secondary Control Enhancement Training – Physical Illness (PASCET-PI), a disease-specific CBT protocol. The authors found that 3 months of CBT was more effective in improving subclinical depressive symptoms than care-as-usual (CAU), which consisted of standard medical care plus a written information sheet about depression. In a later and larger RCT (n= 217), Szigethy et al. [65] confirmed the effectiveness of the PASCET-PI in improving clinical depressive symptoms in IBD youth aged 9-17 years, although a control group receiving supportive non-directive therapy showed similar results.

Very few studies focused on treating *anxiety* in youth with IBD. Reigada et al. [66] conducted a pilot non-randomized trial (n=22) using CBT in youth (mean age 13.2 years) with IBD, and found promising results in reducing clinical anxiety. More recently, a large RCT (n=185, aged 8-17 years) was conducted in pediatric IBD patients to test the effectiveness of a 3-session social learning CBT (SLCBT) versus educational support, although not focusing specifically on anxiety and/or depression. SLCBT led to a significant better improvement in IBD-related QOL and school attendance than educational support, but no differences were observed in improving subclinical anxiety and depression symptoms [67].

**HAPPY-IBD: a study into anxiety and depression in youth with IBD**

Until now, studies in youth with IBD mostly focused on either anxiety or depression. Hence, they did not take into account that anxiety and depression are highly comorbid, and that anxiety can precede depression [68, 69]. In addition, some studies included all youth with IBD, i.e. did not select youth on the presence of any psychological problems, such as anxiety and/or depression [67].

Therefore, the current study (HAPPY-IBD) was designed to 1) investigate both anxiety and depression in youth with IBD and 2) test both the short-and long-term effects of a disease-specific CBT protocol on both anxiety and depressive symptoms. HAPPY-IBD included a multi-center RCT, comparing the effects of the CBT protocol to CAU, consisting of standard medical care. The CBT protocol used was the disease-specific PASCET-PI, which also was used in previous studies.

Until now, no disease-specific CBT protocol was available for youth with IBD and their families in the Netherlands. It is innovative that we studied the effects of the PASCET-PI on both anxiety and depression, as well as on other psychological and medi-

cal outcomes, both at short-term (3 months, directly after the CBT) and longer-term (after 6 and 12 months of follow-up), using internationally validated questionnaires and a psychiatric interview.

We included patients with both subclinical anxiety and/or depression, since we were interested in the possible effect of a disease-specific CBT a) to prevent that subclinical anxiety/depression would develop into clinical psychiatric disorders, and b) to have a positive effect on the disease course (e.g. to prevent clinical relapse or worsening of disease severity). Furthermore, we wanted our study to resemble daily clinical practice as much as possible. Therefore, we chose to use a care-as-usual group. Children with clinical anxiety or depressive disorders were excluded from the RCT, since it would be unethical to randomize children with a clinical psychiatric disorder to a control group.

In this PhD thesis, we aim to answer the following research questions:

1. What is the prevalence of anxiety and depressive symptoms and disorders in children and adolescents with IBD (aged 6-18 years)?
2. Which medical variables are associated with the presence of elevated anxiety and/or depression in youth with IBD (aged 10-25 years)?
3. Which psychological variables are associated with HRQOL in youth with IBD (aged 10-20 years)?
4. What is the short-term and long-term effectiveness of a disease-specific CBT in improving symptoms of anxiety and depression (primary outcomes), HRQOL, negative illness perceptions, coping, social functioning, and sleep problems (secondary outcomes)?

Firstly, we hypothesized that anxiety and depressive symptoms are highly prevalent in youth with IBD. Secondly, clinical disease activity and disease duration were hypothesized to be medical factors associated with the presence of anxiety and/or depression. Thirdly, we expected that illness perceptions, coping, anxiety, and depression were psychological factors that are associated with HRQOL. Fourthly and lastly, we hypothesized that patients in the disease-specific CBT group would improve more compared to the CAU group on their symptoms of anxiety and depression, as well as on their HRQOL, negative illness perceptions, coping, social functioning, and sleep problems. The results of the disease-specific CBT on the medical outcomes will be described in a separate PhD thesis, by Gertrude van den Brink, MD.

## METHODS

Full details of the study design, inclusion, exclusion criteria, the procedure, the intervention, and the used instruments, are described in Chapter 3 (the description of the study protocol) and can be found in the Methods section of Chapter 5, 6, and 7 as well. In short, the study is a RCT with a baseline screening and three follow-up assessments; at 3 months after the baseline screening (i.e. after the disease-specific CBT for those in the CBT group), at 6 months, and at 12 months after the baseline screening, see Figure 1. The follow-up assessments consisted of the same instruments as the baseline screening. The timing and method was similar for both groups.

*Inclusion*: adolescents and young adults (10-25 years) with a confirmed diagnosis of IBD (CD, UC, or IBD-U) were eligible. They were recruited between October 2014 and October 2016 from the pediatric or (pediatric) gastroenterology departments of two academic and four community hospitals. The study consisted of two parts: 1) a baseline screening on symptoms of anxiety and depression and 2) for patients with subclinical anxiety and/or depressive symptoms, a RCT with two conditions (CAU + CBT versus CAU only).

*Part 1, baseline screening*: after providing informed consent, patients, and if applicable parents, filled out online questionnaires for the baseline screening (see below for the included variables). Using age-appropriate questionnaires, patients were screened for anxiety and depression. Patients had elevated symptoms if they scored equal to or higher than the validated cutoffs for elevated anxiety or depression. Those who showed elevated symptoms were invited for a psychiatric interview to determine whether they had clinical anxiety and/or depression. For this study, patients were considered to have clinical anxiety or depression if they met DSM-5 criteria for an anxiety or depressive disorder on the psychiatric interview, and scored equal or above the clinical cutoff on an age-appropriate severity rating scale for anxiety or depression. Scores on these instruments were rated by two independent raters.

*Part 2, RCT*: patients that showed subclinical anxiety and/or depression (i.e. who had elevated scores on the questionnaires, but did not show clinical anxiety or depression according to the psychiatric interview and rating scales) were included in the RCT. This was a multi-center, parallel group RCT, designed according to the guideline for trials in non-pharmacologic treatments [70]. Patients were randomized at a ratio 1:1 to receive either CAU + CBT versus CAU only. Patients in the control group (CAU only) received standard medical care, since this resembles the current care for these patients best. Patients in the CBT group (CAU + CBT) received a disease-specific CBT protocol (Primary and Secondary Control Enhancement Training for Physical Illness; PASCET-PI) [64] added to standard medical care. See Chapter 3, 5 and 6 for more details of the PASCET-PI.

## Psychological and medical variables

In this thesis, the focus will be on the psychological aspects of IBD in youth. The following psychological variables were included in the online questionnaires:

- *Primary psychological outcomes*: anxiety symptoms, depressive symptoms
- *Secondary psychological outcomes*: HRQOL, social functioning
- *Other psychological variables*: illness perceptions, coping styles, quality of sleep, parental anxiety and depression, life events, and family functioning

Simultaneously, information on the following medical variables were collected:

- *Primary medical outcome*: clinical relapse/remission
- *Secondary medical outcomes*: clinical disease activity, inflammatory markers (C-reactive Protein [CRP], Erythrocyte Sedimentation Rate [ESR], and fecal calprotectin), use of IBD medications, necessity of surgical intervention
- *Other medical variables*: disease phenotypes, treatment strategy, Irritable Bowel Syndrome (IBD)-like symptoms, RNA expression profiles and cytokine levels in the plasma and peripheral blood mononuclear cells (PMBC's).

For an extensive description of the assessments instruments, see the Methods sections of Chapter 3-7.

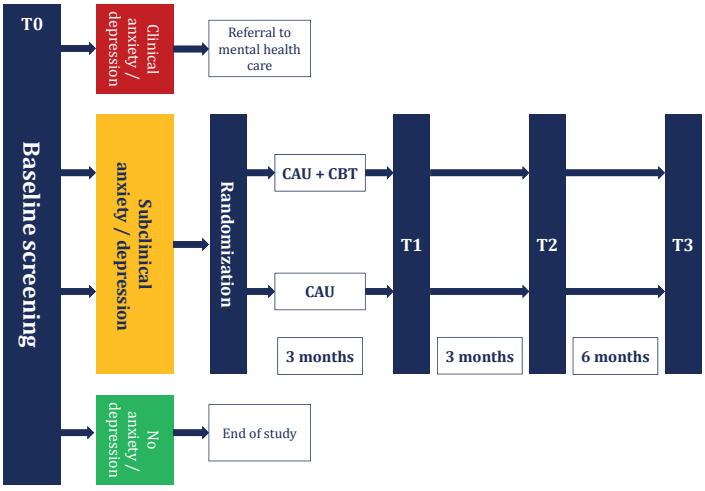



**Figure 1** | Study design of HAPPY-IBD
Abbreviations: CAU= care-as-usual; CBT= cognitive behavioral therapy

## Aims and outline of this thesis

The focus of the present PhD thesis is twofold: 1) investigating anxiety and depression in youth with IBD and 2) evaluating the effectiveness of a disease-specific CBT

compared to care-as-usual in improving anxiety and/or depressive symptoms, HRQOL and other psychological outcomes in these patients. This study is the first RCT studying the effectiveness of a disease-specific CBT protocol (PASCET-PI) on both anxiety and depression. Moreover, we will also examine other psychological and medical outcomes, using internationally validated questionnaires and a psychiatric interview.

Chapter 2 contains a systematic review and meta-analysis on the prevalence of anxiety and depression in children and adolescents with IBD. Multiple studies have examined psychological problems in pediatric IBD. However, it is still not clear to what extent children and adolescents with IBD experience subclinical anxiety and/or depressive symptoms and clinical anxiety and/or depressive disorders. We summarized all available data to provide insight into prevalence rates of anxiety and depressive symptoms and disorders in children and adolescents with IBD. Mikocka-Walus et al. [71] wrote an editorial to this chapter. The editorial and our response [72] can be found in Appendix A.

Chapter 3 is the description of the study protocol of the RCT, testing the effectiveness of the disease-specific CBT, including information on this intervention, the control condition, the assessment instruments and timing.

Chapter 4 and 5 describe the baseline data of our RCT, derived from the screening phase of the study (part 1). The total group of patients consisted of all patients included in the baseline screening preceding the RCT: 1) those without any anxiety and/or depression, 2) those with subclinical anxiety and/or depression, and 3) those with clinical anxiety and/or depression.

In Chapter 4, we examined which medical variables were associated with the presence of anxiety and/or depressive symptoms, and whether these associations were different for different levels of anxiety/depression (none, subclinical, clinical) or were different for patients aged 10-17 years versus patients aged 18-25 years.

In Chapter 5, the results are presented of a study that investigated whether several psychological variables (illness perceptions, coping, anxiety, and depression) were associated to HRQOL after controlling for several demographic and medical variables.

Chapter 6 presents the short-term results of the RCT, the pre-post treatment effects of the disease-specific CBT (i.e. directly after the treatment or 3 months after the baseline screening) on anxiety and depressive symptoms, as well as on HRQOL, compared to CAU.

In Chapter 7 we describe the longer-term effects of the disease-specific CBT on several psychological outcomes at the long-term follow-up, at 6 and 12 months after then baseline screening.

Finally, Chapter 8 provides an overview of all the previous chapters, an overall discussion of the findings, as well as directions for future research and clinical implications.

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# Systematic review with meta-analysis: anxiety and depression in children and adolescents with inflammatory bowel disease

*Luuk Stapersma, *Gertrude van den Brink, Eva M. Szigethy,
†Johanna C. Escher, †Elisabeth M.W.J. Utens

* Both authors contributed equally
† Both authors share last authorship

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## SUMMARY

**Background** The co-existence of psychological problems and paediatric inflammatory bowel disease (IBD) is receiving increasing attention in literature. Most studies investigated anxiety and depression, with prevalence rates varying greatly from 0% to 50%. A systematic review is necessary to provide clear insight in the prevalence of anxiety and depression in paediatric IBD.

**Aim** To systematically evaluate available data on the prevalence of anxiety and depressive symptoms and disorders in paediatric IBD (aged 6-18 year).

**Methods** Comprehensive searches were performed in Embase, Medline Ovid, Web of Science, Cochrane, PubMed, PsychInfo Ovid, Google scholar for studies published from 1994 to 2017. Pooled prevalence rates were calculated using inverse variance heterogeneity models. Meta-regression was used to study if disease type, disease activity and gender influence prevalence.

**Results** 28 studies (N= 8107, mean age: 14.3) were identified. Pooled prevalence estimates were 16.4% (95% Confidence Interval [CI] 6.8-27.3%) for anxiety symptoms and 4.2% (95%CI 3.6-4.8%) for anxiety disorders. Pooled prevalence estimates were 15.0% (95%CI 6.4-24.8%) for depressive symptoms and 3.4% (95%CI 0-9.3%) for depressive disorders. Meta-regression showed no influence of disease type and gender on these prevalence rates, but studies with a higher percentage of active disease had a higher rate of depressive symptoms.

**Conclusion** The described pooled prevalence of anxiety and depressive symptoms is lower than in adult IBD. However, due to varying instruments/cutoffs for measuring symptoms and few studies investigating disorders, the results should be interpreted with caution. Cross-cultural use of the same instruments is needed to gain better insight into prevalence rates.

## INTRODUCTION



Inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis [UC]) is a chronic relapsing inflammatory disorder of the intestine, with increasing incidence and prevalence worldwide [1]. Patients may have abdominal pain, (bloody) diarrhoea, often accompanied by systemic symptoms such as lack of appetite, weight loss and fatigue. IBD has an unpredictable and fluctuating disease course, with relapses and periods of clinical remission. In up to 25% percent of patients, IBD manifests during late childhood and adolescence [2]. Adolescence is already challenging, due to significant psychological, physical and social changes. Having IBD during adolescence can pose a real threat to a healthy psychosocial development. Studies indicate that paediatric IBD patients are at risk for several psychosocial and psychological problems [3, 4]. Most studies focussed on anxiety and/or depressive symptoms, and reported greatly varying prevalence rates, from 2-50% [5, 6] for anxiety symptoms and 0-33% [7, 8] for depressive symptoms. Only a few studies investigated prevalence of anxiety and depressive disorders, which ranged respectively from 3-7% [9, 10] and 1-17% [10, 11] .

In mental health care, a distinction is made between anxiety/depressive symptoms and anxiety/depressive disorders for several reasons. First, patients with a clinical disorder have severe symptoms that cause significant impairment in their daily life. Patients with elevated symptoms (who do not meet all criteria of a clinical disorder) do suffer from these milder symptoms, but do not experience such a significant impairment in their daily life. Second, disorders comprise a combination of symptoms, and are diagnosed using the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in a psychiatric interview. On the other hand, symptoms are often measured using a questionnaire.

The bidirectional relationship between IBD and psychological problems has been previously described and can be explained in terms of the 'brain-gut'-axis. This axis describes that the presence of intestinal inflammation might negatively influence mood and vice versa: anxiety and/or depression may increase intestinal inflammation and may trigger a relapse of IBD [12-15]. While many individual studies looked at the prevalence of anxiety and/or depressive symptoms and disorders in paediatric IBD patients, no comprehensive systematic review or meta-analysis has been conducted.

Unfortunately, the few published reviews on psychological outcomes in paediatric IBD either differed in scope (e.g. did not focus specifically on prevalence rates of anxiety and/or depression) or had several shortcomings. Some reviews only included older studies published in the previous decade [4, 16], whereas others only included studies with a control group [4] or included a small portion of the available paediatric studies [17]. A review by Brooks et al. discussed the impact of psychological morbidity in paediatric IBD (including anxiety and depression, but not their prevalence rates) [18]. Greenley et al. [4]

studied psychosocial adjustment (including anxiety and depression) of adolescents with IBD, but only included studies published before 2007, which used a comparison group or normative data (thus excluding cross-sectional or cohort studies without a comparison group). The authors reported that adolescents with IBD had higher rates of depressive disorders than those with other chronic conditions. However, their prevalence rates of anxiety and depressive symptoms, and anxiety disorders were not significantly different from healthy adolescents or those with other chronic diseases [4]. A third, nearly a decade old review by Ross et al. [16], included studies till 2009, investigating psychosocial functioning and quality of life. They found an increased incidence of anxiety and depressive disorders, varying from 25-73%, in adolescents with IBD [16]. A fourth systematic review included studies published between 2005 and 2014, but studied comorbidity of anxiety and depression in both paediatric and adult IBD, and included only a limited number of the available paediatric studies [17]. Considering the previous reviews, there is a clear need to perform a systematic review with meta-analysis to provide prevalence rates on anxiety and depression in paediatric IBD, including all available studies.

The current systematic review and meta-analysis aims to systematically assess the prevalence rates of anxiety and depressive symptoms and disorders specifically in paediatric IBD, using all studies published between 1994 and 2017 (aim 1). In addition, we aimed to investigate whether disease type, disease activity, or gender influence these prevalence rates (aim 2). It is important to gain more clear insight into the overall prevalence and risk factors of anxiety and depression in paediatric IBD, in order to increase awareness, facilitate early detection of anxiety and depression, and, if necessary, early psychological treatment.

## MATERIALS AND METHODS

This systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)-guidelines [19].

### Eligibility criteria

*Inclusion criteria* were studies concerning a) patients 6-18 years of age (or studies with sub analyses on this age group), b) with IBD, diagnosed according to the current international guidelines, c) examining either anxiety and/or depressive symptoms (using validated screening instruments with at least child self-report data) or anxiety and/or depressive disorders (using a structured psychiatric interview or ICD codes). We chose to include any study design that measured prevalence for anxiety and depression in a paediatric IBD cohort. For studies measuring anxiety and/or depression at various time points, data of only the first assessment was used.

*Exclusion criteria* were studies a) published in non-English languages, b) published before 1994 (studies using DSM-IV, introduced in 1994, or higher), c) using instruments with no separate anxiety or depression scale (e.g. the Internalizing scale or syndrome scale Anxious/Depressed of the Child Behaviour Checklist), d) with a patient cohort already partly described in another included study (no unique cohort), e) that described case reports, case series, qualitative studies, dissertations, or review papers and conference abstracts without published full article.



## Information sources and search

An expert research librarian conducted a comprehensive literature search using Pubmed, Embase, MEDLINE Ovid, Web of Science, Cochrane, PsychINFO Ovid and Google Scholar in December 2017. For Inflammatory Bowel Disease, search terms included Crohn's Disease and ulcerative colitis. For anxiety and depression, search terms included both symptoms and disorders, and fear and panic as well as the most common treatments for these problems (cognitive behavioural therapy and antidepressants), to find intervention trials for their baseline data. The search strategies used for each database are provided in Appendix 1.

## Study selection

Studies meeting inclusion criteria were eligible. In step 1, two investigators (LS and GB) independently screened titles and abstracts of eligible studies. Any disagreement was resolved by consensus or a third reviewer. In step 2 abstracts and if necessary full texts of selected articles were checked globally for the in-/exclusion criteria (i.e. whether a full text was available, if a valid instrument was used, and if the study concerned paediatric patients).

In step 3 full texts of the remaining articles were reviewed thoroughly (by LS/GB). All reference lists were inspected for additional studies. Figure 1 displays the reasons for excluding articles. Reference management was done using EndNote X7.

## Data collection process & Data items

Two independent investigators, using a data extraction from, extracted the following data for each included study: year of publication, study design (e.g. control group present or absent), patient setting (in- or outpatient), country, number of included patients, patient demographics (age, gender), disease characteristics (disease type [CD vs UC], disease activity [active or remission]), measurement method of anxiety and/or depression (questionnaire and/or psychiatric interview) and prevalence rates of anxiety and depressive symptoms and disorders. If prevalence rates for symptoms and disorders were not reported the manuscript, they were calculated using the cutoff for elevated symptoms reported by the authors. Disagreement regarding extracted data was re-

solved by consensus. Original authors were contacted if the data provided in the paper was insufficient to extract a prevalence rate. Authors were also contacted if it was suspected that several articles reported about the same or overlapping patient cohorts. If that was the case, only the article with the most complete data was included in this review. After three attempts to contact authors without success, articles were excluded.

## Quality and risk of bias

The quality and risk of bias of the individual studies was assessed, using a checklist developed by the research team a priori and specifically for this study. The checklist, with a maximum score of 27, was based on the recommendations of Sanderson et al. [20], the NIH Quality Assessment for Observational Cohort and Cross-sectional studies [21, 22] and previously published checklists [17, 23]. Included studies were rated on their method (definition of aim/primary outcomes), recruitment, sample size, whether or not they included a control group, instruments used (psychological and medical), and if confounders were taken into account (see Appendix 2 for the complete checklist). The checklist was piloted using a subsample of studies with minor adjustments afterwards.

## Data synthesis and statistical analyses

Extracted prevalence rates were pooled using inverse variance heterogeneity models (including a double arcsine transformation), that handle between study heterogeneity better than the widely used random effects model [24]. Heterogeneity was assessed using the $I^2$ statistic, with values ≥75% indicating considerable heterogeneity [25]. Reporting bias across studies (e.g. publication bias) was examined visually using "funnel plots" and the more sensitive "Doi plots" and formally using the Luis Furuya-Kanamori (LFK) index [26-29], to see if the prevalence rates changed with increasing sample size. In the funnel plots and Doi plots a higher prevalence is displayed by a higher "Double Arcsin Prevalence", and a higher standard error indicates a lower sample size. To evaluate whether disease type, disease activity or gender influence the prevalence of anxiety and/or depressive symptoms or disorders (aim 2), we repeated the meta-analyses and included disease type (% CD), disease activity (% active disease) or gender (% male) as covariates in three separate weighted meta-regression analyses. Only studies that reported on these covariates were include in these meta-regression analyses. Sensitivity analyses were performed by excluding studies in the lowest tertile of the reported 'quality/risk of bias score' (i.e. with a score of 10 or lower) and removing the largest study for each separate analysis. Additional sensitivity analyses were performed using the random effects model, to provide the opportunity to compare the results with the inverse variance heterogeneity models. All analysis were performed using MetaXL version 5.3 [28] and STATA version 15.0 (Stata corp, College station, TX).

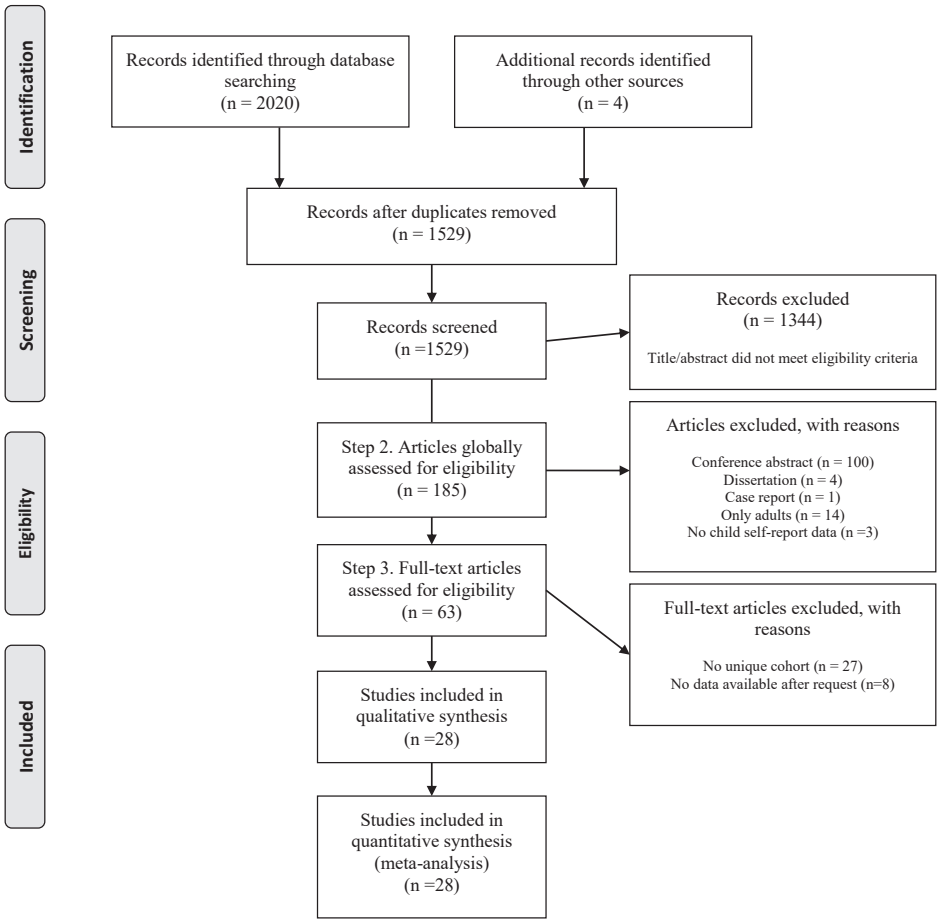


**Figure 1** | PRISMA flow diagram

## RESULTS

### Study selection

During the database search 2020 records were found, 4 additional studies were identified through other sources (i.e. reference lists of included records). 495 out of 2024 records were removed as duplicates. Of 1529 records the title and abstract was screened, 1344 records did not meet inclusion criteria (step 1). In this first step agreement between the investigators was 87.2%. In step 2, 185 articles were globally screened on the inclusion and exclusion criteria, of which 122 were excluded in this step, leaving 63 full-articles to be assessed (step 3). Of these 63 articles, 27 were excluded because they reported on a patient cohort that was already included, for 8 prevalence data were not available after request. The remaining 28 articles were

included in the meta-analysis. For 13 of the 28 articles, prevalence rates were provided after request form the original authors. See Figure 1.

## Study characteristics

A total of 8107 participants were included in the analyses (of which 2 studies provided more than half), 51.3% was male. One study included only female patients [7]. The number of participants per study ranged from 21 to 2733, which a median sample size of 85. Two studies were relatively large with n = 2144 [9] and n = 2733 [11]. Mean age was 14.3 (based on 25 studies that reported a mean age). Three studies included only patients with CD [6, 9, 30]. In the remaining studies that reported disease type, 67.1% had CD. In total, 9 out of 28 studies used a control group. Three studies included healthy adolescents, the other 6 included patients with other chronic diseases (e.g. Cystic fibrosis, Diabetes, Juvenile Idiopathic Arthritis) [5, 9, 31-37]. With respect to geography, 20 studies were from the United States of America, 7 studies were from Europa [10, 32, 35, 36, 38-40], and 1 study from Asia [34]. See Table 1 for an overview of the study characteristics.

Finally, in 23 out of 28 studies, clinical disease activity was measured for CD, with the following indices: Paediatric Crohn's Disease Activity Index (PCDAI) [5, 10, 31, 35, 37, 38, 40-44], short-PCDAI [45], abbreviated PCDAI [44, 46], Harvey Bradshaw Index [6, 47], Physician Global Assessment (PGA) [32, 37, 44, 48, 49], (part of) Children's Somatisation Inventory [8], IBD-symptom questionnaire [33], and Short-Crohn's Disease Activity Index [30, 50]. 25 studies included UC patients and in 21 disease activity was measured using the following indices; Paediatric Ulcerative Colitis Activity Index (PUCAI) [10, 35-38, 40, 42, 44, 46, 47, 50], Physician Global Assessment (PGA) [31, 32, 37, 44, 48, 49], (part of) Children's Somatisation Inventory [8], IBD-symptom questionnaire [33], Clinical score of Kozarek [41, 43], Lichtiger Colitis Activity index [45], and PCDAI [5]. Of the 17 studies that reported percentage active disease, 35.9% of patients had active disease and 64.1% was in remission.

## Study Quality/Risk of bias

Mean score on our checklist was 12.64 (reported range 8-17) with a standard deviation of 2.34. Especially on the items regarding using a control group, sample size, and taking into account confounders, many studies scored 0 or 1 point(s).

**Table 1** | *Overview of study characteristics and prevalence rates*

| Study | Sample size | % Male | % CD | Mean age (range†) | % Active disease | Quality score | Outcome | Method Q or I‡ | Instrument (cutoff for elevated symptoms) | Prevalence (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Anxiety symptoms | Anxiety disorders | Depressive symptoms | Depressive disorders |
| Mackner 2005[5] | 50 | 62 | 76 | 14,7 (11-17) | 38,3 | 10/27 | Anxiety | Q | RCMAS (T-score ≥67) | 2,0 | - | - | - |
| | | | | | | | Depression | Q | CDI (T-score >66) | - | - | 0,0 | - |
| Reigada 2015[6] | 93 | 55 | 100 | 14,7 (9-18) | 16,0 | 13/27 | Anxiety | Q | SCARED (Total score ≥20 or subscales) | 49,5 | - | - | - |
| Reed-Knight 2012[7] § | 31 | 0 | - | 14,3 (11-18) | - | 9/27 | Depression | Q | CDI (T-score >66) | - | - | 0,0 | - |
| Reigada 2011[8] | 36 | 50 | 75 | 15,3 (12-17) | - | 8/27 | Anxiety | Q | SCARED (Total score ≥25) | 22,2 | - | - | - |
| | | | | | | | Depression | Q | CES-D (Total score ≥16) | - | - | 33.3 | - |
| Loftus 2011[9] | 2144 | 54 | 100 | 11,8 (<18) | - | 17/27 | Anxiety | ICD codes | - | - | 3,8 | - | - |
| | | | | | | | Depression | ICD codes | - | - | - | - | 5,5 |
| Engelmann 2015[10] | 47 | 57 | 45 | 15,2 (10-18) | 51,1 | 15/27 | Anxiety | I | CASCAP | - | 6,4 | - | - |
| | | | | | | | Depression | I | CASCAP | - | - | - | 17,0 |
| Barnes 2017[11] § | 2733 | 54 | 63 | 13,8 (<18) | - | 16/27 | Anxiety | ICD codes | - | - | 4,8 | - | - |
| | | | | | | | Depression | ICD codes | - | - | - | - | 0,9 |
| Arvanitis 2016[30] § | 276 | 56 | 100 | 13,2 (9-17) | 17,1 | 14/27 | Anxiety | Q | PROMIS (T-score ≥60) | 16,7 | - | - | - |
| | | | | | | | Depression | Q | PROMIS (T-score ≥60) | - | - | 3,6 | - |
| Marcus 2009[31] | 70 | 56 | 74 | 14,1 (10-17) | - | 13/27 | Depression | Q | CDI-SF (T-score ≥65) | - | - | 1,4 | - |
| Castaneda 2013[32] | 34 | 56 | 50 | 16,3 (13-19) | 58,8 | 15/27 | Depression | Q | BDI (Total score ≥10) | - | - | 32,4 | - |
| Van Tilburg 2015[33] § | 189 | 51 | 68 | 13,8 (7-18) | - | 10/27 | Depression | Q | CDI (Total score ≥11) | - | - | 27,0 | - |
| Jayanath 2014[34] | 26 | 46 | - | - (7-17) | - | 14/27 | Depression | Q | CDI (T-score >55) | - | - | 23,1 | - |
| Jelenova 2016[35] § | 27 | 52 | 63 | 15,1 (13-16) | 13,8 | 10/27 | Anxiety | Q | SAD-state (Total score ≥35) | 17,4 | - | - | - |
| | | | | | | | Depression | Q | CDI (Total score ≥20) | - | - | 16,7 | - |
| Mahlmann 2017[36] § | 21 | 52 | 57 | 13,9 (6-20¶) | 33,3 | 13/27 | Depression | Q | ChilD-S (Total score ≥11) | - | - | 19,1 | - |
| Iturralde 2017[37] § | 23 | 44 | 41 | (12-22$) | 50,0 | 13/27 | Depression | Q | PHQ-9 (Total score ≥11) | - | - | 8,7 | - |
| Herzog 2013[38] | 110 | 56 | 56 | 13,1 (<16) | 37,3 | 17/27 | Depression | Q | CDI (Total score ≥19) | - | - | 0,9 | - |
| Kilroy 2011[39] | 79 | 58 | 52 | 13,9 (9-17) | - | 10/27 | Anxiety | Q | SCAS (unknown cutoff) | 39,2 | - | - | - |

**Table 1** | *Overview of study characteristics and prevalence rates (continued)*

| Study | Sample size | % Male | % CD | Mean age (range†) | % Active disease | Quality score | Outcome | Method Q or I‡ | Instrument (cutoff for elevated symptoms) | Prevalence (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Anxiety symptoms | Anxiety disorders | Depressive symptoms | Depressive disorders | |
| Giannakopoulos 2016[40§] | 85 | 41 | 67 | 13,2 (8-18) | 50,6 | 11/27 | Depression | Q | CDI (Total score ≥15) | - | - | 14,0 | - | |
| Szigethy 2007[41 §] | 156 | - | - | 14,3 (11-17) | - | 12/27 | Depression | Q | CDI (Total score ≥9) | - | - | 23,1 | - | |
| Szigethy 2014[42 §] | 765 | - | - | - (9-17) | - | 13/27 | Depression | Q | CDI (Total score ≥10) | - | - | 32,0 | - | |
| | | | | | | | Depression | I | K-SADS | - | - | - | 10,5 | |
| Thompson 2012[43 §] | 191 | 53 | 73 | 14,2 (11-17) | 53,0 | 13/27 | Depression | Q | CDI (Total score ≥12) | - | - | 26,2 | - | |
| Watson 2017[44] | 81 | 56 | 77 | 14,4 (9-18) | 12,4 | 12/27 | Anxiety | Q | STAIC (T-score >64) | 5,6 | - | - | - | |
| | | | | | | | Depression | Q | CDI-2 (T-score >64) | - | - | 8,5 | - | |
| Schuman 2013[45] | 122 | 52 | 79 | 15,7 (13-17) | 42,6 | 14/27 | Depression | Q | CDI (Total score ≥12) | - | - | 19,7 | - | |
| Reed-Knight 2014[46] | 78 | 51 | 79 | 13,8 (8-17.5) | 37,0 | 15/27 | Depression | Q | CDI (Total score ≥12) | - | - | 12,8 | - | |
| Reigada 2016[47] | 86 | 56 | 86 | 14,7 (11-18) | - | 13/27 | Anxiety | Q | SCARED (Total score ≥20) | 27,0 | - | - | - | |
| Ryan 2013[48 §] | 112 | 56 | 73 | 14,5 (7-18) | 41,9 | 11/27 | Depression | Q | CDI (T-score ≥65) | - | - | 3,6 | - | |
| Walter 2016[49] | 161 | 57 | 78 | 14,5 (11-18) | 26,2 | 10/27 | Anxiety | Q | RCADS (T-score ≥66) | 14,9 | - | - | - | |
| | | | | | | | Depression | Q | RCADS (T-score ≥66) | - | - | 5,0 | - | |
| Reigada 2017[50 §] | 281 | 51 | 78 | 14,7 (12-17) | 31,7 | 13/27 | Anxiety | Q | PROMIS (T-score ≥65) | 6,4 | - | - | - | |
| | | | | | | | Depression | Q | PROMIS (T-score ≥65) | - | - | 2,5 | - | |

*Abbreviations:* SCARED= Screen for Child Anxiety Related Emotional Disorders; RCADS= Revised Child Anxiety and Depression Scale; RCMAS= Revised Children's Manifest Anxiety Scale; SCAS=Spence Children's Anxiety Scale; PROMIS= the Patient-Reported Outcomes Measurement Information System; STAIC= State-Trait Anxiety Inventory for Children; ICD= International Classification of Diseases; CASCAP= Clinical Assessment Scale of Child and Adolescent Psychopathology; K-SADS= Kiddie Schedule for Affective Disorders and Schizophrenia; CDI= Child Depression Inventory; CES-D= Center for Epidemiologic Studies Depression Scale; CDI-SF= CDI Short Form; BDI= Beck Depression Inventory; CDI-2= CDI 2nd Edition; ChilD-S= Children's Depression Screener; PHQ-9=Patient Health Questionnaire-9.

*Notes:* included studies are sorted in order of which they appear in the article, superscript number corresponds with reference list. † age range reported in inclusion criteria; ‡ Q=questionnaire, I=interview; § data after request provided by the (corresponding) author; ¶ all included patients were <18; $ data received of patients <18.

## Prevalence of anxiety symptoms

Ten studies [5, 6, 8, 30, 35, 39, 44, 47, 49, 50], including 1155 participants, reported on the prevalence of anxiety symptoms, using seven different instruments. The pooled estimate of prevalence of anxiety symptoms was 16.4% (95% Confidence Interval [CI] 6.8-27.3%) with a high level of heterogeneity between estimates ($I^2$ = 92.9%, $p$ < .001). See also Figure 2a. Although visual inspection of the funnel plot indicates some asymmetry (see Appendix 3, few studies present with a lower prevalence and a relatively high standard error), the LFK index revealed no significant asymmetry (LFK index: 0.96). This indicates that heterogeneity in outcomes between studies may not be due to publication or reporting bias, but to other factors.

Meta-regression analyses showed that disease type (% CD, $ß$ = .004, $p$ = .699) and gender (% male, $ß$ = .027, $p$ = .506) did not explain the heterogeneity in outcomes. The meta-regression analysis for disease activity could not be performed due to lack of data (only 5 out of 10 studies reported % active disease).

To check whether prevalence rates would change if we removed the 5 studies with a score in the lowest tertile of reported quality/risk of bias (15.5% [95%CI 2.6-31.5%], $I^2$ = 95.6%) or removed the largest study with 280 participants (20.2% [95%CI 9.5-32.3%], $I^2$ = 91.1%) we reran our analyses. Results did not change significantly, and heterogeneity in outcomes was still high. The random effects analysis provided a prevalence rate of 18.1% (95%CI 10.1-27.8%).

## Prevalence of anxiety disorders

Only three studies [9-11] reported on the prevalence of anxiety disorders, with a total of 4924 participants (respectively n=2144 [9], n=47 [10], n=2733 [11]). The pooled estimate of prevalence of anxiety disorders was 4.2% (95%CI 3.6-4.8%). See also Figure 2b. The heterogeneity was low and not significant ($I^2$ = 2.1%, $p$ = .346). The number of included studies was too low to investigate reporting bias, meta-regression or to perform sensitivity analyses. The random effects analysis provided a prevalence rate of 4.2% (95%CI 3.6-4.8%).

## Prevalence of depressive symptoms

Twenty-two studies [5, 7, 8, 30-38, 40-46, 48-50] reported on depressive symptoms (including 2911 participants), using 9 different instruments, including 3 versions of the Child Depression Inventory (CDI). The pooled estimate of prevalence of depressive symptoms was 15.0% (95%CI 6.4-24.8%), with a high level of heterogeneity ($I^2$ = 95.0%, $p$ < .001). See also Figure 2c.

| Author and year | | Statistics per study | | | Prevalence rate and 95% Confidence interval |
|---|---|---|---|---|---|
| | | Prevalence rate | Lower limit | Upper limit | |
| Mackner et al 2005[5] | 1/50 | 0,020 | 0,000 | 0,084 | |
| Reigada et al 2015[6] | 46/93 | 0,495 | 0,393 | 0,596 | |
| Reigada et al 2011[8] | 8/36 | 0,222 | 0,099 | 0,374 | |
| Arvanitis et al 2016[30] | 46/276 | 0,167 | 0,125 | 0,213 | |
| Jelenova et al 2016[35] | 4/23 | 0,174 | 0,042 | 0,360 | |
| Kilroy et al 2011[39] | 31/79 | 0,392 | 0,287 | 0,503 | |
| Watson et al 2017[42] | 4/71 | 0,056 | 0,012 | 0,124 | |
| Reigada et al 2016[47] | 23/86 | 0,267 | 0,179 | 0,367 | |
| Walter et al 2016[49] | 24/161 | 0,149 | 0,098 | 0,209 | |
| Reigada et al 2017[50] | 18/280 | 0,064 | 0,038 | 0,096 | |
| Total | | 0,164 | 0,068 | 0,273 | |

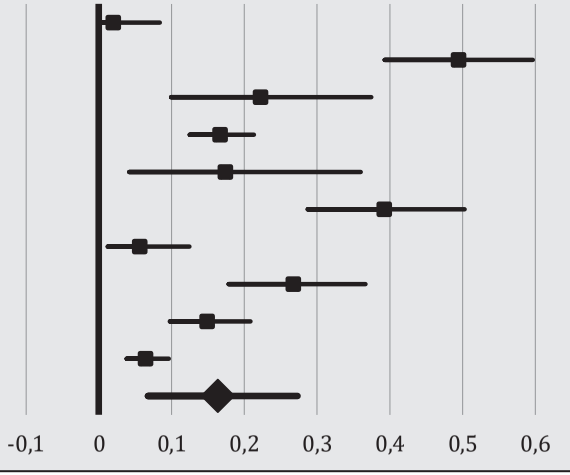


**Figure 2a** | Forest plot prevalence rate anxiety symptoms

*Note.* Sample sizes can differ from those mentioned in Table 1, due to missing data on the outcome measure.

| Author and year | | Statistics per study | | | Prevalence rate and 95% Confidence interval |
|---|---|---|---|---|---|
| | | Prevalence rate | Lower limit | Upper limit | |
| Loftus et al 2011[9] | 81/2144 | 0,038 | 0,030 | 0,046 | |
| Engelmann et al 2015[10] | 3/47 | 0,064 | 0,008 | 0,156 | |
| Barnes et al 2017[11] | 121/2733 | 0,044 | 0,037 | 0,052 | |
| Total | | 0,042 | 0,036 | 0,048 | |

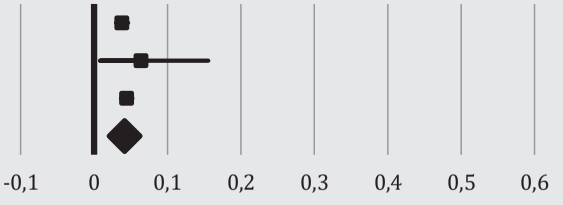


**Figure 2b** | Forest plot prevalence rate anxiety disorders
*Note.* Sample sizes can differ from those mentioned in Table 1, due to missing data on the outcome measure.

| Author and year | | Statistics per study | | |
|---|---|---|---|---|
| | | Prevalence rate | Lower limit | Upper limit |
| Mackner et al 2005[5] | 0/50 | 0,000 | 0,000 | 0,034 |
| Reed-Knight et al 2012[7] | 0/31 | 0,000 | 0,000 | 0,055 |
| Reigada et al 2011[8] | 12/36 | 0,333 | 0,187 | 0,497 |
| Arvanitis et al 2016[30] | 10/276 | 0,036 | 0,017 | 0,062 |
| Marcus et al 2009[31] | 1/70 | 0,014 | 0,000 | 0,060 |
| Castaneda et al 2013[32] | 11/34 | 0,324 | 0,175 | 0,492 |
| Van Tilburg et al 2015[33] | 51/189 | 0,270 | 0,209 | 0,336 |
| Jayanath et al 2014[34] | 6/26 | 0,231 | 0,086 | 0,415 |
| Jelenova et al 2016[35] | 4/24 | 0,167 | 0,040 | 0,347 |
| Mahlmann et al 2017[36] | 4/21 | 0,190 | 0,046 | 0,391 |
| Iturralde et al 2017[37] | 2/23 | 0,087 | 0,002 | 0,245 |
| Herzog et al 2013[38] | 1/110 | 0,009 | 0,000 | 0,039 |
| Giannakopoulos et al 2016[40] | 12/85 | 0,141 | 0,074 | 0,224 |
| Szigethy et al 2007[41] | 36/156 | 0,231 | 0,168 | 0,300 |
| Szigethy et al 2014[42] | 245/765 | 0,320 | 0,288 | 0,354 |
| Thompson et al 2012[43] | 50/191 | 0,262 | 0,202 | 0,327 |
| Watson et al 2017[44] | 6/71 | 0,085 | 0,029 | 0,162 |
| Schuman et al 2013[45] | 24/122 | 0,197 | 0,131 | 0,272 |
| Reed-Knight et al 2014[46] | 10/78 | 0,128 | 0,062 | 0,213 |
| Ryan et al 2013[48] | 4/112 | 0,036 | 0,008 | 0,080 |
| Walter et al 2016[49] | 8/161 | 0,050 | 0,021 | 0,089 |
| Reigada et al 2017[50] | 7/280 | 0,025 | 0,009 | 0,047 |
| Total | | 0,150 | 0,064 | 0,248 |

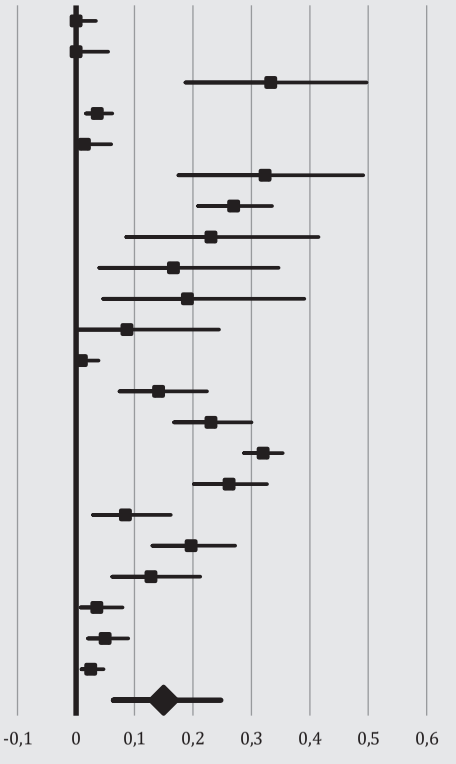


**Figure 2c** | Forest plot for the meta-analysis on the prevalence rate of depressive symptoms
*Note.* Sample sizes can differ from those mentioned in Table 1, due to missing data on the outcome measure.

| Author and year | | Statistics per study | | | Prevalence rate and 95% Confidence interval |
|---|---|---|---|---|---|
| | | Prevalence rate | Lower limit | Upper limit | |
| Loftus et al 2011[9] | 118/2144 | 0,055 | 0,046 | 0,065 | |
| Engelmann et al 2015[10] | 8/47 | 0,170 | 0,074 | 0,293 | |
| Barnes et al 2017[11] | 28/2733 | 0,010 | 0,007 | 0,014 | |
| Szigethy et al 2014[42] | 80/765 | 0,105 | 0,084 | 0,127 | |
| Total | | 0,034 | 0 | 0,093 | |

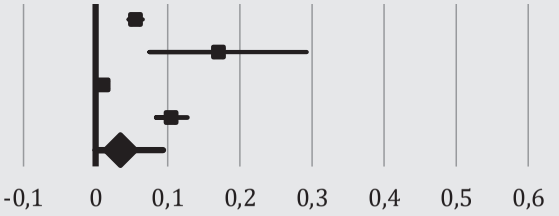


**Figure 2d** | Forest plot prevalence rate depressive disorders
*Note.* Sample sizes can differ from those mentioned in Table 1, due to missing data on the outcome measure.

The funnel plot and Doi plot showed significant asymmetry (LFK index: -2.80) (see Appendix 3). Visual inspection of the funnel plot indicates that there is a lack of studies with a low prevalence rate with a relatively high standard error. Hence, heterogeneity between studies may be due to publication or reporting bias. Meta-regression analyses showed that disease type (% CD, $\beta$ = -.009, $p$ = .125) and gender (% male, $\beta$ = -.003, $p$ = .748) did not explain the heterogeneity in prevalence rates of depressive symptoms between studies.

Disease activity (% active disease) showed a significant effect on the prevalence of depressive symptoms ($\beta$ = .021, $p < .05$), indicating that in studies with a higher percentage of active disease the prevalence rate of depressive symptoms was higher. Removing the 6 studies with a score in the lowest tertile of reported quality/risk of bias (15.5% [95%CI 5.3-27.2%], $I^2$ = 95.6%) or removing the largest study with 765 participants (10.2% [95%CI 4.9-16.2%], $I^2$ = 91.8%) did not significantly change the prevalence rate for depressive symptoms, heterogeneity was still high. In addition, excluding the study with only female patients [7] did not change the results. The random effects analysis provided a prevalence rate of 12% (95%CI 6.9-18.2%).

### Prevalence of depressive disorders

Four studies [9-11, 42] reported on the prevalence of depressive disorders, with a total of 5689 participants (respectively, n=2144 [9] , n=47 [10], n=2733 [11], n=765 [42]). The pooled estimate of prevalence of depressive disorders was 3.4% (95%CI 0-9.3%), with a high level of heterogeneity ($I^2$ = 98.3, $p < .001$). See also Figure 2d. The number of included studies was too low to investigate reporting bias, meta-regression or to perform sensitivity analyses. The random effects analysis provided a prevalence rate of 6.2% (95%CI 1.6-13.1%).

## DISCUSSION

This first systematic review and meta-analysis examining the prevalence of anxiety and depression in paediatric IBD showed that the estimated prevalence rate was 16.4% for anxiety symptoms (based on 10 studies), 4.2% for anxiety disorders (based on 3 studies), 15.0% for depressive symptoms (based on 22 studied) and 3.4% for depressive disorders (based on 4 studies). Differences between the prevalence rates calculated using the two different methods were small.

Our findings show higher prevalence rates of anxiety and depressive symptoms compared to a community sample of Dutch adolescents [51], but a lower prevalence of depressive symptoms compared to a community sample in the United States. The prevalence rate of anxiety symptoms was comparable [52]. Furthermore, our meta-

analysis shows that the prevalence of anxiety /depressive symptoms is lower in paediatric IBD, compared to available meta-analyses in other paediatric patient groups, such as diabetes and asthma (range 27-33%) [53, 54]. The same trend has been shown in adult IBD; a higher prevalence of anxiety/depression, compared to the general population/ healthy controls, but a lower prevalence compared to patients with another chronic disease [17]. In addition, prevalence rates are also lower than reported in adult IBD. Neuendorf et al. showed a pooled prevalence rate of 35.1% for anxiety symptoms (based on 51 studies), 20.7% for anxiety disorders (based on 4 studies), 21.6% for depressive symptoms (based on 67 studies), and 15.2% for depressive disorders (based on 5 studies) [55]. There are several possible explanations for the differences in prevalence rates between children and adults. The prevalence rates of anxiety and depressive symptoms are found to be higher in adults than in children and adolescents [56, 57], and for some anxiety disorders and for depressive disorders it has been found that their prevalence increases with age [58, 59]. Furthermore, with longer disease duration of IBD, disease related complications due to irreversible bowel damage will occur, thus increasing the burden of disease. Finally, the increasing responsibilities in adulthood, and the detrimental influence of IBD on relationships and work, impact daily life even more than in childhood. However, one has to bear in mind that comparing pooled prevalence rates to each other is difficult, considering the great variation in the used instruments and cutoffs. A similarity between adult and paediatric studies is, that compared to studies investigating anxiety and depressive *symptoms,* studies investigating anxiety/depressive *disorders* are underrepresented.

In our meta-analysis, we did not find an influence of disease type on prevalence rates of anxiety symptoms, anxiety disorders and depressive disorders. In contrast, in adult IBD, an influence of disease type was found, with a higher prevalence rate of depressive symptoms in CD patients than in UC patients [55]. Methodological differences might explain these contrasting findings: we could only study disease type as a proportion (e.g. % CD of the total sample), whereas Neuendorf et al. could statistically compare the prevalence in patients with CD versus UC. Unfortunately, it was not possible to assess the influence of disease activity on anxiety symptoms, whereas this has been shown to significantly influence prevalence in adult IBD [55]. Disease activity did significantly influence the prevalence rate of depressive symptoms: a higher prevalence was found in studies with more patients with active disease. These findings are in accordance with earlier findings in adult IBD [17, 55]. Future studies should investigate whether patients with higher disease activity (e.g. moderate or severe) also have a higher prevalence of anxiety/depression compared to the patients with mild disease activity.

Gender did not affect prevalence rates in our study, results of earlier studies showed mixed findings [9, 18]. To what extent factors such as socio-economic status, use of cor-

ticosteroids, disease duration, age of diagnosis, or presence of perianal disease impact the prevalence of anxiety and depression in paediatric IBD, should be investigated in future studies [18].

Several methodological differences of the 28 included studies, give rise to heterogeneity and make us cautious in drawing firm conclusions. Firstly, although all studies used validated instruments to assess anxiety or depressive symptoms, numerous different instruments were used, not all validated in paediatric IBD. Different cutoffs for the same instruments were used, and some used raw total scores, while others used (varying) T-scores. For example, for the CDI, cutoff scores ranged from 9 [42] to 19 [38] or 20 [35] and for the SCARED, cutoff scores ranged from 20 [6, 47] to 25 [8] (see also Table 1). For future cross-cultural comparison of studies, we recommend to use the same, comparable cutoffs for each instrument. In addition, only 4 studies investigated anxiety/depressive disorders [9-11, 42], and used two different methods (DSM based psychiatric interview versus ICD codes). These different methods, added to the low number of included studies increased heterogeneity and may limit the reliability of the results. More studies investigating anxiety and depressive disorders are warranted to evaluate if they are prevalent in paediatric IBD.

Secondly, cross-cultural generalisability of the results is limited, considering that most studies came from North America (71%), only a few came from Europe (25%), and only one came from Asia (4%). Thirdly, 23 studies measured clinical disease activity, but for some studies the suitability of the measures of disease activity is debatable. Two studies used non- validated indices for paediatric IBD (i.e. the children's somatisation index [8] and the "IBD symptom questionnaire" [33]), and others used ("adult") IBD disease activity indexes, also not validated in paediatric IBD [6, 30, 41, 43, 45, 47, 50]. None of the included studies reported on mucosal disease activity, 5 measured the inflammatory marker C-reactive protein (CRP) [32, 38, 42, 44, 46] and 2 measured faecal calprotectin [32, 44], but none related this to the presence of anxiety or depression.

Fourthly, no study presented prevalence rates separately for IBD subtypes, disease activity (active vs remission) and gender. Therefore, if available, these characteristics could only be incorporated in the meta-regression analysis as covariates (as percentages, e.g. % CD). Presenting data separately for these and other subgroups (e.g. patients that had received bowel surgery or perianal disease) would facilitate the use of meta-analytic approaches in the future and help understand if certain subgroups are more at risk for anxiety and/or depression than others.

Finally, 2 studies provided more than half of the included patients, 19/28 (68%) studies were small (N<150), only 9 out of 28 (32%) studies had a control group and mean study quality was moderate. Larger studies, preferably cohort studies with a control group which control for confounders are warranted to increase the quality of research.

The strengths of our study include a systematic search to include all studies examining the prevalence of anxiety and depression in paediatric IBD. In addition, providing separate analysis for anxiety/depressive symptoms versus disorders is important and insightful. Furthermore, the meta-regression approach strengthens our analyses. Finally, we performed the meta-analyses with both the inverse variance heterogeneity and the random effects model.

Inevitably, this work has some limitations. First, inclusion was limited to English published papers. Second, conference abstracts without a full published article had to be excluded. This may have introduced bias. Third, the heterogeneity between the included studies forces us to be careful drawing conclusions. However, we feel performing a meta-analysis (instead of only presenting the data as systematic review) was useful for several reasons. Firstly, knowing about this high heterogeneity is very important. Secondly, we tried to explore with our meta-regression analyses if certain factors could explain the high heterogeneity and showed that, in patients with depressive symptoms, this was partly explained by disease activity. Future studies would benefit from a study design which allows for subgroup-analyses to investigate heterogeneity.

Recommendations for future studies to limit this heterogeneity and improve quality of research are extensively described by Mikocka-Walus and colleagues [17] and include using the same validated screening measures and clinical diagnostic measures (psychiatric interview) with the same comparable cutoffs, including comparison groups (healthy and other chronically ill controls), control for confounders (psychiatric history), measuring IBD outcomes, present data separately for IBD subtypes and for disease activity categories. At last, the results of the analyses concerning reporting bias show that publication and reporting bias cannot be ruled out.

In conclusion, this systematic review and meta-analysis indicates that symptoms of anxiety and depression are prevalent in paediatric IBD, with comparable pooled prevalence rates of anxiety symptoms and depressive symptoms (16.4% and 15.0%). Due to high heterogeneity in used instruments and cutoffs, results must be interpreted with caution. To gain better insight into the prevalence of anxiety and depressive symptoms it is necessary to systematically screen paediatric IBD patients with the same validated instruments, using the same cutoffs. More studies are necessary to determine the prevalence of anxiety/depressive disorders using a standardized psychiatric interview following DSM criteria. In order to assess whether certain subgroups are more at risk than others, it is advised to use the same validated methods of assessing clinical disease activity, and to include objective inflammatory parameters (such as CRP, faecal calprotectin).

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# APPENDICES

## Appendix 1. Search strategies for all databases

**Embase.com**

('inflammatory bowel disease'/exp OR ((inflamma* NEAR/3 bowel* NEAR/3 disease*) OR ibd OR crohn* OR (ulcer* NEAR/3 (colit* OR colorectit*)) OR Ileocolit* OR (Terminal* NEAR/3 Ileitis)):ab,ti) AND ('anxiety'/de OR 'anxiety disorder'/exp OR 'fear'/de OR 'depression'/exp OR 'antidepressant agent'/de OR 'cognitive therapy'/de OR 'emotion'/de OR (anxi* OR fear* OR depressi* OR panic* OR (cogniti* NEAR/3 therap*) OR emotion* OR antidepress*):ab,ti) AND (child/exp OR adolescent/exp OR 'young adult'/de OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR pediatrics/exp OR childhood/exp OR 'child development'/de OR 'child growth'/de OR 'child health'/de OR 'child health care'/exp OR 'child care'/exp OR 'childhood disease'/exp OR 'child psychiatry'/de OR 'child psychology'/de OR 'pediatric ward'/de OR 'pediatric hospital'/de OR (adolescen* OR infan* OR child* OR kid OR kids OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR ((young OR early*) NEAR/3 (adult* OR women OR men OR woman OR man))):ab,ti)

**Medline ovid**

(exp "Inflammatory Bowel Diseases"/ OR ((inflamma* ADJ3 bowel* ADJ3 disease*) OR ibd OR crohn* OR (ulcer* ADJ3 (colit* OR colorectit*)) OR Ileocolit* OR (Terminal* ADJ3 Ileitis)).ab,ti.) AND (exp "anxiety"/ OR exp "Anxiety Disorders"/ OR "fear"/ OR "depression"/ OR "Depressive Disorder"/ OR "Depressive Disorder, Major"/ OR "Antidepressive Agents"/ OR "Cognitive Therapy"/ OR "emotions"/ OR (anxi* OR fear* OR depressi* OR panic* OR (cogniti* ADJ3 therap*) OR emotion* OR antidepress*).ab,ti.) AND (exp Child/ OR exp Infant/ OR exp Adolescent/ OR exp "Child Behavior"/ OR exp "Parent Child Relations"/ OR exp "Pediatrics"/ OR exp "Child Welfare"/ OR "Child Development"/ OR exp "Child Health Services"/ OR exp "Child Care"/ OR "Child Psychiatry"/ OR "Psychology, Child"/ OR "Hospitals, Pediatric"/ OR (adolescen* OR infan* OR child* OR kid OR kids OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ age*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR ((young OR early*) ADJ3 (adult* OR women OR men OR woman OR man))).ab,ti.)

**Psycinfo ovid**

(((inflamma* ADJ3 bowel* ADJ3 disease*) OR ibd OR crohn* OR (ulcer* ADJ3 (colit* OR colorectit*)) OR Ileocolit* OR (Terminal* ADJ3 Ileitis)).ab,ti.) AND (exp "depression"/ OR exp "Anxiety Disorders"/ OR "fear"/ OR "Depression (Emotion)"/ OR "Major Depression"/ OR "Antidepressant Drugs"/ OR "Cognitive Therapy"/ OR "emotions"/ OR (anxi* OR fear* OR depressi* OR panic* OR (cogniti* ADJ3 therap*) OR emotion* OR antidepress*).ab,ti.) AND (100.ag. OR (adolescen* OR infan* OR child* OR kid OR kids OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ age*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR ((young OR early*) ADJ3 (adult* OR women OR men OR woman OR man))).ab,ti.)

**Cochrane**

(((inflamma* NEAR/3 bowel* NEAR/3 disease*) OR ibd OR crohn* OR (ulcer* NEAR/3 (colit* OR colorectit*)) OR Ileocolit* OR (Terminal* NEAR/3 Ileitis)):ab,ti) AND ((anxi* OR fear* OR depressi* OR panic* OR (cogniti* NEAR/3 therap*) OR emotion* OR antidepress*):ab,ti) AND ((adolescen* OR infan* OR child* OR kid OR kids OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR ((young OR early*) NEAR/3 (adult* OR women OR men OR woman OR man))):ab,ti)

**Web of science**

TS=((((inflamma* NEAR/2 bowel* NEAR/2 disease*) OR ibd OR crohn* OR (ulcer* NEAR/2 (colit* OR colorectit*)) OR Ileocolit* OR (Terminal* NEAR/2 Ileitis))) AND ((anxi* OR fear* OR depressi* OR panic* OR (cogniti* NEAR/2 therap*) OR emotion* OR antidepress*)) AND ((adolescen* OR infan* OR child* OR kid OR kids OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEAR/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR ((young OR early*) NEAR/2 (adult* OR women OR men OR woman OR man)))) )

**Google scholar**

"inflammatory bowel disease"|crohn|"ulcerative colitis" anxiety|fear|depression|depressive|emotion|antidepressants adolescents|adolescence|infants|children|"young|early adulthood|adults|women|men"

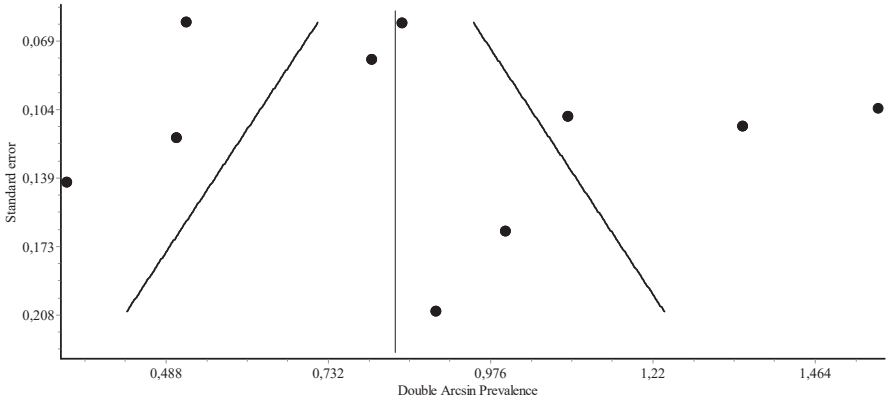
## Appendix 2. Quality/risk of bias checklist

| | |
|---|---|
| Method<br>(max. 2 points) | Clearly stated aim/research question (yes = 1 point)<br>Clearly stated outcome(s) (yes = 1 point) |
| Recruitment<br>(Max. 9 points) | Clearly defined in- and exclusion criteria (yes = 1 point)<br>Convenience sample (0 points) vs. systematic sampling (consecutive, random, registries: 1 point)<br>Response rate reported (Not reported = 0, less < 50% = 1 point, 50-75% = 2 points, > 75% = 3 points)<br>Reasons for non-participation described (yes =1 point)<br>External validity (monocenter = 0 points, multicenter = 1 point, multicenter and mixed [tertiary AND community hospitals] = 2 points)<br>Study population clearly described? (e.g. age, ethnicity, gender) (yes = 1 point) |
| Control group?<br>(Max. 3 points) | Normative data (with ref. and correct language/country; 3 points)<br>Normative data (with ref. but other language/country; 2 point)<br>Normative data (otherwise; e.g. not specified, no ref, etc.; 1 point)<br>OR<br>Both healthy controls and chronically ill controls (3 points)<br>Healthy controls (2 points)<br>Other chronically ill controls (1 point) |
| Sample Size IBD patients<br>(Max. 4 points) | Interpretation (low <150 = 1 points – medium 150-250 = 2 point – high >250 = 3 points)[1]<br>Power calculation or justification of sample size (yes = 1 point) |
| Measures IBD activity (max. 3 points) | Disease activity index (e.g. PCDAI/PUCAI/PGA) (1 point)<br>Inflammatory parameters (CRP, ESR, calprotectin) (1 point)<br>Endoscopy with severity scoring (1 point) |
| Measures of anxiety and depression<br>(Max. 3 points) | Screening performed with validated self-report scales (1 point)<br>Diagnostic interview / DSM or ICD 10 codes (1 point)<br>Additional parent- or caregiver-report (1 point) |
| Confounders<br>(Max. 3 points) | 'Taken into account with regard to anxiety/depression prevalence'<br>Disease activity taken into account (1 point)<br>IBD subtype taken into account (1 point)<br>Objectified prior psychiatric history taken into account (1 point) |

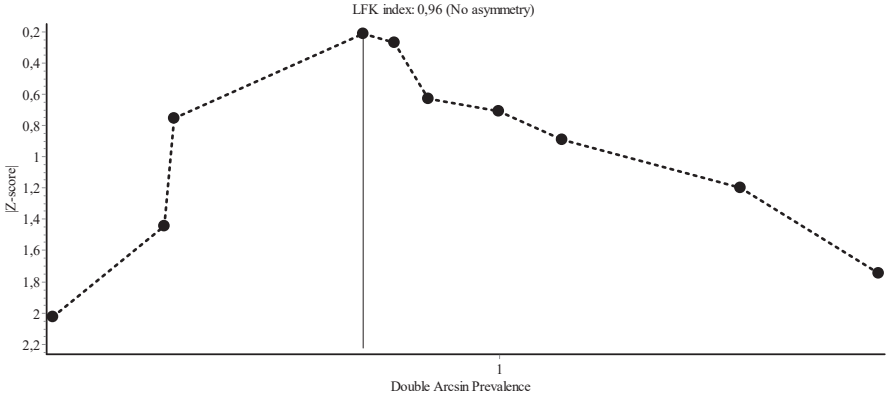
**Maximum score:** 27

[1]**Based on** Arya et al. 2012 – Sample Size Estimation in Prevalence Studies

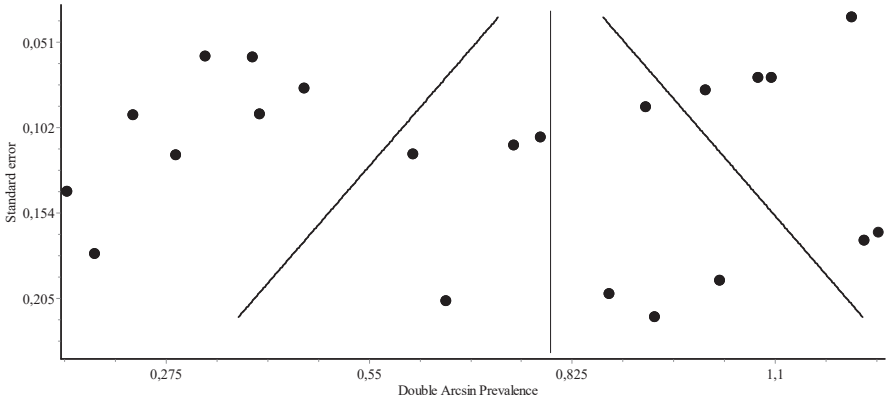
## Appendix 3. Funnel and Doi plots for anxiety and depressive symptoms



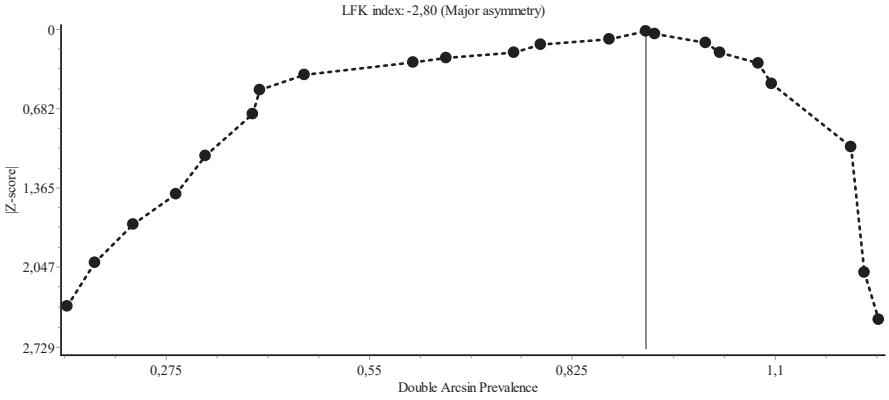

a) Funnel plot anxiety symptoms




b) Doi plot anxiety symptoms
Abbreviations: LFK= Luis Furuya-Kanamori index




c) Funnel plot depressive symptoms




d) Doi plot anxiety symptoms
Abbreviations: LFK= Luis Furuya-Kanamori index

# Effectiveness of disease-specific cognitive behavioral therapy on depression, anxiety, quality of life and the clinical course of disease in adolescents with inflammatory bowel disease: study protocol of a multicenter randomized controlled trial (HAPPY-IBD)

*Gertrude van den Brink, *Luuk Stapersma, Hanan El Marroun, Jens Henrichs, Eva M. Szigethy, Elisabeth M.W.J. Utens, Johanna C. Escher

* Both authors contributed equally

BMJ Open Gastroenterology; 2016, 3: e000071. doi:10.1136/bmjgast-2015-000071

3

## ABSTRACT

**Introduction** Adolescents with inflammatory bowel disease (IBD) show a higher prevalence of depression and anxiety, compared to youth with other chronic diseases. The inflammation-depression hypothesis might explain this association and implies that treating depression can decrease intestinal inflammation and improve disease course. The present multicenter randomized controlled trial (RCT) aims to test the effectiveness of an IBD-specific Cognitive Behavioral Therapy protocol in reducing symptoms of subclinical depression ànd anxiety, while improving quality of life (QoL) and disease course in adolescents with IBD.

**Methods and analysis** Adolescents with IBD (10-20 years) from seven hospitals undergo screening (online questionnaires) for symptoms of depression and anxiety. Those with elevated scores of depression (CDI ≥13 or BDI-II ≥14) and/or anxiety (SCARED: boys ≥26, girls ≥30) receive a psychiatric interview. Patients meeting criteria for depressive/anxiety disorders are referred for psychotherapy outside the trial. Patients with elevated (subclinical) symptoms are randomly assigned to medical care-as-usual (CAU; n=50) or CAU plus IBD-specific CBT (n=50). Main outcomes: 1) reduction in depressive and/or anxiety symptoms after three months, 2) sustained remission for 12 months. Secondary outcomes: QoL, psychosocial functioning, treatment adherence. In addition, we will assess inflammatory cytokines in peripheral blood mononuclear cells and whole blood RNA expression profiles. For analysis, multilevel linear models and Generalized Estimating Equations will be used.

**Ethics and dissemination** The Medical Ethics Committee of the Erasmus MC approved this study. If we prove that this CBT improves emotional well-being as well as disease course implementation is recommended.

**Trial registration:** ClinicalTrials.gov: NCT02265588

## BACKGROUND

Inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis [UC]) is a chronic relapsing inflammatory disorder of the intestine, with increasing incidence and prevalence worldwide [1]. Patients have abdominal pain, bloody diarrhea, often accompanied by systemic symptoms such as lack of appetite, weight loss and fatigue. IBD has a fluctuating course, with relapses (increased clinical disease activity) and periods of clinical remission. In up to 25% percent of patients, IBD manifests during late childhood and adolescence [2-4]. Adolescence is a challenging life phase, with significant psychological, physical and social changes. Having IBD during adolescence is a threat to healthy psychosocial development, making transition to adulthood more difficult.



Adolescent IBD patients frequently experience psychological and social problems [5]. They often have low self-esteem and report stress concerning their disease and future [6]. In addition, their quality of life is reduced [2, 7, 8], due to the unpredictable course of disease, embarrassing symptoms, frequent hospital visits or admissions and (side effects of) medical treatment. Furthermore, the possible extra intestinal manifestations (EIM) (e.g. Primary sclerosing cholangitis [PSC], arthritis), complications (e.g. strictures) and surgical treatments (e.g. resections) reduce quality of life significantly [2, 8-12].

Depressive symptoms are common, and occur in 20-40% of adolescents with IBD [13-18]. Anxiety, reported in 30-50% of IBD adolescents, is even more common [7, 19]. In many young patients, symptoms of both depression and anxiety occur together [20, 21]. Not surprisingly, early onset of mental health problems can predict poor long-term medical and psychological outcome [22-24].

Taken together, it is clear that psychological problems are often found in young IBD patients. The inflammation-depression hypothesis has been proposed to explain the association between psychological problems and IBD, and implies that treating emotional symptoms can decrease intestinal inflammation and thus improve disease course [25]. This hypothesis will be discussed in detail later in this introduction.

### Factors associated with depression and anxiety in IBD

Medical, psychological and family factors are associated with depression and anxiety in IBD and can influence the effectiveness of treatment of emotional problems in IBD. Known medical factors are: being recently diagnosed with IBD [26], a diagnosis of Crohn's disease (versus ulcerative colitis) [27], a history of surgery [27, 28], active disease [26-32], non-adherence to therapy [31] and IBS (like) symptoms [33]. Psychological factors are: high levels of perceived stress [26], negative cognitive coping [15], low self-esteem [8, 34], and sleep disturbance [32]. Family factors are: parental stress [35,

36], low socio economic status [26, 27, 31], stressful life events [37], and unhealthy family functioning [10, 34, 37]. In pediatric patients, active disease [15, 18, 19, 38, 39] and low socio-economic status [15] are associated with depression and/or anxiety.

In the opposite direction, emotional problems have also been shown to influence disease activity. Psychological stress can trigger a relapse in IBD [30, 40-44] and lead to a more difficult-to-treat (refractory) disease [30]. Moreover, emotional problems decrease the ability to cope with physical symptoms, increase the sensitivity to abdominal pain [45], increase medical service use and decrease therapy adherence [16, 19, 29, 46, 47].

Altogether, these findings emphasize the existence of a bidirectional relationship between emotional problems and disease activity in patients with IBD. We therefore expect that early recognition and treatment of emotional problems is necessary to improve both mental health and the clinical course of disease.

## Inflammation-depression hypothesis

The 'inflammation-depression hypothesis' or ´brain-gut hypothesis' proposes that intestinal inflammation, by means of increased production of pro-inflammatory cytokines (e.g. tumor necrosis factor alpha [TNF-α]), is known to directly and indirectly affect the brain and thereby increase symptoms of depression [48]. It is also suggested that psychological stress can increase depressive symptoms by increasing inflammation [25, 48, 49].

Most evidence for this hypothesis comes from animal studies in which experimental (psychological) stress has shown to induce and reactivate inflammation in colitis models [44]. It is suggested that these stress induced alterations in inflammation are mediated through changes in Hypothalamic-Pituitary-Adrenal (HPA) axis function and alterations in bacterial mucosal interactions [25, 44, 50-52]. Similarly, human studies also show the pro-inflammatory effect of experimental [25, 50] and (early) life stress [52] and show elevated levels of inflammatory markers in depressed patients [49, 53-56].

There are few pediatric IBD studies examining the relationship between inflammation and depression [48]. Furthermore, the brain-gut hypothesis mainly focuses on depression, the relation between inflammation and anxiety has been studied less extensively [57]. Reviews by Hou et al. and Salim et al. show the existing evidence in animal models linking inflammation with anxiety [58, 59]. In humans, a chronic anxiety state has been shown to negatively affect immune function and several studies report a positive correlation between anxiety and increased inflammatory markers [57-60]. To our knowledge, little is known about the association between anxiety and inflammation in IBD. The present study will contribute to more understanding of this association [19, 31].

## CBT for adolescent IBD patients

From all different psychotherapies, CBT is the most evidence based psychotherapy to reduce symptoms of anxiety and depression [12, 61, 62].

For adolescents with IBD, Szigethy et al. developed a disease-specific CBT program called PASCET-PI (Primary and Secondary Control Enhancement Training – Physical Illness) (see Intervention) [63]. They performed a RCT in adolescents with IBD and subclinical depression (total N=41). A 40% reduction in depressive severity in the PASCET-PI group was found compared to the control group, receiving care-as-usual [17]. These positive effects maintained 1 year after treatment [23]. However, anxiety was not addressed. Only a few pediatric studies have integrated the clinical course of disease or disease activity as an outcome parameter. Szigethy et al. compared the effect of two different psychotherapies in pediatric IBD patients with (sub)clinical depression and found that both therapies had a significant impact in improving depression while CBT was associated with a greater reduction in disease activity [64]. Reigada et al. showed in a CBT-pilot with 9 (pediatric) patients and only comorbid anxiety, that 90% no longer had an anxiety disorder and half of the patients had a reduction in IBD severity [65].

Although the aforementioned studies showed promising results, larger scale randomized studies are necessary to evaluate the longitudinal effect of CBT in pediatric IBD and to identify potential moderators of CBT success. To the best of our knowledge, at present there are no randomized controlled trials assessing simultaneously the effect of CBT on the two psychological outcomes (symptoms of depression or anxiety) and the clinical course of disease in adolescent IBD patients.

## Aim and hypothesis

The present study's aim is to test the effectiveness of the disease specific CBT program (PASCET-PI) in reducing symptoms of depression *and* anxiety in adolescents with inflammatory bowel disease in order to improve quality of life and to improve the clinical course of disease. We hypothesize that the PASCET-PI will reduce symptoms of both depression and anxiety, improve quality of life, reduce intestinal inflammation and will promote sustained clinical remission.

# METHODS AND DESIGN

## Study design

This study is a prospective multicenter randomized controlled trial, with baseline screening (T0) and three follow-up assessments (T1 – T3). At baseline, adolescents (age 10-20 years) with IBD are screened for symptoms of depression and anxiety by means

of an online questionnaire. Patients with elevated (subclinical) symptoms of depression and/or anxiety, but no clinical disorder, are randomized into two conditions. The control condition entails standard medical care-as-usual (CAU); psychological care is not standard in the Dutch medical care system. Patients in the experimental condition receive standard medical care plus the disease-specific CBT (PASCET-PI). Patients are recruited from 2 academic hospitals and 5 community hospitals in the South-West region of the Netherlands[1]. The design of this study is following the CONSORT guidelines for RCT's.

## Inclusion & exclusion criteria

*Inclusion* criteria are 1) patients between 10-20 years with diagnosed IBD and 2) informed consent provided by patients and (if applicable) parents.

*Exclusion* criteria are 1) mental retardation (parent report), 2) current psychopharmacological treatment for depression or anxiety, 3) current psychological treatment, 4) having received manualized CBT in the past year (at least 8 sessions), 5) insufficient mastery of the Dutch language, 6) diagnosed bipolar disorder, schizophrenia/psychotic disorder, autism spectrum disorders, obsessive-compulsive disorder, posttraumatic or acute stress-disorder or substance use disorder, 7) selective mutism (physician reported), and 8) already participating in an intervention study.

## Recruitment and procedure (see Figure 1)

The treating (pediatric) gastroenterologist, nurse practitioner or physician assistant informs eligible patients about this study and hands out the written patient information. Parents are asked for informed consent if patients are younger than 18 years; if patients aged 18 years or older still live in their parents' house, participation of parents is optional. After having given informed consent, patients (and parents) receive an e-mail with online questionnaires (see Table 1). If this screening shows self-reported subclinical symptoms of depression and/or anxiety, a patient is selected for further participation in the study. The Dutch versions of the Child Depression Inventory (CDI; ages 10-17) [66], Beck Depression Inventory (BDI-II; ages 18-20) [67] are used to assess depressive symptoms, whereas the Screen for Child Anxiety Related Disorders (SCARED; ages 10-20) [68] is used to assess anxiety symptoms. Subclinical depressive symptoms are defined as a score equal to or above the cutoff on the CDI (13) [66] or the BDI-II (14) [67]. Subclinical anxiety symptoms are defined as 1) a score equal to or above the cutoff on the total scale of the SCARED (26 for boys, 30 for girls) or 2) a score equal to or above the cutoff (8) on one of the subscales [69].

1 Erasmus MC(-Sophia), Leiden University Medical Centre (LUMC), Haga (Juliana Children's) Hospital, Reinier de Graaf Gasthuis, Maasstad Hospital, Amphia Hospital, and Albert Schweitzer Hospital.

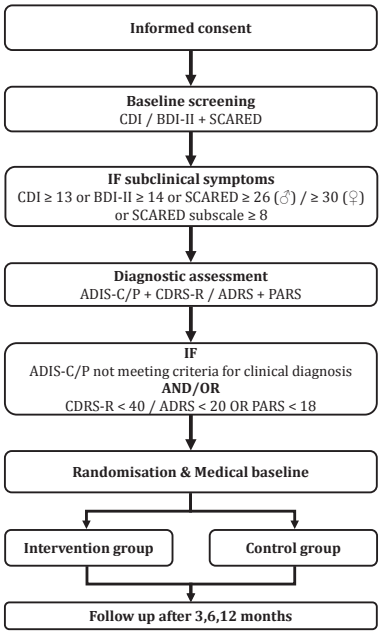



**Figure 1** | Flow chart study design
Abbreviations: CDI= Child Depression Inventory; BDI-II= Beck Depression Inventory – Second Edition; SCARED= Screen for Child Anxiety Related Emotional Disorders; ADIS-C/P= Anxiety Disorders Interview Schedule - Child and Parent Version; CDRS-R= Child Depression Rating Scale - Revised; ADRS= Adolescent Depression Rating Scale; PARS= Pediatric Anxiety Rating Scale

Next, in patients with these subclinical symptoms, the Anxiety Disorders Interview Schedule - Child and Parent Version (ADIS-C/P) [70, 71] is administered by a research psychologist by telephone. Thereafter, the severity of depressive and/or anxiety symptoms is rated by the research psychologist using the Child Depression Rating Scale - Revised (CDRS-R; ages 10-12) [72], the Adolescent Depression Rating Scale (ADRS; ages 13-20) [73], and the Pediatric Anxiety Rating Scale (PARS; ages 10-20) [74]. Patients are excluded for randomization if they meet criteria for a clinical depressive or anxiety disorder on the ADIS-C/P and score equal to or above the clinical cutoff on the CDRS (20) [75], ADRS (40) [73], or PARS (18) [74]. Instead, these patients are referred for attuned psychological treatment, since it would be unethical to randomize them. For patients with subclinical depression and/or anxiety, the medical researcher performs the randomization and arranges the medical baseline assessment.

All patients included in our study are well phenotyped with regard to duration and severity of disease, age at diagnosis, growth and pubertal development, clinical course of disease, number and type of surgical interventions and hospitalizations. The Paris classification is collected at diagnosis and from the most recent endoscopy, to see if extension of disease has occurred.

## Randomization and blinding

Patients are allocated to PASCET-PI or CAU group by means of computer-based, block randomization, stratified per center. Sealed envelopes sequentially numbered are provided by the Department of Biostatistics of the Erasmus Medical Center. Participants assigned to the treatment group start treatment within a maximum of 4 weeks.

To prevent bias in the assessment, the research psychologist completing the diagnostic interviews at T0 – T3 is blinded for the outcome of randomization. In addition, physicians assessing the patient's disease activity are blinded. The patients and therapists are asked not to discuss the psychotherapy with the treating physician. Unblinding takes place if patients are excluded from the study (either by withdrawal or an acute need for care).

**Table 1** | *Outcomes, covariates, instruments and informants at each time point*

| | Measurements | T0 baseline | T1 3 months | T2 6 months | T3 12 months |
|---|---|---|---|---|---|
| **Main psychological outcomes** | | | | | |
| Change in symptoms of depression | CDI (10-17 year) | Pt | Pt | Pt | Pt |
| | BDI-II (18-20 year) | Pt | Pt | Pt | Pt |
| | ADIS-C/P | Pt, Pr | Pt, Pr | Pt, Pr | Pt, Pr |
| | CDRS-R (10-12 year) | Ps | Ps | Ps | Ps |
| | ADRS (13-20 year) | Ps | Ps | Ps | Ps |
| Change in symptoms of anxiety | SCARED | Pt | Pt | Pt | Pt |
| | ADIS-C/P | Pt, Pr | Pt, Pr | Pt, Pr | Pt, Pr |
| | PARS | Ps | Ps | Ps | Ps |
| **Main medical outcome** | | | | | |
| Sustained remission | | | | | M |
| **Secondary psychological outcomes** | | | | | |
| (Change in) Quality of life | TACQOL (10-15 year) [76] | Pt | Pt | Pt | Pt |
| | TAAQOL (16-20 year) [77] | Pt | Pt | Pt | Pt |
| | IMPACT-III [78] | Pt | Pt | Pt | Pt |
| (Change in) Psychosocial functioning | SSRS [79] | Pt | Pt | Pt | Pt |
| | YSR (10-17 year) [80] | Pt | Pt | Pt | Pt |
| | ASR (18-20 year) [81] | Pt | Pt | Pt | Pt |
| **Secondary medical outcomes** | | | | | |
| (Change in) Disease activity | PUCAI (Ulcerative colitis) | M | M | M | M |
| | PCDAI (Crohn's disease) | M | M | M | M |
| | Physician Global Assessment [46] | M | M | M | M |
| Inflammatory markers | CRP | Pt | Pt | Pt | Pt |
| | ESR | Pt | Pt | Pt | Pt |
| | Fecal calprotectin | Pt | Pt | Pt | Pt |

**Table 1** | *Outcomes, covariates, instruments and informants at each time point (continued)*

| | Measurements | T0 baseline | T1 3 months | T2 6 months | T3 12 months |
|---|---|---|---|---|---|
| Use of IBD medication | Steroids, anti-TNF blockers, immunomodulators | M | M | M | M |
| Necessity of surgical intervention | | M | M | M | M |
| *Psychological covariates* | | | | | |
| Demographic factors | Rotterdam's quality of life interview [82] | Pr | | | |
| Illness perception | B-IPQ [83] | Pt | Pt | Pt | Pt |
| Cognitive Coping Styles | CERQ [84] | Pt | Pt | Pt | Pt |
| Quality of sleep | SSR [85] | Pt, Pr | Pt, Pr | Pt, Pr | Pt, Pr |
| Parental anxiety and depression | DASS-21 [86] | Pr | | | |
| Life events | Stress scale thermometer [87] | Pt, Pr | Pt, Pr | Pt, Pr | Pt, Pr |
| | Life events questionnaire from CERQ | Pt | | | Pt |
| Family functioning | FAD-GF [88] | Pr | Pr | Pr | Pr |
| *Medical covariates* | | | | | |
| Disease phenotypes | Medical file analysis using Paris Classification | M | | | |
| Treatment strategy | Report of treating physician / medical file analysis | M | M | M | M |
| IBS-like symptoms | Questionnaire based on ROME III criteria IBS | M | M | M | M |
| RNA expression profiles | Blood sample | M | M | | |
| Cytokine levels in plasma & peripheral blood mononuclear cells (PMBCs) | Blood sample | M | M | | |

*Abbreviations*: CDI= Child Depression Inventory, BDI-II, Beck Depression Inventory – Second Edition, ADIS-C/P= Anxiety Disorders Interview Schedule - Child and Parent Version, CDRS-R= Child Depression Rating Scale - Revised, ADRS= Adolescent Depression Rating Scale, SCARED= Screen for Child Anxiety Related Emotional Disorders, PARS= Pediatric Anxiety Rating Scale, TACQOL= TNO-AZL questionnaire for Children's health-related Quality Of Life, TAAQOL= TNO-AZL ques-

tionnaire for Adult health-related Quality Of Life, SSRS= Social Skills Rating System, YSR= Youth Self-Report, ASR= Adult Self-Report, PCDAI= Pediatric Crohn's Disease Activity Index, PUCAI= Pediatric Ulcerative Colitis Activity Index ,CRP= C-reactive Protein, ESR= Erythrocyte Sedimentation Rate, B-IPQ= Brief - Illness Perception Questionnaire, CERQ= Cognitive Emotion Regulation Questionnaire, SSR= Sleep Self-Report, DASS-21= Depression, Anxiety and Stress Scale - 21-item version, FAD-GF= Family Assessment Device - General Functioning scale, IBS= Irritable Bowel Syndrome, PMBC= peripheral blood mononuclear cells.CDI: Child Depression Inventory, BDI-II, Beck Depression Inventory – Second Edition, ADIS-C/P: Anxiety Disorders Interview Schedule - Child and Parent Version, CDRS-R: Child Depression Rating Scale - Revised, ADRS: Adolescent Depression Rating Scale, SCARED: Screen for Child Anxiety Related Emotional Disorders, PARS: Pediatric Anxiety Rating Scale, TACQOL: TNO-AZL questionnaire for Children's health-related Quality Of Life, TAAQOL: TNO-AZL questionnaire for Adult health-related Quality Of Life, SSRS: Social Skills Rating System, YSR: Youth Self-Report, ASR: Adult Self-Report, PCDAI: Pediatric Crohn's Disease Activity Index, PUCAI: Pediatric Ulcerative Colitis Activity Index ,CRP: C-reactive Protein, ESR: Erythrocyte Sedimentation Rate, B-IPQ: Brief - Illness Perception Questionnaire, CERQ: Cognitive Emotion Regulation Questionnaire, SSR: Sleep Self-Report, DASS-21: Depression, Anxiety and Stress Scale - 21-item version, FAD-GF: Family Assessment Device - General Functioning scale, IBS: Irritable Bowel Syndrome, PMBC: peripheral blood mononuclear cells.
*Note:* Pr= parent report, Pt= patient (self-report), M= medical file/(pediatric) gastroenterologist, Ps= psychologist

## Intervention

The PASCET-PI focuses on behavioral activation, cognitive restructuring and problem solving skills to change maladaptive behaviors, cognitions and coping strategies [61]. Although originally designed to treat depression, most of the components of PASCET-PI are common for all CBT protocols, and have much overlap with components of CBT protocols specifically designed for anxiety (except for a fear hierarchy). Therefore, PASCET-PI can also be properly used for anxiety is. Disease-specific components, encompass the illness narrative (i.e. perceptions and experience of having IBD), therapy for pain and immune functioning, disease-specific psycho-education, social skills training and emphasis on IBD related cognitions and behaviors. Parents are provided with psycho-education about being a CBT-coach helping their child coping with IBD [17, 89].

The PASCET-PI consists of ten weekly sessions, delivered in three months (see Table 2). 6 sessions are face to face (1 hour) and 4 sessions are telephone-sessions (30 minutes). Three parental sessions are held at the beginning, middle and end of treatment. For adult patients (≥ 18 year) who still live with their parents, this is recommended but voluntarily. Adult patients who do not live with their parents, participate without their parents. Thereafter, three 30-minute booster sessions (one per month) are provided by telephone. For the current study the original PASCET-PI was translated into the Dutch language. During this study patients will receive medical care according to the current guidelines. Psychological interventions, other than the PASCET-PI for the intervention group, are not allowed.

### Training and protocol adherence

Before providing the PASCET-PI, all licensed (healthcare) psychologists had followed a PASCET-PI training (developed and given by Eva M. Szigethy). To prevent protocol drifting they receive monthly PASCET-PI supervision by a senior clinical psychologist. All treatment sessions are audiotaped and a random 20% is rated by independent raters (senior clinical psychologist and master's students Psychology) using the PASCET-PI Protocol Adherence Checklist (PPAC) [63].



## Outcome measures

In Table 1 an overview of all variables and instruments at each time point is provided, with informants specified. All the psychological questionnaires used are (inter)nationally validated instruments, for which psychometric properties have been established in the Netherlands. Due to lack of space, instruments for the main psychological and medical outcomes are described in detail below. Instruments for secondary outcomes and covariates are mentioned only. Covariates will be analyzed as either confounder, mediator, or moderator.

**Table 2** | *Outline of the PASCET-PI [61]*

| Session number | Content of session |
|---|---|
| Session 1<br>*Live* | Introduction of ACT & THINK model and PASCET-PI, build alliance, psychoeducation about IBD and depression or anxiety, illness narrative |
| Session 2<br>*Live* | Mood monitoring, explaining link between feelings, thoughts and behaviors, discussing feeling good and feeling bad, problem-solving |
| Session 3<br>*By telephone* | Link between behavior and feelings: **A**ctivities to feel better |
| Session 4<br>*Live* | Be **C**alm and Confident: relaxation exercises |
| Session 5<br>*Live* | Be Calm and **C**onfident: positive self vs negative self, training social skills |
| Session 6<br>*By telephone* | **T**alents: developing talents and skills makes you feel better |
| Session 7<br>*Live* | Social problem solving, discussing the ACT skills and introduction of the THINK skills with discussing negative thoughts (**T**hink positive) |
| Session 8<br>*By telephone* | **H**elp from a friend, **I**dentify the 'Silver Lining', and **N**o replaying bad thoughts |
| Session 9<br>*By telephone* | **K**eep trying – Don't give up, making several plans to use the ACT & THINK skills |
| Session 10<br>*Live* | Quiz on ACT & THINK model, discussing use of ACT & THINK skills in the future, updating illness narrative |
| Booster 1<br>*By telephone* | Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills |
| Booster 2<br>*By telephone* | Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills |

**Table 2** | *Outline of the PASCET-PI [61] (continued)*

| Session number | Content of session |
|---|---|
| Booster 3<br>*By telephone* | Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills |
| Family 1<br>*Live* | Parental view on IBD, family situation, psycho-education about IBD and depression or anxiety, introduction of ACT & THINK model and PASCET-PI |
| Family 2<br>*Live* | Parental view on progress, the ACT & THINK skills that are most effective for patient, expressing emotions within family, family communication, family stress game |
| Family 3<br>*Live* | Parental view on progress, family communication, parental depression or anxiety |

### Main psychological outcome measures: changes in symptoms of depression and anxiety

Changes in symptoms of depression are assessed by the CDI and the BDI-II (to cover the complete age range). The CDI (used for ages 10-17) is a 27 item self-report scale (response categories 0-2: total score 0-54). It has excellent reliability (Cronbach's alpha >.85) and moderate to good validity [66]. The BDI-II (used for ages 18-20) is a 21 item self-report scale (response categories 0-3: total score 0-63). The BDI-II has excellent reliability (Cronbach's alpha >.85) and good to excellent validity [67]. In addition, (changes in) the severity of the depressive symptoms will be rated with the CDRS-R or the ADRS. The CDRS-R (used for ages 10-12) is one of the most used rating scales for depression in children [72]. The ADRS (used for ages 13-20) is developed specifically for adolescent depression [73]. Changes in symptoms of depression are analyzed using Z-scores of CDI and BDI-II, and CDRS-R and ADRS.

Changes in symptoms of anxiety are assessed by the SCARED (used for ages 10-20), a 69-item screening instrument (response categories 0-2: total score 0-138) containing five subscales: general anxiety disorder, separation anxiety disorder, specific phobia, panic disorder, and social phobia. Cronbach's alpha in the normative sample is .92 for the total score and between .66 and .87 for the subscales. Satisfactory concurrent validity has been shown [68]. In addition, changes in the severity of anxiety symptoms will be rated with the PARS [74], for which a high internal consistency has been reported [75].

For both depression and anxiety, the semi-structured interview ADIS-C/P (child and parent version) is administered. This diagnostic interview assesses diagnoses of depressive or anxiety disorders. DSM-IV symptoms are reviewed as either present ('Yes') or absent ('No') [70, 71].

**Main medical outcome measure: sustained remission at 12 months**

Sustained remission of IBD (absence of clinical relapse) is continued clinical remission with no relapses, without the need to escalate treatment, use of new induction treatment (except for the first 8 weeks after baseline), hospitalize or perform bowel surgery during the first 12 months. In case of active disease at the time of enrollment, sustained remission at 12 months means continued remission after 8 weeks of induction treatment starting at baseline. The Pediatric Crohn's Disease Activity Index (PCDAI) and the Pediatric Ulcerative Colitis Activity Index (PUCAI) are used to score disease activity, and to score remission or relapse. The PCDAI (for Crohn's Disease) is a validated, multi-item, physician-reported measure that comprises items on history (abdominal pain, stools, activity level), physical examination, height and weight, as well as laboratory parameters. Scores range from 0-100, with higher scores representing more active disease [90, 91]. The PUCAI is a clinical index on disease activity for ulcerative colitis, scored by the physician, which has been validated in multiple international drug studies and comprises items on abdominal pain, rectal bleeding, stool frequency and consistency and activity level. Scores range from 0-85, with higher scores representing more active disease [92]. For CD and UC patients, remission is defined as PCDAI <10, and PUCAI <10 , respectively. For CD, relapse is defined as PCDAI >30 or an increase of >15 points and intensification of medical treatment. For UC, relapse is defined as PUCAI >34 or an increase of ≥20 points for UC and intensification of medical treatment [90, 92, 93].

**Secondary outcomes**

Secondary psychological outcomes are IBD-related quality of life and social functioning.

Secondary medical outcomes are disease activity, inflammatory markers in blood (C-reactive protein) and stool (calprotectin), use of IBD medication, and necessity of surgery (see Table 1).

**Psychological and medical covariates**

Several factors associated with depression and anxiety in IBD (e.g. IBS-like symptoms, cognitive coping, parental stress) will be assessed because they can confound, mediate or moderate the effect of CBT on medical and psychological outcomes. Psychological covariates assessed are: illness perception, cognitive coping, quality of sleep, parental anxiety and/or depression, stressful life events, family functioning, and demographic factors.

Medical covariates encompass: disease phenotype, treatment strategy, disease activity, irritable bowel syndrome – like symptoms. Blood samples for immunological analysis will be drawn at baseline and after 3 months. For cytokine analysis, one EDTA

tube (10 ml) will be drawn. Peripheral blood mononuclear cells (PBMCs) will be isolated and the plasma stored at -80°C. Serum levels of pro-inflammatory cytokines (TNFα, Il-1, Il-1α, IL6, Il-8) will be assessed in plasma and supernatant of PBMCs in culture using respectively Cytokine Bead Analysis (CBA) or ELISA. Furthermore, intracellular flow cytometry will be performed on in vitro stimulated PBMCs. For the RNA expression analysis, 2,5 ml venous blood will be collected in PAXgene tubes (PreAnalytiX) and stored at –20°C until RNA extraction. Total cellular RNA will be extracted using the PAXgeneTM blood RNA kit (Qiagen) according to the manufacturer's protocol. Gene expression profiles of pro- and anti-inflammatory genes in peripheral blood leucocytes will be assessed by Affymetrix U133 2.0 plus GeneChips.

## Data Collection: follow up assessments

Follow-up assessments take place at similar moments in the CBT and CAU group: three (T1), six (T2) and twelve (T3) months after randomization. Each follow-up assessment consists of a regular medical visit and a psychological assessment (online questionnaires and diagnostic psychiatric interview) for the patient and, if applicable, parents. Patients with a clinical depressive or anxiety disorder (according to the same criteria as at baseline) or with an urgent need of psychological help, are excluded. To ensure participation throughout the study, patients receive a small reward after completing the last follow-up assessment.

## Withdrawal

Patients can withdraw from the study without any consequences at any time for any reason. Those who withdraw are asked to complete the follow-up assessments.

## Sample size

The target population is a group of approximately 350 IBD patients aged 10-20 years. Based on our previous studies concerning psychological problems in physically ill adolescents, the expected response rate will be above 80% [94], which corresponds with ± 280 patients. Based on literature, around 40% of adolescents with IBD will suffer from increased symptoms of depression or anxiety. Of those patients 10% will experience clinical depression or anxiety. Of the remaining ±100 patients 50 patients will be randomized to the treatment condition (CBT and CAU) and 50 to CAU. Sample size is based on two-tailed tests with size of $\alpha = 0.05$ using a repeated measures design with estimated correlation between time-points of 0.6. For the effect of CBT on symptoms of depression small to medium effect sizes are expected (Cohen's $d > 0.3$) [95, 96], for the effect on symptoms of anxiety medium to large effect sizes are expected (Cohen's $d > 0.6$) [97, 98] For the effect of CBT on sustainment of remission (no clinical relapse), a medium effect size is expected ($\omega = 0.3$). Based on clinical experience in our hospital,

in the CAU group 40% of patients will have sustained remission during 12 months. We hypothesize that 70% of patients will have sustained remission in the treatment group, reflecting a medium effect size. Using the target population of N = 100 and the estimated effects on depression, anxiety and sustainment of remission, we will have sufficient power (> 0.85).

### Statistical analyses

The main analyses will be conducted using an intention-to-treat approach. Where appropriate, secondary analysis will be conducted using a per protocol basis. To test the effectiveness of the PASCET-PI, we will compare the CBT group to the CAU group on 1) change in symptoms of depression and anxiety, and 2) sustained remission (absence of clinical relapse). For 1) multilevel linear models will be used, for 2) a Generalized Estimating Equation approach (GEE) will be used. Covariates (e.g. illness perception, cognitive coping, disease phenotypes, medical treatment strategy, inflammatory markers) will be included into the multilevel linear models and the GEE to identify which factors influence the effectiveness of the disease-specific CBT. Multiple imputation will be used to deal with missing values.



## DISCUSSION

PASCET-PI has proven to be effective in reducing depression in adolescent IBD patients. However, the effect on anxiety, quality of life, and disease course has hardly been studied systematically. We will perform a prospective randomized controlled trial to examine the effectiveness of the PASCET-PI on both symptoms of depression *and* anxiety, on quality of life, and on clinical course of the inflammatory disease.

This study has several strengths. First, as this study examines the effect of disease-specific CBT on both psychological problems *and* disease course, it will provide insight in the complex interplay between inflammation and depression or anxiety in pediatric patients. We will study possible effects of reduction in depression or anxiety on cytokine expression and RNA expression profiles before and after CBT for subclinical depression or anxiety. Second, the disease-specific CBT will target both depression and anxiety, which is important as these problems have a negative impact on medication adherence and long-term medical and psychological outcomes [16, 19, 23, 24, 29, 45-47]. Third, this study will provide important information about the prevalence of depression and anxiety among adolescent IBD patients in an European country such as the Netherlands, as compared to other studies that were performed mainly in the United States. Cultural differences may play a role in coping with disease-related anxiety and depression. Fourth, the PASCET-PI encompasses IBD-specific components,

which matches patients' IBD-related concerns and problems very well. If proven effective, the PASCET-PI can be very helpful for treatment of current and also for prevention of future psychological problems. A fifth strength of the study is the random and longitudinal nature of the design. Patients will be randomly assigned to the experimental or control condition. It is known that academic hospitals treat more severe IBD cases than community hospitals. Therefore, the randomization will be stratified for academic versus community hospitals. Randomized patients will complete several follow-up assessments, which allows us to evaluate long-term effects of the PASCET-PI.

In conclusion, there is a compelling need to improve the emotional wellbeing of the adolescent IBD patients who suffer from (subclinical) depression or anxiety symptoms. If the PASCET-PI proves to be effective, in treating both subclinical depression and anxiety, in improving quality of life, and in preventing clinical relapse, screening for and treatment of psychological problems in IBD adolescents should be incorporated in standard care.

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# Clinical disease activity is associated with anxiety and depressive symptoms in adolescents and young adults with inflammatory bowel disease

Gertrude van den Brink, Luuk Stapersma, Lotte Vlug, Dimitris Rizopoulos, Alexander G. Bodelier, Herbert van Wering, Pamela C.W.M. Hurkmans, Rogier J.L. Stuyt, Danielle M. Hendriks, Joyce A.T. van der Burg, Elisabeth M.W.J. Utens, Johanna C. Escher

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## SUMMARY

**Background** Youth with inflammatory bowel disease (IBD) are at risk for developing anxiety and depressive symptoms with a reported 20-50% prevalence rate.

**Aim** This prospective study aims to: 1) describe the prevalence and severity of anxiety and depressive symptoms in a large Dutch cohort of young IBD patients, and 2) identify demographic and clinical risk factors for anxiety and depression.

**Methods** IBD patients (n=374; 10-25 years) were screened for anxiety, depression and quality of life using validated age-specific questionnaires. Patients with elevated scores for anxiety and/or depressive symptoms received a diagnostic interview assessing psychiatric disorders. Demographic and clinical characteristics were retrieved from medical charts. Multiple logistic regression analysis was performed to identify risk factors for anxiety and/or depression.

**Results** Patients (mean age 18.9 years, 44.1% male, Crohn's disease 60.4%) had disease in remission (75.4%), or mild, moderate and severe clinical disease activity in respectively 19.8%, 2.7% and 2.1%. Mild anxiety/depressive symptoms were present in 23.6% and severe symptoms in 12.4% of patients. Elevated symptoms of either anxiety (28.3%), depression (2.9%) or both (15.8%) were found and did not differ between adolescents (10-17 years) and young adults (18-25 years). Active disease significantly predicted depressive symptoms (Odds Ratio (OR) 4.6 [95% Confidence Interval [CI] 2.4-8.8], $p<0.001$). Female gender (OR 1.7 [95%CI 1.1-2.7]), active disease (OR 1.9 [95%CI 1.1-3.2]) and a shorter disease duration (OR 1.3 [95%CI 0.6-1.0) (all $p<0.025$) significantly predicted anxiety and/or depressive symptoms.

**Conclusions** Considering the high prevalence of anxiety and depressive symptoms, psychological screening is recommended in young IBD patients. Screening facilitates early recognition and psychological treatment. Female patients and patients with active disease are the most vulnerable.

## INTRODUCTION

Inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis [UC]) is a chronic relapsing inflammatory disorder of the intestine, with rising incidence, in the United States as well as in Europe [1]. In up to 25% of patients IBD develops and manifests during childhood or adolescence [2], a phase with significant physical, cognitive and psychosocial challenges [3].

A chronic disease, at this age, is a threat to a healthy psychosocial development [4]. It has been observed that particularly adolescents with IBD are at risk for psychological problems such as anxiety and depression, and thereby decreased quality of life [5, 6]. The bidirectional relationship between IBD and psychological problems has been described before and can be explained in terms of the 'brain-gut'-axis, meaning that the presence of anxiety and/or depression can increase intestinal inflammation and may contribute to disease relapse, and vice versa: intestinal inflammation can negatively influence mood [7, 8].



Symptoms of anxiety and/or depression are often found in pediatric IBD patients. Reported prevalence rates range from 20-50% for anxiety [9-11] and 25-40% for depression [5, 10, 12]. Although some studies report lower rates [13], prevalence in pediatric IBD seems to be higher compared to other chronic diseases [14, 15]. In adult IBD patients, a recent systematic review showed similar prevalence rates [16] suggesting that psychological problems persist or arise in adulthood [17]. As it is known that anxiety can precede depression, and anxiety and depressive symptoms often occur together [18], it is worthwhile to study them simultaneously. In addition, combining adolescents and young adult patients in research is also important [19], considering they are at a unique stage in their emotional, cognitive and social development. The impact of a chronic disease and the accompanied challenges in this stage are different from their pediatric or adult counterparts.

Insight in risk factors for anxiety and depression in young IBD patients is necessary to help health care professionals identify those at risk. It may assist in selecting patients that need psychological screening and/or treatment. In patients with emotional problems, improving psychological health is expected to lead to a decrease in IBD related morbidity [20] reduced health care utilization and improvement of quality of life [21].

Previous studies report a variety of risk factors for anxiety and depression. In adult IBD, active disease has been associated with both anxiety and depression [16, 22, 23]. Other studies showed that female IBD patients [23] and patients with lower socio economic status [24] are at risk for anxiety, and that a younger age at diagnosis is associated with depression [25]. In addition, prior surgery and perianal disease are correlated with both anxiety and depression [26].

In pediatric IBD, the majority of studies also show active disease to be associated with both anxiety and depressive symptoms [5, 11, 21]. Furthermore, female gender

[13], older age at diagnosis [5], fatigue [27], abdominal pain [12, 28], low socioeconomic status [29] and steroid use [5, 29] were correlated with depression. In addition, female gender [13] and abdominal pain [11] have shown a correlation with anxiety. In both pediatric and adult patients, disease type [5] and anti-TNF-α use [29] did not seem to be a risk factor for anxiety and depression.

The current study investigates the presence of and risk factors for anxiety and depressive symptoms in a unique large European cohort of young IBD patients, consisting of adolescents (10-17 years) and young adults (18-25 years) from regional as well as tertiary hospitals. In addition, this study provided a unique opportunity to also study the severity of anxiety and/or depressive symptoms. This study aims (1) to describe the prevalence and severity of anxiety and depressive symptoms; and (2) to identify demographic and clinical risk factors for symptoms of anxiety and/or depression. We hypothesize that clinical disease activity will be the greatest risk factor. Additionally, we expect female sex and steroid use to be associated with anxiety and/or depressive symptoms.

## MATERIALS AND METHODS

### Design

In the present cross-sectional study a large cohort of adolescents (10-17 years) and young adults (18-25 years) with IBD were screened for anxiety and depressive symptoms and HRQOL. According to the World Health Organization, adolescence encompasses individuals in the age group 10-19. In The Netherlands governmental legislation as well as medical practice uses the age of 18 years to define the start of adulthood. At 18, a patient has finished high school and is also transferred from pediatric to adult medical care. Therefore, in this study, the adolescent group consists of 10-17 year old patients and the young adult group of 18-25 year old patients. This study preceded a randomized controlled trial investigating the effectiveness of cognitive behavioral therapy in youth with IBD and subclinical anxiety and/or depression (NCT02265588). For the randomized trial, based on previous literature regarding the effectiveness of CBT for anxiety and depressive symptoms, medium to large effects for anxiety symptoms [30] and medium effects for depressive symptoms [31] were expected. This corresponds to $\varphi$ >0.40 for anxiety symptoms, and to $\varphi$ >0.30 for depressive symptoms. With 70 patients included in the randomized trial, the study had a power of >85% for anxiety symptoms (beta-error 0.14) and medium power for depressive symptoms (>60%) (beta-error 0.39) with an alpha-error of 0.05 (2 sided test)

To include 70 patients in the randomized trial, a total of 350 patients needed to be screened. This was calculated based on the following: a) 5% of patients will have on or more exclusion criteria b) an expected participation rate of 80% (based on previous

studies in chronically ill adolescents) [32], c) and expected prevalence rate of anxiety/depressive symptoms of 35% [5, 9, 11]. Taking into account a 5% drop out rate, we aimed to include 375 patients.

The following in- and exclusion criteria were used: 1) age 10 to 25 years and 2) diagnosis of IBD, according to the current diagnostic criteria [33-35]. Exclusion criteria were: 1) intellectual disability, 2) current treatment for mental health problems (pharmacological and/or psychological), 3) insufficient mastery of the Dutch language, 4) a diagnosis of selective mutism, bipolar disorder, schizophrenia, autism spectrum disorder, obsessive-compulsive disorder, posttraumatic or acute stress-disorder, or substance use disorder, 5) cognitive behavioral therapy in the past year (at least 8 sessions), and 6) participation in another interventional study.



Initially, only patients aged 10-20 years were included. A few months after the start of recruitment, patients of 21-25 years were also included, to include the young adult group and to be able to include a sufficient number of patients for the randomized controlled trial.

In-and exclusion criteria were assessed by the treating physicians. Insight into the numbers of patients with exclusion criteria was only provided by the pediatric departments (so for patients 10-17 years of age). In total 384 of these adolescents with IBD were treated in the participating hospitals. Of those, 174 patients gave consent to participate. Of the remaining 210 patients, 125 patients had no interest in participating in the study and 85 patients fulfilled the exclusion criteria (intellectual disability n=14, current psychological treatment n=33 (exact diagnosis not provided), autism spectrum disorder n=20, posttraumatic stress-disorder n=3, obsessive-compulsive disorder n=2, already participating in an intervention study n=9, insufficient mastery of the Dutch language n=4). 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.

## Procedure

Consecutive patients were recruited between October 2014 and September 2016 from the outpatient clinic in two academic hospitals and four community hospitals in the Southwest region of the Netherlands. We aimed to include a diverse cohort, including all stages of disease. However, the majority of patients was included at least 3 months after diagnosis (nine patients were included within 3 months after diagnosis). After written informed consent of patients and, if applicable, their parents or caregivers, an e-mail with a link to online questionnaires was sent. It was emphasized that results would be most valuable if patients and parents completed the questionnaires without help of their parents (and vice versa), and if they would give honest answers. Assistance was offered by the research team by email or telephone if necessary. In addition,

it was stressed that irrespective of the outcome of the questionnaires, patients could decide whether or not to proceed in the randomized controlled trial. It was explained to patients that participation in the screening phase was valuable in itself, because it would increase insight in the prevalence of anxiety and depressive symptoms of adolescents and young adults with IBD and it would give patients insight in their own level of anxiety and depressive symptoms.

## Measures

### Demographic characteristics

**Gender** and **age** were retrieved from the medical charts. **Socioeconomic status** was classified using the occupational level from the parents or, if patients lived on their own, patients themselves [36].

### Clinical characteristics

**Clinical disease activity** was assessed by four validated instruments. For CD, the short Pediatric Crohn's Disease Activity Index (10-20 years) [37] and the Crohn's Disease Activity Index (21-25 years) [38] was used. For UC, the Pediatric Ulcerative Colitis Activity Index (10-20 years) [39] and the partial Mayo score (21-25 years) [40, 41].To combine all four measures, the categorical predefined classifications remission, mild, moderate, and severe were used.

**Disease type, age at diagnosis, disease duration, presence of perianal disease at diagnosis, previous bowel surgery, current therapy, steroid dependence past three months** and **number of relapses the preceding year** were retrieved from the medical charts. **Relapse** was defined as 'physician reported relapse necessitating treatment intensification'. **Disease location at diagnosis** and **extension of disease** was assessed using the Paris or Montreal classification [42]. We defined limited disease as 'E1' or 'E2' for UC and 'L1' for CD. Extensive disease was defined as 'E3' or 'E4' for UC and 'L2', 'L3' or 'L4a/b' for CD. The following inflammatory parameters were collected if available: C-reactive protein, Erythrocyte Sedimentation Rate, hemoglobin, hematocrit, leukocyte count, thrombocyte count and fecal calprotectin.

### Anxiety and depression

**Anxiety** was assessed using the 69-item Screen for Child Anxiety Related Disorders (SCARED, for ages 10-20) and the anxiety scale of the Hospital Anxiety and Depression Scale (HADS-A, for ages 21-25), both self-report instruments. Five SCARED subscales were used: general anxiety disorder, separation anxiety disorder, specific phobia, panic disorder, and social phobia (response categories 0-2: total score 0-138). Satisfactory reliability and validity have been reported [43]. The cutoffs for elevated symptoms of anxiety were total SCARED score ≥26 for boys, ≥ 30for girls, or a SCARED-subscale

score ≥ 8 [44]. The HADS anxiety scale consists of 7 items, rated on a 4-point scale (response categories 0-3; total score 0-21). Excellent reliability has been found. Patients had elevated symptoms of anxiety if they scored 8 or higher [45]. Because initially only 10-20 year old patients were included, we chose to use the SCARED, which is validated up to 19 years of age [46], also for 20 year old patients. Later, when 21-25 year old patients were included as well, the HADS-A was added.

**Depression** was assessed using the Child Depression Inventory (CDI, for ages 10-17) and the Beck Depression Inventory, second version (BDI-II, for ages 18-25). The CDI is a 27-item self-report scale (response categories 0-2, total score 0-54). Good reliability and validity of the Dutch version have been established and a CDI score of 13 or higher reflected elevated symptoms of depression [47]. The BDI-II is a 21-item self-report scale (response categories 0-3, total score 0-63), with a score of 14 or higher indicating elevated symptoms of depression. It has excellent reliability and good to excellent validity [48].



### Severity of anxiety and depression

In patients with elevated anxiety and/or depressive symptoms, severity was assessed by a (telephonic) psychiatric diagnostic interview performed by a trained psychologist (Anxiety Disorders Interview Schedule - Child and Parent Version (ADIS-C/P) [49, 50]. Severity of anxiety was rated using the Pediatric Anxiety Rating Scale (PARS; ages 10-20) [51] and the Hamilton Anxiety rating scale (HAM-A; ages 21-25) [52]. Depressive severity was rated using the Child Depression Rating Scale - Revised (CDRS-R; ages 10-12) [53], the Adolescent Depression Rating Scale (ADRS; ages 13-20) [54], and the Hamilton Depression Rating Scale (HAM-D; ages 21-25) [55]. For this study, we grouped the patients with anxiety and/or depressive symptoms, to describe the patients with 'a psychological burden'. This group includes patients suffering from either anxiety symptoms or depressive symptoms, or both. The term 'anxiety/depressive symptoms' is used to refer to this patient group. Anxiety/depressive symptoms were classified as 'severe' if they met the criteria for a clinical depressive or anxiety disorder on the ADIS-C/P and a score equal to or above the clinical cutoff on the CDRS (40) [56], ADRS (20) [54], or PARS (18) [51]. The remaining group of patients was classified as having subclinical or mild anxiety and/or depression. See Figure 1.

### Health-related quality of Life

Health-related quality of Life (HRQOL) was assessed by the IBD-disease specific self-report questionnaires IMPACT-III (ages 10-20, because initially only 10-20 year old patients were included) and IBDQ (ages 21-25), both having good psychometric properties [57-60]. The IMPACT-III contains of 35 items (score 1-5; range 35-175) which cover six domains: IBD-related symptoms, systemic symptoms, emotional functioning, social

functioning, treatment related concerns, and body image. The IBDQ contains 32 items (score 1-7; range 32-224) that cover four domains: bowel, systemic, social, and emotional functioning. For both questionnaires, a higher score reflects better quality of life.

## Statistical analysis

Frequency analyses were conducted to describe the prevalence of anxiety and depressive symptoms (aim 1). Exploratory tests (one-way ANOVA, Kruskal-Wallis and Chi-Square test) were conducted to provide insight in differences between patients with no, mild and severe anxiety and/or depressive symptoms.

Multiple imputation with chained equations (MICE) with ten imputations (m=10) was used to impute the missing values in the variable socio-economic status [61]. Missing data on outcome variables were not imputed. Results for complete cases and multiple imputation analysis were compared. To compare the variables in the regression model to each other, the continuous variables were standardized and used in the model as z-scores.

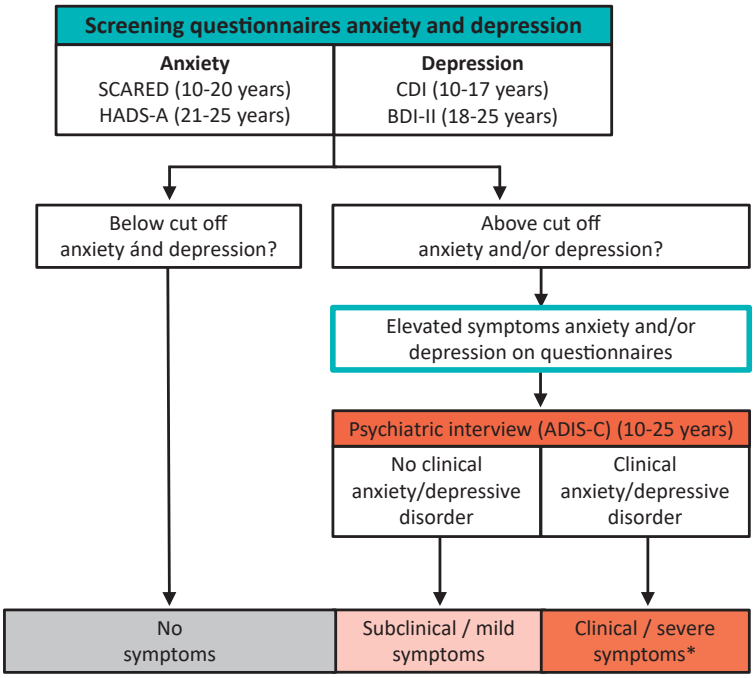


**Figure 1** | Flowchart screening anxiety/depression
Abbreviations: SCARED= Screen for Child Anxiety Related Emotional Disorders; HADS-A= Hospital Anxiety and Depression Scale – Anxiety scale; CDI= Child Depression Inventory; BDI-II= Beck Depression Inventory-second edition ADIS-C= Anxiety Disorders Interview Schedule for Children
Notes: * indicative of a disorder. Cutoff scores for each questionnaire are specified in the text

To identify risk factors for symptoms of anxiety and depressive symptoms (aim 2), we conducted four regression analyses with the following outcomes. I: absence/presence of anxiety/depressive symptoms, II: severity of anxiety/depressive symptoms, III: absence/presence of anxiety symptoms and IV: absence/presence of depressive symptoms. Analysis III and IV were performed to investigate risk factors specific for anxiety or depressive symptoms. For analysis I, III and IV a binomial logistic regression and for analysis II an multinomial logistic regression was conducted. Subgroup analysis was performed for patients 10-17 and 18-25 years. In the regression analysis, the $\alpha$-level was adjusted for multiple comparison, considering Bonferroni correction is considered conservative [62], it was set at $p < 0.025$. Adequacy of the models was assessed using the appropriate 'Goodness-of-Fit' tests.

Data analysis were performed using Statistical Package for the Social Sciences, Version 21.0 (IBM SPSS Statistics for Windows, Armonk, NY) and the computing environment R for multiple imputation (R Development Core Team, 2016. R Foundation for Statistical Computing, Vienna, Austria).



## RESULTS

### Patients characteristics

A total of 374 adolescents and young adults (mean age: 18.92 years, SD 4.13) completed the assessment. Almost fifty percent of patients were <18 years of age. Most patients had CD (60.4%) and the majority had inactive disease (75.4%), but 33.4% had relapsed in the year prior to this assessment. More than one third of the patients was receiving treatment with a biological (35.8%) and 285 patients (76.2%) had extensive disease. 16.3% received IBD-related surgery in the past, of which half had a resection of small and/or large intestine (7.5%) and half had abscess drainages, fistula surgery or balloon dilatations (8.8%). See Table 1.

### Prevalence of anxiety and depression

372 patients completed the depression questionnaires (CDI and BDI-II), 373 the anxiety questionnaires (SCARED, HADS-A). Of the 371 patients with complete data on both anxiety and depression, 176 (47.4%) patients experienced elevated symptoms of anxiety and/or depression. Anxiety symptoms were more prevalent than depression: elevated symptoms of either anxiety, depression or both were found in respectively 106 (28.3%), 11 (2.9%) and 59 (15.8%) patients. 195 patients (52.1%) did not show any elevated symptoms. Of the 371 patients, 168 patients were included in the two tertiary hospitals, 204 in four community hospitals. Prevalence rates did not significantly differ between academic or community hospitals for elevated symptoms of either

anxiety (27.5% vs 29.4%), depression (2.4% vs 3.4%) or both (15.0% vs 16.7%) ($\chi^2(3)=.98$, $p=0.808$).

**Table 1** | *Patient characteristics (N=374)*

| | | **Mean ± SD or n (%)** |
|---|---|---|
| Gender, Male | | 165 (44.1) |
| Age (years) (% <18 years) | | 18.92 ± 4.13 (45.5%) |
| Age at diagnosis (years) (% < 18 years) | | 15.40 ± 4.33 (71.4%) |
| Duration of disease (years) (Median;IQR) | | 2.45 (1.1-5.1) |
| Socioeconomic status (N = 346) | Low | 61 (17.6) |
| | Middle | 144 (41.6) |
| | High | 141 (40.8) |
| Type of disease | CD | 226 (60.4) |
| | UC | 128 (34.2) |
| | IBD-U | 20 (5.3) |
| Paris/Montreal classification at diagnosis†: | CD: location‡, (N = 226) | |
| | L1 | 38 (16.8) |
| | L2 | 38 (16.8) |
| | L3 | 100 (44.2) |
| | + L4a/L4b | 50 (22.1) |
| | CD: behaviour | |
| | nonstricturing. nonpenetrating (B1) | 216 (95.6) |
| | stricturing. penetrating or both (B2B3) | 10 (4.4) |
| | perianal disease | 47 (20.8) |
| | UC: extent (N = 148)§ | |
| | limited: E1 + E2 | 51 (34.5) |
| | extensive: E3 + E4 | 97 (65.5) |
| | UC: severity. ever severe | 20 (13.5) |
| Clinical disease activity | Remission | 282 (75.4) |
| | Mild | 74 (19.8) |
| | Moderate | 10 (2.7) |
| | Severe | 8 (2.1) |
| Current medication use | Aminosalicylates | 116 (31.0) |
| | Immunomodulators | 175 (46.8) |
| | Biologicals | 134 (35.8) |
| | Corticosteroids¶ | 36 (9.6) |
| | Topical treatment¥ | 20 (5.3) |
| | No medication | 26 (7.0) |
| Steroid dependence past 3 months | | 55 (14.7) |

**Table 1** | *Patient characteristics (N=374) (continued)*

| | | Mean ± SD or n (%) |
|---|---|---|
| Relapses preceding year | 1 relapse | 103 (27.5) |
| | ≥2 relapses | 22 (5.9) |
| Bowel resection in history | | 28 (7.5) |
| Extra intestinal manifestations [II] | | 57 (15.2) |

*Abbreviations*: SD= standard deviation, IQR= interquartile range, CD= Crohn's Disease, UC: ulcerative colitis, IBD-U: IBD-unclassified.
*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 [¶]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%)



Of the patients <18 years, 34.9% showed elevated anxiety, compared to 23.2% in the ≥18 age group. This was not significantly different. For depression and anxiety/depression combined, differences between the <18 and ≥18 age group were small and not significantly different.

Of the 131 patients with elevated anxiety, <21 years of age (and who completed the SCARED questionnaire), 122 of 131 patients (93.1%) scored above the established cutoff for 1 or more anxiety domains. Specified per domain, generalized anxiety was found in 45.8%, separation anxiety in 23.7%, specific phobia (consisting of animal phobia, blood phobia and situational phobia) in 55.7%, panic symptoms in 19.8% and social phobia in 48.8% of the 131 patients.

### Health-related quality of life

Mean IMPACT-III score (patients <21 years, N=256) was 142.7 (±19.3 SD, range: 76-174) and mean IBDQ score (patients ≥21 years, N=110) was 178.7 (range: 97-224; data not shown).

## Prevalence of mild and severe anxiety/depressive symptoms

Of the 177 patients with elevated symptoms of anxiety/depression, 134 patients completed a psychiatric interview assessing severity of psychological symptoms. The other 43 patients did not consent to the interview, because they only consented to the questionnaires and/or were not willing to participate in the larger research project, including the randomized controlled trial, for which the psychiatric interview was a necessary part. Clinical, severe symptoms were found in 46 (34.3%) and mild symptoms in 88 (65.6%) patients. Of the 46 patients with clinical symptoms, 23 (50%) fulfilled the criteria for an anxiety disorder, 5 (10.8%) for a depressive disorder, and 15 (32%) fulfilled the criteria for both anxiety and depressive disorders. The other

three patients did not fulfill the criteria for an anxiety or depressive disorder, but severity of other psychological problems was clearly reported by parents during the psychiatric interview. One patient showed extreme rebellious behavior, the other irritability and tantrums. For the last patient, only parents reported depressed mood and signs of social and specific anxiety. In all three patients, family functioning was severely disturbed and continuing in the randomized controlled trial was not ethical, so psychological help was provided directly after screening.

## Differences between patients with no mild and severe anxiety/ depressive symptoms

Exploratory analysis showed that clinical disease activity was significantly higher in patients with severe anxiety/depressive symptoms, compared to patients with mild ($U = 1092.5$, $z = -5.1$, $p<0.001$) and no anxiety/depressive symptoms ($U = 2255.0$, $z = -6.8$, $p<0.001$). Fecal calprotectin and Erythrocyte Sedimentation Rate were significantly higher in patients with severe anxiety/depressive symptoms compared to patients with no anxiety/depressive symptoms. See Tables 2 and 3 and Figure 2.

## Multiple regression analysis: risk factors for anxiety and depressive symptoms

### Risk factors for anxiety/depressive symptoms

Female patients (Odds Ratio [OR] 1.7 [95%CI 1.1-2.7], p=0.021) and patients with active disease (OR 1.9 [1.1-3.2], p=0.023) had higher odds of experiencing anxiety/depressive symptoms than male patients or patients in remission (see Table 4). Subgroup analysis showed that active disease (OR 3.07 [95%CI 1.3-7.3], p=0.011) and disease duration (OR 0.66 [95%CI 0.5-0.9], p=0.018) were significantly associated with having anxiety/depressive symptoms in patients ≥18 years (data not shown).

### Risk factors for mild and severe anxiety/depressive symptoms

Overall multinomial logistic regression analysis showed that gender ($\chi^2(2)=9.2$, $p=0.010$) and disease activity ($\chi^2(2)=26.0$, $p<0.001$) significantly influenced severity of anxiety/depressive symptoms. Firstly, when comparing no to mild anxiety/depressive symptoms, analysis showed that female gender (OR 2.2 [95%CI 1.2-3.8], p=0.008) was associated with mild anxiety/depressive symptoms. Secondly, when comparing mild to severe anxiety/depressive symptoms analysis showed that active disease (OR 7.1 [95%CI 2.8-17.7, $p<0.001$) was associated with severe anxiety/depressive symptoms.

**Table 2** | *Differences between patients with no, mild and severe symptoms of anxiety/depression*[†]

| | | | No N = 195 | Mild N = 88 | Severe N = 46 | *p* |
|---|---|---|---|---|---|---|
| Gender | Female | n (%) | 97 (49.7) | 58 (65.9) | 34 (73.9) | 0.002 |
| Disease duration (years) | | Median (IQR) | 2.7 (1.3-6.1) | 2.0 (1.0-4.8) | 1.7 (0.9-3.6) | 0.014 |
| Disease activity | Remission | n (%) | 162 (83.1) | 67 (76.1) | 16 (34.8) | <0.001 |
| | Mild | n (%) | 26 (13.3) | 21 (23.9) | 21(45.7) | |
| | Moderate | n (%) | 6 (3.1) | 0 | 2 (4.3) | |
| | Severe | n (%) | 1 (0.5) | 0 | 7 (15.2) | |
| Steroid use | | n (%) | 13 (6.7) | 9 (10.2) | 9 (19.6) | 0.025 |
| Relapse preceding year | No | n (%) | 137 (70.3) | 57 (64.8) | 22 (47.8) | 0.025 |
| | 1 | n (%) | 49 (25.1) | 27 (30.7) | 17 (36.9) | |
| | >1 | n (%) | 9 (4.6) | 4 (4.5) | 7 ( 15.2) | |
| HRQOL | IMPACT-III (N=226) | Mean ± SD | 152.9 ± 13.9 | 138.4 ± 14.7 | 115.0 ± 17.4 | <0.001 |
| | IBDQ (N=101) | Mean ± SD | 192.8 ± 16.9 | 164.5 ± 15.4 | 138.9 ± 26.6 | <0.001 |

***Abbreviations***: IQR= interquartile range, SD= standard deviation, HRQOL= Health-related quality of life, IBDQ= Inflammatory Bowel Disease Questionnaire.
***Note***: [†]Total N=329 (134/177 patients with elevated symptoms received the psychiatric interview, resulting in 88 patients with mild and 46 patients with severe anxiety/depressive symptoms).

**Table 3** | *Inflammatory parameters in patients with no, mild and severe anxiety/depressive symptoms*

| | | No N = 195 | Mild N = 88 | Severe N = 46 | *p* |
|---|---|---|---|---|---|
| C-Reactive protein (mg/L) | available samples | 154 | 73 | 37 | |
| | median (IQR) | 2.0 (1.0-5.0) | 2.2 (0.7-6.0) | 3.0 (1.0-9.0) | 0.087 |
| Hemoglobin (mmol/L) | available samples | 166 | 82 | 41 | |
| | median (IQR) | 8.2 (7.7-9.0) | 8.2 (7.7-8.7) | 7.9 (7.1-8.3) | 0.011 |
| Hemocrit (L/L) | available samples | 160 | 79 | 40 | |
| | median (IQR) | 0.41 (0.38-0.44) | 0.40(0.38-0.42) | 0.39 (0.36-0.40) | 0.024 |
| Leukocytes ($10^9$/L) | available samples | 165 | 81 | 41 | |
| | median (IQR) | 6.7 (5.4-8.4) | 5.8 (5.5-8.8) | 7.2 (6.0-10.2) | 0.362 |
| Trombocytes ($10^9$/L) | available samples | 164 | 82 | 41 | |
| | median (IQR) | 296 (243.3-357.5) | 311.5 (246.8-358.8) | 326 (228.5-387.5) | 0.671 |
| Erythrocyte Sedimentation Rate (mm/h) | available samples | 89 | 52 | 23 | |
| | median (IQR) | 7.0 (3.0-19.0) | 6.0 (3.3-19.5) | 16.0 (6.0-23.0) | 0.047 |
| Faecal calprotectin (µg/g) | available samples | 67 | 48 | 23 | |
| | median (IQR) | 106.0 (34.0 -645.0) | 295.1 (30.8-807,8) | 602.3 (163.0-1173.0) | 0.037 |

***Abbreviations***: IQR= interquartile range

### Risk factors for anxiety symptoms

Female patients (OR 1.8 [95%CI 1.1-2.9], p=0.013) and patients with active disease (OR 1.9 [95%CI 1.1-3.2], p=0.019) had higher odds of experiencing anxiety symptoms than male patients and patients in remission. See Table 4. Subgroup analysis showed that active disease was significantly associated with anxiety symptoms in patients ≥18 years (OR 2.6 [95%CI 1.1-6.1], p=0.025) (data not shown).

### Risk factors for depressive symptoms

Patients with active disease had higher odds of having depressive symptoms, compared to patients in remission (OR 4.6 [95%CI 2.4-8.8], p<0.001) (See Table 4). Subgroup analysis showed that active disease was significantly associated with depressive symptoms in patients ≥18 years (OR 7.7 [95%CI 2.8-21.2], *p*<0.001) (data not shown).

**Table 4** | *Factors associated with elevated anxiety/depressive, anxiety or depressive symptoms*

| | | **Anxiety/depressive symptoms[I] N = 177** | | | **Anxiety symptoms[II] N = 166** | | | **Depressive symptoms [III] N = 70** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **OR** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** |
| Age (years) | - | 0.82 | 0.64-1.05 | 0.121 | 0.72 | 0.56-0.92 | **0.010** | 1.41 | 1.00-2.00 | 0.049 |
| Gender | Male | | | | | | | | | |
| | Female | 1.72 | 1.09-2.73 | **0.021** | 1.81 | 1.13-2.88 | **0.013** | 1.61 | 0.86-3.01 | 0.138 |
| Socioeconomic status | Low | | | | | | | | | |
| | Middle | 0.88 | 0.45-1.71 | 0.707 | 1.01 | 0.52-1.98 | 0.971 | 1.47 | 0.62-3.49 | 0.382 |
| | High | 0.69 | 0.36-1.33 | 0.268 | 0.80 | 0.41-1.56 | 0.512 | 0.66 | 0.27-1.63 | 0.364 |
| Disease type | CD | | | | | | | | | |
| | UC | 1.12 | 0.56-2.26 | 0.745 | 1.17 | 0.58-2.36 | 0.663 | 2.14 | 0.85-5.41 | 0.108 |
| | IBD-U | 0.74 | 0.24-2.25 | 0.597 | 0.85 | 0.28-2.60 | 0.776 | 0.85 | 0.18-3.97 | 0.837 |
| Disease duration (years) | - | 0.75 | 0.58-0.97 | **0.027** | 0.82 | 0.64-1.07 | 0.144 | 0.72 | 0.50-1.03 | 0.075 |
| Disease activity | Remission | | | | | | | | | |
| | Active disease | 1.87 | 1.10-3.21 | **0.023** | 1.90 | 1.11-3.24 | **0.019** | 4.58 | 2.38-8.80 | **<0.001** |
| Perianal disease | | 0.93 | 0.45-1.90 | 0.835 | 0.78 | 0.37-1.62 | 0.497 | 1.29 | 0.49-3.39 | 0.606 |
| Previous Bowel surgery | | 1.16 | 0.44-3.09 | 0.767 | 1.14 | 0.44-2.98 | 0.791 | 0.97 | 0.27-3.48 | 0.960 |
| Current medication | 5-ASA | 0.81 | 0.38-1.71 | 0.573 | 0.82 | 0.38-1.75 | 0.606 | 0.40 | 0.14-1.10 | 0.075 |
| | Immunomodulators | 0.84 | 0.49-1.44 | 0.519 | 0.88 | 0.51-1.51 | 0.632 | 0.69 | 0.33-1.45 | 0.330 |
| | Biologicals | 1.10 | 0.59-2.05 | 0.759 | 1.29 | 0.69-2.40 | 0.429 | 0.62 | 0.27-1.45 | 0.269 |
| | Corticosteroids | 1.65 | 0.57-4.80 | 0.361 | 1.75 | 0.60-5.14 | 0.308 | 0.83 | 0.24-2.87 | 0.769 |
| | Enemas | 0.76 | 0.27-0.19 | 0.616 | 0.87 | 0.30-2.49 | 0.795 | 1.45 | 0.43-4.90 | 0.554 |
| | No Medication | 0.58 | 0.19-1.77 | 0.339 | 0.77 | 0.25-2.35 | 0.644 | 0.63 | 0.15-2.60 | 0.520 |

**Table 4** | *Factors associated with elevated anxiety/depressive, anxiety or depressive symptoms (continued)*

| | | Anxiety/depressive symptoms[I] N = 177 | | | Anxiety symptoms[II] N = 166 | | | Depressive symptoms [III] N = 70 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OR | 95% CI | *p* | OR | 95% CI | *p* | OR | 95% CI | *p* |
| Relapse preceding year | No relapse | | | | | | | | | |
| | 1 relapse | 1.05 | 0.63-1.75 | 0.850 | 1.08 | 0.65-1.80 | 0.777 | 1.33 | 0.69-2.56 | 0.391 |
| | ≥2 relapses | 1.12 | 0.39-3.17 | 0.836 | 1.04 | 0.37-2.95 | 0.938 | 1.44 | 0.45-4.64 | 0.539 |
| Disease extension | Limited | | | | | | | | | |
| | extensive | 0.66 | 0.39-1.14 | 0.140 | 0.64 | 0.37-1.11 | 0.110 | 1.00 | 0.50-1.98 | 0.994 |
| Steroid use < 3 months | | 0.84 | 0.35-2.01 | 0.701 | 0.79 | 0.33-1.92 | 0.602 | 1.41 | 0.49-4.09 | 0.524 |

***Abbreviations*: OR=** odds ratio, CI= confidence interval, CD= Crohn's disease, UC= ulcerative colitis, IBD-U= indeterminate colitis, 5-ASA= 5-aminosalicylic acid.
***Notes***. [I] 2 missing, total 372; [II] 1 missing, total 373; [III] 2 missing, total 372



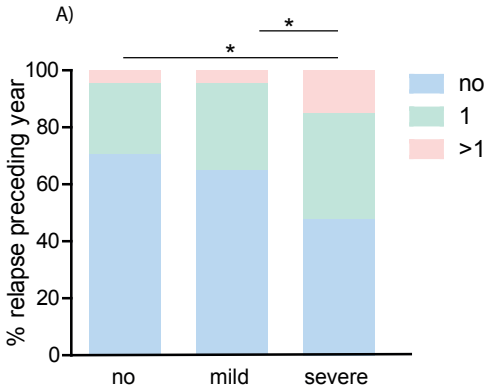


**Figure 2a** (left) | Patients with severe anxiety/depressive symptoms had more relapse preceding year compared to patients with mild or no anxiety/depressive symptoms
Note: * $p<0.05$

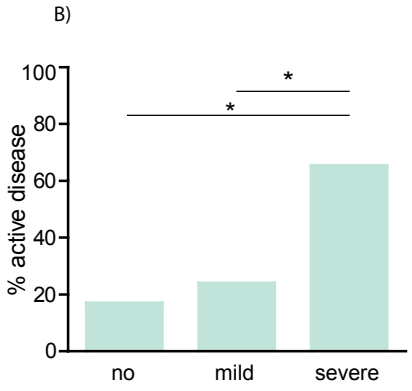


**Figure 2b** (right) | A higher percentage of active disease was found patients with severe anxiety/depressive symptoms compared to patients with mild or no anxiety/depressive symptoms
Note: * $p<0.05$

## DISCUSSION

This study is unique in describing the prevalence, severity and risk factors of symptoms of anxiety and depression, in Europe's largest cohort of pediatric and young adult patients with IBD. In the current study, the prevalence of anxiety/depressive symptoms was high, almost 50%. This is almost three times higher than reported in a community sample of Dutch adolescents [63]. Anxiety symptoms where far more

prevalent than depressive symptoms (28.3% vs 2.9%), but they also often occurred concomitantly (15.8%). It is well known that anxiety and depressive symptoms can coexist [18], but few studies investigated the presence of both anxiety and depressive symptoms in young patients with IBD. Compared to previous studies, our cohort has a higher prevalence of anxiety symptoms [9-11], whereas prevalence of depressive symptoms seems to be lower [5, 10, 64]. We expect that the prevalence rates vary depending on the activity and severity of disease. For example, a prevalence of ±5% was reported in a study cohort of mild and uncomplicated disease (only patients in remission, oral medication [no steroids] and IBD diagnosis >1 year; 13). The most prevalent anxiety domains found in our study were social phobia, generalized anxiety and specific phobia, which is similar to other studies [11, 12]. The low prevalence of depressive symptoms in our cohort can be explained by the low CDI total cutoff score used in the other studies, using cutoff points of 9 [5] or 10 [12], which correspond to (T-)scores within the average range [64, 65]. It could have been that patients in those studies were labeled as having depressive symptoms, where in fact their scores might have been in the normal range. Secondly, the higher percentage of patients with active disease in the other studies could also explain the higher rates of depressive symptoms.

A major strength of our study is that we studied the severity of anxiety/depressive symptoms, based on severity scores given during the psychiatric interview. Of the 177 patients with elevated anxiety/depressive symptoms, 134 patients agreed to this interview. 46 patients were diagnosed with severe symptoms and where referred for psychological consultation and treatment (12.2% of the total sample). Exploratory analysis showed that patients with severe symptoms had significantly higher disease activity, used steroids more frequently, experienced more relapses in the preceding year and had a lower quality of life than patients with mild or no symptoms. It is important to note that, relapses in the preceding year, as an indicator for disease severity, were associated with severity of anxiety/depressive symptoms. In addition, disease duration was also significantly shorter in the group with mild and severe anxiety/depressive symptoms, which may indicate that patients with a longer disease duration have more time to adapt and build adaptive coping strategies. This is supported by the study from Walter et al. [13], that included only patients with a longer that one year prior diagnosis of IBD and found a 13% prevalence of anxiety and depressive symptoms. It is not likely that patients in the mild and severe group suffered from an adjustment disorder due to recent diagnosis of IBD, as the majority of patients had a disease duration >3 months. Considering the fact that not all patients agreed to the psychiatric interview (24.2% refused), the severe group could well be an underestimation, implying that the group with severe anxiety/depressive symptoms might even be larger.

Our findings confirm our hypothesis that clinical disease activity is an important risk factor for anxiety and depression. This corresponds to previous findings [5, 11, 16, 21, 22, 29] and implies that disease control is important for physical health as well as mental health. It also emphasizes that attention should be given to emotional health in times of active disease. Studies that have shown an association between anxiety/depression and relapse [8], as part of the brain-gut axis, support this recommendation. In addition, in line with previous studies [66], we showed that female gender is a significant risk factor for anxiety and depression. This is probably not a consequence of an IBD-specific cause, because it parallels the well-known gender differences in the general population [67]. We failed to find a significant association between steroid use and anxiety and/or depressive symptoms, which is in agreement with the finding from Reed-Knight et al. [64] and several studies in adults with IBD [66], but in contrast to other pediatric IBD studies [5, 29]. This is likely due to the low number of patients using steroids in our cohort (9.6%). Due to these small numbers we were not able to take the dosage into account, which most aforementioned studies did. Moreover, this study investigated whether the risk factors for anxiety symptoms or for depressive symptoms would be different. Analysis showed that age and gender were significantly associated with anxiety, but not with depressive symptoms. This could reflect the actual situation, but could also be a consequence of the fact that the group with depressive symptoms was smaller. Surprisingly, socio economic status was not associated with anxiety and/or depression, whereas other studies did find this association [29].



Major strengths of this study are that data were collected consecutively and concern a unique study population: pediatric as well as young adult IBD patients from regional as well as tertiary medical centers, which makes the results generalizable. In addition, and contrary to other studies [5, 11, 27, 29], we assessed anxiety and depression concomitantly as this has implications for subsequent psychological treatment. Furthermore, to the best of our knowledge, we are the first to address the severity of the anxiety and depressive symptoms and show that 12.2% of our cohort suffers from severe anxiety/depressive symptoms. Moreover, our large cohort has few missing values, allowing us to directly perform multiple regression analysis, which does not introduce the (multiple testing) bias which is applied in studies that first perform univariate analysis to select significant variables for the multiple or multivariate analysis.

This study has several limitations. Firstly, considering that most patients were in clinical remission in our cohort and that the group with active disease mostly consisted of patients with mild disease activity, the prevalence estimates of anxiety and depressive symptoms could have been an underestimation. Secondly, because of the wide age range (10-25 years) we had to use 2 different validated questionnaires both for anxiety and depression and consequently could not work with continuous data.

While the use of validated cutoff scores is highly accepted, it does limit options for analyses. Furthermore, the BDI-II as well as the CDI contains questions concerning for example sleep disturbance, fatigue and reduced appetite. These items are also called 'somatic items' because they can both relate to a physical illness or be an indicator of depression. It is suggested that these instruments could overestimate the presence of depressive symptoms in physically ill patients. There is ongoing debate about the best strategy for this issue: some argue that these items should be removed, but others argue the entire screen instrument is more valid because these symptoms do not always correlate to disease activity and do respond to psychological treatment [68]. Further research is necessary to provide an evidence based strategy regarding the use of these instruments in physically ill patients. In addition, we tried to investigate differences in risk factors for anxiety and depressive symptoms between the pediatric and young adult population. Analysis did not show significant risk factors in the < 18 age group, which could have reflected the actual situation, but could also be explained by low power, or the fact that other predictors, that were not included in the regression model (for example fatigue or abdominal pain), more strongly influence anxiety/depressive symptoms in younger patients. Thirdly, not all patients were willing to participate in the psychiatric interview and this could have led to and underestimation of the group with severe anxiety/depressive symptoms. Furthermore, the purpose of the psychiatric interview was to differentiate severe/clinical from mild/subclinical anxiety/depressive symptoms and not to establish the presence of other psychiatric disorders. Although this would have been interesting, the study was not designed to do so, and there is not much evidence to suspect the presence of other psychiatric disorders in youth with IBD [69]. Fourthly, due to logistic constraints inflammatory markers (e.g. C-Reactive protein, fecal calprotectin) were not available for all patients and could not be used in the regression models, but have shown to be different between the severe and no anxiety/depressive symptoms group. Although the validated clinical disease activity indices are frequently used in research, there is debate about the actual correlation to intestinal inflammation. Finally, our study did not encompass validated measures of abdominal pain, irritable bowel syndrome and fatigue, while these factors are shown to be correlated with anxiety and depression [28]. Including these measures would have increased the length of our questionnaire and the risk of non-completion, therefore we chose not to include them in this study.

Despite these limitations, this study provides valuable information about the prevalence and risk factors of anxiety and/or depression in adolescents and young adult patients with IBD. We report a high prevalence of anxiety/depressive symptoms of almost 50%. Analyses showed active disease and female gender to be the most important predictors. In conclusion, we have shown that the prevalence of anxiety and depressive symptoms is high in adolescent and young adult IBD patients. These

psychological problems can have a significant impact on the burden of disease and can lead to increased health care costs. Therefore we recommend psychological screening in adolescent and young adult IBD patients. Screening facilitates early recognition and early psychological treatment, in order to improve psychological well-being and clinical course of disease. Physicians should be aware that female patients and patients with active disease are the most vulnerable.

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# Illness perceptions and depression are associated with health-related quality of life in youth with inflammatory bowel disease

Luuk Stapersma, Gertrude van den Brink, Jan van der Ende,
Eva M. Szigethy, Alexander G. Bodelier, Herbert M. van Wering,
Pamela C.W.M. Hurkmans, M. Luisa Mearin,
Andrea E. van der Meulen – de Jong, Johanna C. Escher,
Elisabeth M.W.J. Utens

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## ABSTRACT

**Background** In youth with inflammatory bowel disease (IBD), health-related quality of life (HRQOL) has been shown to be affected by individual disease factors and specific psychological factors. The innovative aim of this study is to examine the *combined* impact of psychological factors (illness perceptions, cognitive coping, anxiety, and depression) on HRQOL, over and above the associations of demographic and disease factors with HRQOL in youth with IBD.

**Methods** Data on clinical disease activity, illness perceptions, cognitive coping, anxiety, depression, and HRQOL were prospectively collected in 262 consecutive youth (age 10-20, 46.6% male) with confirmed IBD. Multiple linear regression analyses tested the associations of demographic, disease, and psychological variables with HRQOL in separate groups for Crohn's disease (CD; N=147) and ulcerative colitis and IBD unclassified (UC/IBD-U; N=115), using age-specific validated instruments.

**Results** In both disease groups more negative illness perceptions ($\beta$ = -.412; $\beta$ = -.438, $p < .001$) and more depression ($\beta$ = -.454; $\beta$ = -.279 , $p < .001$) were related to lower HRQOL. In the UC/IBD-U group, more anxiety was related to lower HRQOL ($\beta$ = -.201, $p = .001$). The model with the psychological variables explained a large and significant amount of variance in both groups: 74%; 83%; respectively ($p < .001$).

**Conclusions** In 10-20-year-old IBD patients, negative illness perceptions and depression were significantly and more strongly associated with lower HRQOL than demographic and disease factors. Thus, it is important to integrate psychological factors in the treatment for IBD patients. To improve HRQOL in young IBD patients, psychological interventions should be targeted at negative illness perceptions and depression.

## INTRODUCTION

Inflammatory bowel disease (IBD) is a disabling chronic gastrointestinal condition, with two predominant subtypes: Crohn's disease (CD) and ulcerative colitis (UC). In up to 25% of patients, IBD starts in late childhood or adolescence [1-3]. The designation IBD unclassified (IBD-U) is used for patients in which it is not (yet) possible to make a distinction between CD and UC. IBD is characterized by periods of clinical disease activity and remission, and presents with symptoms such as abdominal pain, bloody diarrhea, fatigue and weight loss [4]. In adolescence, growth failure and delayed pubertal development is common, specifically in Crohn's disease. The adolescent life phase is characterized by development on several domains (biological, psychological, social, cognitive, academic). Having a chronic disease such as IBD can affect all these domains, for example not only becoming more independent from parents, developing long-term friendships, starting secondary education, forming an own identity, but also experimenting with alcohol and drugs, seeking and finding a (side) job and having romantic relationships. The teenage years are a crucial period of transition from childhood to young adulthood [5]. IBD and its medical treatment may severely impact psychosocial functioning: health-related quality of life (HRQOL) in children and adolescents (further referred to as youth) with IBD is significantly lower than in healthy peers [6, 7]. Furthermore, high prevalence rates varying from 20-50% for anxiety and depression are found in these patients [8-11]. A recent meta-analysis in children and adolescents showed pooled prevalence rates for anxiety and depressive symptoms of 15%, and for anxiety and depressive disorders of 3-4% [12].

Other psychological factors are also important to consider in patients with IBD, such as illness perceptions and coping, because these have been shown to be related to psychosocial outcomes (such as HRQOL, general functioning or adjustment to IBD). Illness perceptions refer to the cognitive and emotional representations a patients forms about his or her disease [13]. These representations cover several dimensions, i.e. consequences (the expected effects of the disease), timeline (expectations about the duration of the disease), cause (thoughts about the cause of the disease), controllability (the extent to which the individual believes he or she can control the disease with or without treatment), identity (how the individual describes the symptoms and perceives as part of the disease), concern (worries about the disease), and emotions (the emotional response to the disease) [13, 14]. Coping refers to intentional efforts to regulate negative emotions in response to harm, threat or challenges [15, 16], in this study dealing with IBD. Coping encompasses both cognitive and behavioral regulation. Cognitive coping is implicated in the etiology and the maintenance of anxiety and depression [17, 18], and is therefore important as well in studying youth with IBD.

The Common Sense Model (CSM) is a model to describe the relationships between disease characteristics, illness perceptions, coping, and anxiety, depression and HRQOL, originally developed by Leventhal and Diefenbach [13]. In this model, illness characteristics (such as clinical disease activity) lead to certain thoughts about the illness, the so-called illness perceptions of a patient. These illness perceptions influence the type of coping the patient uses to deal with his/her symptoms. Together, these factors lead to positive or negative illness outcomes, for example anxiety, depression, or HRQOL. In patients with IBD, several relationships have been found between these variables, mostly in adults. Below it will be explicitly mentioned if studies were conducted in youth with IBD. For example, more clinical disease activity has been found to be associated with more anxiety and depression separately [20, 21]. Previous studies have also demonstrated a relationship between clinical disease activity and HRQOL, with a mediating role for anxiety and depressive symptoms [20, 22]. Furthermore, negative illness perceptions are associated with lower HRQOL in adults with IBD [25] and also with more psychological problems in youth with IBD [26]. Coping was associated with anxiety and depression [23] or adjustment to IBD [27] in adults, and found as predictor of depression in youth with IBD as well [28].

Unfortunately, very little is known on how all the factors described above together affect health outcomes, more specifically HRQOL in young IBD patients. Only a few studies examined several psychological factors simultaneously. In adults, illness perceptions [24] and coping [23] have been reported to impact the relationship between clinical disease activity on HRQOL. Recently, Van Tilburg et al. [29] showed in adolescents with IBD that patient-reported disability (as outcome) was associated not only with clinical disease activity, but also with a combined latent construct 'psychological factors' (including coping, pain beliefs, anxiety, and depression). However, they did not control for demographic factors (gender, age, socioeconomic status), and did not include other disease factors, such as disease type, and disease duration. In addition, there is some evidence that these disease factors are associated with HRQOL [21, 30, 31], and with anxiety and/or depression as well [26, 32]. Moreover, because the authors used a combined psychological construct, their findings provide no insight on which psychological factors in particular psychological interventions for youth with IBD should focus.

The complex interplay between clinical disease activity, illness perceptions, coping, anxiety, and depression makes it challenging to attune both the medical and psychological treatment to the individual needs of IBD patients to improve their HRQOL. The surplus value of the present study in a cohort of youth with IBD is that it aims to clarify the association of a combination of psychological factors (illness perceptions, cognitive coping, anxiety, and depression) with HRQOL, over and above demographic and disease factors. By selecting the 10-20-year age range, we cover the

period of transition from childhood to young adulthood. More specific insight on how psychological factors are associated with HRQOL in these vulnerable youth, can offer guidance on which factors psychological interventions should focus. Ultimately, with tailored psychological interventions, the course of the IBD and of possible psychological problems may be positively affected. We hypothesize that clinical disease activity is negatively associated with HRQOL. Furthermore, we hypothesize that psychological factors (i.e. illness perceptions, cognitive coping, anxiety, and depression), when tested simultaneously, are associated with HRQOL, even after controlling for clinical disease activity and other demographic and disease factors.

## MATERIALS AND METHODS

### Design

The present cross-sectional cohort study is based on a large patient sample (N=374), completing the baseline assessment of a multicenter randomized controlled trial (RCT), investigating a disease-specific cognitive behavioral therapy in youth with IBD and symptoms of anxiety and/or depression (trial registration number: NCT02265588, see also Van den Brink & Stapersma et al. [33]). In the current study only data from patients aged 10-20 years were used (N=262).

*Inclusion criteria* were: 1) age 10 to 20 years and 2) diagnosis of IBD, according to the consensus criteria [34] [35, 36].

*Exclusion criteria* were: 1) intellectual disability, 2) current treatment for mental health problems (pharmacological and/or psychological), 3) insufficient mastery of the Dutch language, 4) a diagnosis of selective mutism, bipolar disorder, schizophrenia, autism spectrum disorder, obsessive-compulsive disorder, posttraumatic or acute stress-disorder, or substance use disorder, 5) cognitive behavioral therapy in the past year (at least 8 sessions), and 6) participation in another intervention study.

### Procedure

Consecutive patients and their parents were recruited between October 2014 and September 2016 from the outpatient clinic in two academic hospitals and four community hospitals in the Southwest region of the Netherlands. Patient information was given and written informed consent was requested in all patients and, if applicable their parents or caregivers. Patients (and parents), who consented to participate, received an e-mail with a link to online questionnaires. Clinical disease activity was scored by the (pediatric) gastroenterologist around the time of inclusion (i.e. within approximately a month around the time of inclusion, median = 3.42 weeks).

## Measures

### Control variables

**Gender, age, disease type, and disease duration** of the patients were derived from their medical record. **Socioeconomic status** (SES) was determined using the occupational level from the parents or, if they lived on their own, patients themselves. Using the standard coding system of Statistics Netherlands ([37]), occupations were categorized in low, middle and high. For gender and SES dummy variables were created to use in the analyses.

**Clinical disease activity** was assessed by two validated clinical disease activity instruments. For CD the short Pediatric Crohn's Disease Activity Index (sPCDAI) and for UC the Pediatric Ulcerative Colitis Activity Index (PUCAI) was used. The sPCDAI comprises six items on medical history (abdominal pain, stools), well-being, physical examination (abdomen), weight and extra-intestinal manifestations [38]. Scores range from 0-90. [39]. The PUCAI comprises six items on abdominal pain, rectal bleeding, stool frequency and consistency, and activity level. Scores range from 0-85.

### Psychological factors

**Illness perceptions** were assessed by the Brief Illness Perceptions Questionnaire (B-IPQ; [14, 44]). This 9-item self-report questionnaire assesses cognitive and emotional representations of illness, covering eight dimensions: consequences, timeline, personal control, treatment control, identity, concern, emotions, and understanding. All dimensions are scored on an 11-point Likert-scale (0: not at all – 10: very much/severely). A higher score represents more negative illness perceptions. Good test-retest reliability and concurrent validity has been found [14], and the B-IPQ has been used before in adolescents with IBD [45]. Internal consistency (Cronbach's alpha) for the current sample was .81 in the CD group and .81 in the UC/IBD-U group.

**Cognitive coping** was measured with the Cognitive Emotion Regulation Questionnaire (CERQ). This self-report scale consists of 36 items, scored 1-5, with nine subscales (e.g. self-blame, acceptance, putting into perspective, positive refocusing, positive reappraisal, and catastrophizing). These scales are divided into two domains: adaptive cognitive coping (e.g. positive reappraisal, putting in perspective) and maladaptive cognitive coping (e.g. self-blame, catastrophizing). A higher score indicates more use of a particular coping style. Good reliability and construct validity has been found [46]. Both adaptive coping and maladaptive coping were used as variable in the analyses. For adaptive cognitive coping, internal consistency was .90 in the CD group and .93 in the UC/IBD-U group. For maladaptive cognitive coping, internal consistency was .88 in the CD group and .90 in the UC/IBD-U group.

**Anxiety** was assessed using the 69-item self-report questionnaire Screen for Child Anxiety Related Disorders (SCARED). The SCARED contains five subscales: general

anxiety disorder, separation anxiety disorder, specific phobia, panic disorder, and social phobia, rated on a 3-point scale (0-2: total score 0-138). Satisfactory reliability and validity has been reported [47]. The cutoffs for elevated anxiety were total score ≥ 26 for boys, ≥ 30 for girls, or subscale score ≥ 8 [48]. These were only used to decide whether patients had elevated anxiety, i.e. could be included in the RCT. Internal consistency for the current sample was .95 in the CD group and .94 in the UC/IBD-U group.

**Depression** was assessed using the Child Depression Inventory (CDI, for ages 10-17) and the Beck Depression Inventory, second version (BDI-II, for ages 18-20). The CDI is a 27-item self-report scale (0-2, total score 0-54). Good reliability and validity have been established. A CDI score of 13 or higher reflected elevated depression [50]. The BDI-II is a 21-item self-report scale (0-3, total score 0-63). It has excellent reliability and good to excellent validity. A BDI-II score of 14 or higher reflected elevated symptoms of depression [51]. The cutoffs for the CDI and BDI-II were only used to decide whether patients had elevated depression, i.e. could be included in the RCT. For the CDI, internal consistency was .85 in the CD group and .86 in the UC/IBD-U group. For the BDI-II, internal consistency was .91 in the CD group and .84 in the UC/IBD-U group. To be able to combine patients of all ages within the disease groups, depression scores were created a Z-score for depression using either the CDI or the BDI-II (depending on age).

**Health-related quality of life** was assessed by the IBD-disease specific self-report IMPACT-III, which covers six domains: IBD-related symptoms, systemic symptoms, emotional functioning, social functioning, treatment related concerns, and body image [52]. The 35 items are scored (1-5; total score 35-175). Good psychometric properties have been found [53]. The total score was used, and a higher total score indicates better HRQOL. Although the IMPACT-III originally was designed for youth up to 18 years, we also used it for the patients of 19 and 20 years. This allowed us to combine all patients in to one group for each disease type. This was substantiated by excellent internal consistency in both disease groups: .93 in the CD group and .94 in the UC/IBD-U group.

## Statistical analyses

To test whether the associations of demographic, disease and psychological factors with HRQOL are different for CD than for UC/IBD-U, multiple linear regression analyses were performed for the two disease groups separately: CD (N=147) and UC/IBD-U (N=115). UC and IBD-U were combined, since the group with IBD-U patients was quite small (N=18), IBD-U often resembles UC more than CD [55], and IBD-U has often a similar treatment approach as UC [56]. All variables were continuous, except for gender and SES. For these variables dummy variables were included in the analyses. The abovementioned cutoffs for the SCARED, CDI, and BDI-II were only used to determine the proportion of patients with elevated anxiety or depressive symptoms. For the remaining questionnaires no cutoffs were used.

The multiple linear regression analyses were run with two blocks/models, using HRQOL as outcome. In the first block, the demographic and disease variables (gender, age, disease duration, SES, and clinical disease activity) were entered simultaneously in the first regression model. In the second block, the psychological factors (illness perceptions, cognitive coping, anxiety, and depression) were added simultaneously to the variables entered in the first block. To account for missing values, multiple imputation with chained equations was applied using SPSS (m =15 for approximately 15% of missing data; [57]). As a sensitivity analysis we also performed a complete case analysis (N=116; N=104 for the CD and UC/IBD-U groups respectively), to see whether the multiple imputations had an effect on the results. A p-value of $< .05$ was considered significant. SPSS Version 24 was used for the analyses (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). A statistician (JE) supported and advised in analyzing and interpreting the data and results.

### Ethical considerations

This study was performed conform the Declaration of Helsinki and approved by the Institutional Review Board of the Erasmus MC and of each participating center.

## RESULTS

### Patient characteristics

In total 552 patients (aged 10-25 years) were invited for a randomized controlled trial (RCT) and 382 agreed to participate (response rate = 69%). Eight patients had incomplete data. From the final 374 youth, 262 were aged 10-20 years and were included in the current study. Demographic, disease and psychological characteristics are presented in Table 1. In disease groups (CD and UC/IBD-U), the percentage of patients with active disease (mild-moderate-severe) was 31.3% and 30.4%, respectively. Overall, 50% of the patients had elevated anxiety, 17.9% had elevated depression, and 16.8% had both. For HRQOL, illness perceptions, and cognitive coping no cutoffs are available, so means with ranges are provided in Table 1.

### Influence of demographic, disease and psychological variables on HRQOL; results of multiple linear regression analyses per disease group

In Table 2-3, the standardized estimates, their significance, and the proportion of explained variance for each regression model (model 1 with demographic and disease factors and model 2 with psychological factors added) in the two disease groups are provided. Results are presented from the analyses on the imputed datasets. Results from the complete case analyses were similar (data not shown).

As is seen in Table 2, in the CD group (N=147), female gender and clinical disease activity were significantly associated with HRQOL in the first model, explaining 37% of the variance in HRQOL. After adding the psychological factors, clinical disease activity (ß = -.170, p = .001), more negative illness perceptions (ß = -.412, p < .001), and more depressive symptoms (ß = -.454, p < .001) were associated with lower HRQOL. The second model explained 74% of the variance in HRQOL, with a significant change in explained variance ($R^2$ change = 37%, p < .001).

**Table 1** | *Demographic and disease characteristics of total sample of IBD patients (10-20 years)*

| | | Group | | |
|---|---|---|---|---|
| | | **CD** | **UC/IBD-U** | **Total** |
| | | N=147 | N=115 | N=262 |
| **Demographic characteristics** | | | | |
| Age (years), mean (SD) | | 17.19 (2.52) | 16.15 (2.98) | 16.74 (2.77) |
| Male (%) | | 50.3 | 41.7 | 46.6 |
| SES (%)[a] | Low | 17.7 | 13.0 | 15.6 |
| | Middle | 32.7 | 40.9 | 36.3 |
| | High | 38.1 | 43.5 | 40.5 |
| **Disease characteristics** | | | | |
| Disease type (%) | CD | 100 | 0 | 56.1 |
| | UC | 0 | 84.3 | 37.0 |
| | IBDU | 0 | 15.7 | 6.9 |
| Age at diagnosis (years), mean (SD) | | 14.25 (3.02) | 13.18 (3.97) | 13.78 (3.50) |
| Disease duration (years), median (IQR) | | 2.26 (0.97-4.39) | 1.90 (0.62-4.73) | 2.03 (0.81-4.56) |
| Active disease (%)[b] | | 31.3 | 30.4 | 30.9 |
| **Psychological characteristics** | | | | |
| Elevated anxiety symptoms (%)[c] | | 49.7 | 50.4 | 50.0 |
| Elevated depressive symptoms (%)[c] | | 15.6 | 20.9 | 17.9 |
| Elevated anxiety and depression (%)[c] | | 14.3 | 20.0 | 16.8 |
| HRQOL, mean (range) | | 143.36 (76-174) | 141.91 (82-173) | 142.72 (76-174) |
| Illness perceptions, mean (range) | | 34.75 (3-69) | 36.69 (9-70) | 35.63 (3-70) |
| Adaptive cognitive coping, mean (range) | | 57.67 (20-92) | 55.72 (21-97) | 56.78 (20-97) |
| Maladaptive cognitive coping, mean (range) | | 25.05 (16-59) | 25.12 (16-56) | 25.08 (16-59) |

***Abbreviations*: SD=** standard deviation, SES= socio-economic status, CD= Crohn's Disease, UC= ulcerative colitis, IBDU= inflammatory bowel disease unclassified, IQR= Inter Quartile Range, HRQOL= health-related quality of life, sPCDAI= short Pediatric Crohn's Disease Activity Index, PUCAI= Pediatric Ulcerative Colitis Activity Index, SCARED= Screen for Child Anxiety Related Emotional Disorders, CDI= Child Depression Inventory, BDI-II= Beck Depression Inventory, Second edition
***Notes*:** [a] Not for all patients SES was available: CD N=130, UC/IBD-U N=112. Total group N=242. [b] Scored above cutoff for active disease on sPCDAI (≥10 points) or PUCAI (≥10 points). [c] Scored above cutoff on SCARED (anxiety), CDI (depression; 10-17 year) and/or BDI-II (depression 18-20 year).

**Table 2** | *Influence of demographic, disease, and psychological variables on HRQOL; results of multiple linear regression analysis – CD group (N=147)*

| | | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|---|
| | | *ß* | SE *ß* | *p*-value | *ß* | SE *ß* | *p*-value |
| **Block 1** | | | | | | | |
| Gender | Male | | | | | | |
| | Female | -.230 | .072 | **.002*** | -.055 | .051 | .283 |
| Age | | -.075 | .077 | .330 | -.054 | .056 | .330 |
| SES | Low | | | | | | |
| | Middle | .029 | .098 | .768 | .070 | .069 | .315 |
| | High | .051 | .097 | .600 | -.042 | .067 | .533 |
| Disease duration | | .123 | .072 | .086 | .064 | .049 | .193 |
| Clinical disease activity | | -.482 | .071 | **< .001*** | -.170 | .053 | **.001*** |
| **Block 2** | | | | | | | |
| Illness perceptions | | | | | -.412 | .063 | **<.001*** |
| Adaptive cognitive coping | | | | | .012 | 0.49 | .803 |
| Maladaptive cognitive coping | | | | | .018 | .058 | .759 |
| Anxiety | | | | | .019 | .077 | .801 |
| Depression | | | | | -.454 | .077 | **<.001*** |
| $R^2$ (CI), *p*-value | | .37 (.24-.49), $p <$ **.001*** | | | .74 (.65-.80), $p <$ **.001*** | | |

***Abbreviations***: SE= standard error, SES= socioeconomic status, CI= confidence interval
***Note***: * significant with $p < .05$

**Table 3** | *Influence of demographic, disease, and psychological variables on HRQOL; results of multiple linear regression analysis – UC/IBD-U group (N=115)*

| | | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|---|
| | | *ß* | SE *ß* | *p*-value | *ß* | SE *ß* | *p*-value |
| **Block 1** | | | | | | | |
| Gender | Male | | | | | | |
| | Female | -.276 | .081 | **.001*** | -.101 | .044 | **.022*** |
| Age | | -.298 | .082 | **<.001*** | -.193 | .045 | **<.001*** |
| SES | Low | | | | | | |
| | Middle | -.130 | .126 | .302 | -.033 | .066 | .619 |
| | High | -.101 | .126 | .424 | -.047 | .067 | .483 |
| Disease duration | | .201 | .083 | **.015*** | .087 | .044 | **.045*** |
| Clinical disease activity | | -.289 | .081 | **<.001*** | -.066 | .046 | .156 |
| **Block 2** | | | | | | | |
| Illness perceptions | | | | | -.438 | .056 | **<.001*** |
| Adaptive cognitive coping | | | | | .036 | .046 | .156 |
| Maladaptive cognitive coping | | | | | -.029 | .052 | .584 |
| Anxiety | | | | | -.201 | .060 | **.001*** |
| Depression | | | | | -.279 | .061 | **<.001*** |
| $R^2$ (CI), *p*-value | | .32 (.18-.46), $p <$ **.001*** | | | .83 (.76-.88), $p <$ **.001** | | |

***Abbreviations***: SE= standard error, SES= socioeconomic status, CI= confidence interval
***Note***: * significant with $p < .05$

In the UC/IBD-U group (N=115), female gender, age, disease duration, and clinical disease activity were significantly associated with HRQOL in the first model, explaining 32% of the variance in HRQOL. After adding the psychological factors, female gender (ß = -.101, p = .022), lower age (ß = -.193, p < .001), shorter disease duration (ß = .087, p = .045), more negative illness perceptions (ß = -.438, p < .001), more anxiety symptoms (ß = -.201, p = .001), and more depressive symptoms (ß = -.279, p < .001) were associated with lower HRQOL. The second model explained 83% of the variance, with a significant change in explained variance ($R^2$ change = 51%, p < .001).

## DISCUSSION

This study examined the influence of psychological factors on HRQOL over and above the influence of demographic and disease factors in youth with IBD, and analyzed the results separately for CD and UC/IBD-U. Partly in line with our first hypothesis, in the first model, without the psychological factors included, female gender and clinical disease activity were significantly associated with HRQOL, as were age and disease duration only in the UC/IBD-U group. However, when adding a combination of all psychological factors simultaneously in the second model, the influence of demographic and disease factors was reduced. Subsequently, illness perceptions and depression were associated with HRQOL in youth with IBD, even when controlling for demographic and disease factors. More negative illness perceptions and more depression were associated with a lower HRQOL, in both the CD group and the UC/IBD-U group. A difference between the disease groups was that, in the UC/IBD-U group, anxiety was associated with HRQOL as well. Most importantly, adding the psychological factors resulted in a significant increase in the proportion of explained variance, from approximately 35% by the first model to 74-83% by the second model, in both groups. This high proportion of explained variance underlines the importance of psychological factors contributing to HRQOL in patients with IBD.

These results provide insight in which psychological factors play a role in youth with IBD. Consistently in the two disease groups, negative illness perceptions and depression in particular prove their significant role, whereas cognitive coping and was not associated with HRQOL. This was also found in previous studies, which reported that illness perceptions and depression were associated with disease outcomes [25, 29]. Therefore, we recommend to pay attention to these factors when treating patients. Our results suggest that in youth with UC/IBD-U, anxiety should be considered as well.

There are several explanations for only finding an association between anxiety and HRQOL in youth with UC/IBD-U. Firstly, the nonsignificant relationship between anxiety and HRQOL in youth with CD cannot be explained by a difference in the

prevalence of elevated anxiety symptoms between the CD and UC/IBD-U groups (49.7% versus 50.4%). Secondly, one might postulate that anxiety is not strongly related to HRQOL in youth with IBD. Although we found a high prevalence of anxiety symptoms in the current sample (see Table 1 and [32]), presence of anxiety symptoms as such may not have to impact the HRQOL of youth with CD. In children and adolescents the available studies did not show evidence for differences between CD and UC [26], but Sarid et al. [58] showed worse psychosocial outcomes in patients with UC [24, 59]. Thirdly, anxiety and depression are highly comorbid, have overlapping symptoms and anxiety is considered a precursor of depression [60, 61]. So anxiety may have played a role in preceding depressive symptoms in these patients. It is possible that anxiety and depression both explained variance in HRQOL, but that depression is more strongly related to HRQOL, and therefore diminished the relationship between anxiety and HRQOL in the patients with CD. More research is needed to unravel the interplay between anxiety and depression in youth with IBD. In their benchmark review, Cummings et al. [62] describe several pathways for the anxiety and depression comorbidity in children and adolescents. They also stress the importance of studying specific anxiety disorders for their comorbidity with depression. In IBD, very few studies tested specific anxiety problems (e.g. [11]). As a result, to our knowledge, there are no studies that investigated how specific anxiety problems are related to depressive symptoms in patients with IBD. Fourthly, in adults, several studies reported on the relationship between anxiety and HRQOL in both patients with CD and UC [63, 64]. Anxiety might be more impairing for adults with IBD than for youth with IBD, since adults may have to deal with more disease-related anxieties and worries concerning their daily and social functioning (impact of IBD on employment, career perspectives, income, finding a sexual partner, starting a family, etc.). Lastly, anxiety symptoms may be IBD-specific, i.e. anxiety or worries surrounding their IBD symptoms (e.g. bloody stools, the necessity of a stoma or surgery). These worries are often exorbitant to the actual context, but can have a negative impact [65, 66]. More specifically, higher IBD-specific anxiety was associated with lower HRQOL in youth with both CD and UC [65]. However, we are not aware of studies that examined differences between CD and UC with respect to IBD-specific anxiety in youth. Perhaps, youth with UC/IBD-U experience different IBD-specific worries than youth with CD, for example since youth with UC/IBD-U more often have alarming bloody stools than youth with CD.

Although the CSM postulates that coping is an important factor, in our study, cognitive coping was not significantly related to HRQOL, when simultaneously added to the model with the other psychological factors. Cognitive coping may not be related to HRQOL in IBD patients, as was also found in earlier studies examining individual psychological factors [24, 59]. This is in contrast with the results of a review including a wide range of illnesses in adults, that found that coping was a stronger predictor

for health outcomes than illness perceptions [67]. Perhaps, coping plays a different role in IBD than in other illnesses. On the other hand, the type of coping may be of importance , since we only tested cognitive coping styles (and not for example behavioral). However, the results of two adult IBD studies including problem-focused and emotion-focused coping are mixed [68, 69], and therefore do not support this explanation completely.

Comparing the results between patients with CD and UC/IBD-U, showed differences in the second model: a significant association of clinical disease activity with HRQOL in the CD group, and a significant association of gender, age and disease duration with HRQOL in de UC/IBD-U group. Most likely, these differences cannot be explained by differences between the two groups, since the groups were similar with respect to the percentages of active disease, males versus females and the disease duration (see Table 1). Only in the CD group, clinical disease activity was associated with HRQOL, even after adding the psychological factors to the model. To our knowledge, in youth, no studies have specifically examined differences between CD and UC with respect to the relationship between clinical disease activity and HRQOL. Patients with CD have a more heterogeneous clinical presentation and are affected by growth failure, more often than patients with UC and IBD-U [1]. The heterogeneous clinical presentation and growth failure can lead to a lower HRQOL. A recent review of Knowles et al. [70] showed that HRQOL was significantly lower for patients with active disease, although no information was provided about differences between CD and UC/IBD-U. In children and adolescents with IBD (both CD and UC), some studies have shown that clinical disease activity remained associated with HRQOL, even when anxiety/depression [20] [22] [71], and parental stress [71, 72] were included as mediators. It was therefore not tested, as in our study, what the influence is of demographic, disease, and psychological factors on the relationship between clinical disease activity and HRQOL. It seems that the relationship between clinical disease activity and HRQOL is not a direct relationship as such.

Only in the UC/IBD-U group, gender, age, and disease duration were significantly associated with HRQOL, even after adding the psychological factors to the model. For gender, previous studies in youth with IBD did not find an association with HRQOL [73-75]. These studies all included both CD and UC patients, but the majority of youth had CD (>70%), which may have masked the association between gender and HRQOL in the UC patients. However, it remains unclear what role gender has in affecting HRQOL, especially since gender is associated with more anxiety and depressive symptoms in general [76], as well as in our own cohort [32]. Anxiety and depressive symptoms are known to affect HRQOL in youth with IBD [22, 71]. For age, our results indicated that older age was associated with lower HRQOL in youth with UC/IBD-U. This is accordance with Otley et al. [75], who also reported that older age was as-

sociated with lower HRQOL in the first year after diagnosis of IBD. However, in their sample a large majority of youth was diagnosed with CD (77%). Other studies did not find association between age and HRQOL [31, 77] or the reversed association (lower HRQOL in younger patients; [21]). These mixed findings were confirmed in a review on predictors of HRQOL in youth with IBD [6]. Finally, in our study a shorter disease duration was associated with a lower HRQOL in youth with UC/IBD-U. Previous studies have suggested that it seems that disease duration is not associated with HRQOL in general, but only within the first months after diagnosis (of both CD and UC/IBD-U) [31, 75]. However, these studies included mainly CD patients (77% and 100% respectively) [31, 75]. In our sample, only 20% had a disease duration of 6 months or shorter. Therefore, our results suggest that for youth with CD in the first 6 months after the diagnosis, disease duration is not associated with HRQOL. For UC and IBD-U this relationship is unclear less clear defined. Although these differences between the disease groups are important to notice, the most important finding remains that, overall, in both disease groups, illness perceptions and depression were significantly associated with HRQOL.

## Strengths

Our sample (N=262) is one of the largest European samples and innovative in studying the influence of both disease, demographic and psychological factors in youth with IBD. Our large sample covers a broad age range, using internationally validated and age-attuned instruments. This age range is an important life phase, as several biological and psychosocial changes take place, and a chronic disease such as IBD can have negative consequences for the transition to adulthood. In addition, our sample was derived from 6 centers (both urban and rural areas), making generalization of our findings stronger. In addition, and contrary to other studies that only included either anxiety or depression (e.g.[8, 11]), we assessed both anxiety and depression, as this had implications for subsequent psychological treatment. Most importantly, whereas previous studies mostly examined individual relationships between disease factors, psychological factors and HRQOL, we aimed to test the influence of disease, demographic and psychological factors simultaneously. An advantage of this approach is that the current study took into account the interrelationships between all the factors in their associations with HRQOL.

## Limitations

The number of patients with active disease (mostly mild clinical disease activity) was low (25%), although this number is often found in population-based cohorts of patients with IBD. It may be that the associations between the psychological variables and HRQOL are not the same for patients that have more active disease. Nevertheless, studies with a higher proportion of patients with active disease reported similar re-

sults [6, 22, 71, 72]. However, despite these findings, it is still possible that for patients with moderate to severe clinical disease activity, the relationships between illness perceptions, depression and HRQOL are different. Since evidence has been found for a negative impact of clinical disease activity on anxiety, depression and/or HRQOL (e.g.[11, 26]), even stronger relationships may be found in patient populations with more active disease. Another limitation is that our data were cross-sectional and conclusions on causal relationships cannot be drawn. Longitudinal studies are needed to examine causal relationships over time. Until now, only few studies have been conducted that were able to draw conclusion on causal relationships. For example, a recent study in adults with IBD found evidence for a bidirectional and causal relationship between disease activity and anxiety/depression [80]. However, such studies have not been conducted investigating HRQOL. A last limitation is that we had a response rate of approximately 70%, which can have caused bias, for example if patients with a lower HRQOL were more inclined to participate than those with higher HRQOL. However, we were not able to compare the HRQOL of responders and non-responders.



## Clinical implications

These results stress the importance of psychological factors for HRQOL in youth with IBD, over and above demographic and disease variables. In our study sample, 75% of the patients were in clinical remission. Therefore, treating (pediatric) gastroenterologists should pay attention to these psychological factors, in all patients and not only in patients with active disease. We recommend screening for negative illness perceptions and internalizing problems. This can be done either during a medical visit or using short (online) questionnaires prior to the medical visit. Our results also have implications for psychological treatment of these patients: interventions for improving HRQOL should focus on negative illness perceptions and depression, and also on anxiety for youth with UC/IBD-U. For example, cognitive behavioral therapy (CBT) has been proven effective in using techniques to restructure thoughts, such as negative illness perceptions [81]. Importantly, at the beginning of a psychological intervention disproportionate, unrealistic or incorrect thoughts and ideas should be identified. At this phase, it is important to determine whether a patient has disproportionate or incorrect negative illness perceptions. These can then be crucial when practicing cognitive and behavioral techniques. Naturally, the techniques of CBT can be used to improve depression and anxiety as well [82, 83].

In conclusion, our study found that negative illness perceptions and depression are negatively associated with HRQOL in youth with IBD, even after controlling for several demographic and disease factors, with also other psychological factors (i.e. coping, anxiety) taken into account. These factors seriously influence HRQOL, even in our cohort with low clinical disease activity, and should be considered by the medical

team. Our results indicate that, irrespective of the clinical disease activity, psychological treatment should focus on the way these young IBD patients perceive their disease and on their depressive symptoms. For youth with UC and IBD-U, anxiety and worries should receive attention as well.

## Compliance with ethical standards

### Disclosure of potential conflicts of interest

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### Informed consent

Informed consent was obtained from all individual participants included in the study.

### Research involving human participants and/or animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

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# Effectiveness of disease-specific cognitive behavioral therapy on anxiety, depression and quality of life in youth with inflammatory bowel disease: a randomized controlled trial

Luuk Stapersma, Gertrude van den Brink, Jan van der Ende, Eva M. Szigethy, Ruud Beukers, Thea A. Korpershoek, Sabine D.M. Theuns-Valks, Manon H.J. Hillegers, Johanna C. Escher, Elisabeth M.W.J. Utens

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## ABSTRACT

**Objective** To evaluate the effectiveness of a disease-specific cognitive behavioral therapy (CBT) protocol on anxiety and depressive symptoms, and health-related quality of life (HRQOL) in adolescents and young adults with inflammatory bowel disease (IBD).

**Methods** A parallel group randomized controlled trial, conducted in 6 centers of (pediatric) gastroenterology. Included were 70 adolescents and young adults (10-25 years) with IBD and subclinical anxiety and/or depressive symptoms. Patients were randomized into two groups, stratified by center: a) standard medical care (care-as-usual; CAU) plus disease-specific manualized CBT (Primary and Secondary Control Enhancement Therapy for Physical Illness; PASCET-PI), with 10 weekly sessions, 3 parent sessions and 3 booster sessions (n=37) or b) CAU only (n=33). Primary analysis concerned the reliable change in anxiety and depressive symptoms after 3 months (immediate post-treatment assessment). Exploratory analyses concerned 1) the course of anxiety and depressive symptoms and HRQOL in subgroups based on age, and 2) the influence of age, gender, and disease type on the effect of the PASCET-PI.

**Results** Overall, all participants improved significantly in their anxiety and depressive symptoms and HRQOL, regardless of group, age, gender, and disease type. Primary chi-square tests and exploratory linear mixed models showed no difference in outcomes between the PASCET-PI (n=35) and the CAU group (n=33).

**Conclusions** In youth with IBD and subclinical anxiety and/or depressive symptoms, preliminary results of immediate post-treatment assessment indicated that a disease-specific CBT added to standard medical care did not perform better than standard medical care in improving psychological symptoms or HRQOL. ClinicalTrials.gov: NCT02265588.

## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are two types of inflammatory bowel disease (IBD). IBD is a chronic disease, that is characterized by episodes of exacerbation (with increased clinical symptoms) and clinical remission. Symptoms are abdominal pain, (bloody) diarrhea, fatigue, fever, and weight loss [1]. In pediatric IBD (especially CD) malnutrition, resulting in delay of growth and puberty is common [2]. Adolescents and young adults (also referred to as youth) with IBD have a high risk for anxiety and/or depression [3], possibly related to the unpredictable disease course and embarrassing symptoms [4]. Moreover, the inflammation-depression(-/anxiety) hypothesis is thought to explain the bidirectional association between inflammation in IBD and anxiety and/or depression. This hypothesis states that inflammation increases vulnerability for emotional symptoms and that treating these symptoms can decrease inflammation and thus improve disease course [5].

In general, prevalence studies show elevated levels of anxiety and depressive symptoms in respectively 39-50% [6, 7], and in 38-55% [8, 9] of adolescents with IBD. Only, a few studies report lower prevalence rates [10]. Furthermore, a meta-analysis showed higher rates of depressive and internalizing disorders in IBD youth, compared to other chronic conditions [4].



At present, cognitive behavioral therapy (CBT) is the most effective evidence-based psychological treatment for anxiety and depression in youth [11]. Until now, only a few studies evaluated CBT for youth with IBD. In a randomized controlled trial (RCT) Szigethy et al. [12] found promising results of a disease-specific CBT in reducing depressive symptoms in 41 adolescents with IBD and subclinical depression. Furthermore, in a later study (N=178) the same disease-specific CBT was effective in reducing depressive symptoms and improving health-related quality of life. However, supportive nondirective therapy (SNDT) had equally favorable outcomes [9]. Reigada et al. [13] found improvement in anxiety, pain, and disease activity in 9 adolescents with anxiety disorders receiving CBT. In addition, a large recent trial in pediatric patients with IBD (N=185), not selected on the presence of either somatic or psychological symptoms at baseline, examined the effect of a social learning and cognitive behavioral therapy (SLCBT) of only three sessions versus educational support. Although SLCBT outperformed educational support in improving IBD-related quality of life and school attendance, the authors found no difference between the two groups on anxiety and depression. The authors proposed low levels of disease activity and the short duration of the psychological treatment as possible explanations [14].

Taken together, CBT for youth with IBD seems beneficial. The mixed findings described above may be due to differences in the included patients, since some studies focused on either anxiety or depression separately [9, 12, 13] or included all IBD

patients rather than those selected on anxiety or depression [14]. However, anxiety can precede depression, and anxiety and depression often occur together [15, 16], so investigating both is important. Moreover, for CBT to be effective for anxiety/depression, patients have to experience at least elevated levels of anxiety and/or depressive symptoms, so selecting patients at baseline may be necessary [17]. Therefore, the present multi-center RCT aims to test the effectiveness of a disease-specific CBT on symptoms of both anxiety and depression, as well as on health-related quality of life (HRQOL) in adolescents and young adults with IBD (age 10-25 years). This age range was chosen to cover the clinically relevant phases of adolescence and young adulthood, when IBD is often diagnosed [2] and can affect the many psychosocial changes that take place (e.g. becoming independent and identity formation).

The primary research question was: Compared to standard medical care only, what is the effect of a disease-specific CBT added to standard medical care, on the level of anxiety and depressive symptoms, from pre- to post assessment, in adolescents and young adults with IBD aged 10-25 years?

Additional research questions were: 1) What is the course of anxiety and depressive symptoms and HRQOL in subgroups based on age, regarding the effect of CBT? And 2) What is the influence of age, gender, and disease type on the course of anxiety and depressive symptoms and HRQOL, regarding the effect of CBT? By these questions we aim to examine which patients may benefit most from the disease-specific CBT. We hypothesized that patients in the disease-specific CBT group would improve more on anxiety and/or depressive symptoms and HRQOL compared to patients who received only standard medical care. In addition, we expected to find more effect of CBT in young adult patients (as they already face more life challenges, and could benefit more from the CBT skills than children), in women (as they often experience more anxiety and/or depressive symptoms than men) and in patients with CD (as the systemic symptoms in CD increase the burden of disease). We also investigated how patients (and parents) evaluate the disease-specific CBT (i.e. what is the social validity of the disease-specific CBT).

## METHODS

### Design and procedure

This multi-center parallel group randomized controlled trial was designed according to the CONSORT guidelines for trials of non-pharmacologic treatments [18]. The trial had two arms. Patients in the experimental group received a disease-specific CBT protocol (Primary and Secondary Control Enhancement Training for Physical Illness; PASCET-PI) [12] added to standard medical care. The control group received standard

medical care (care-as-usual, CAU) only, as this resembles the current care best. Initially, only patients aged 10-20 years were included. A few months after the start of the recruitment, patients of 21-25 years were also included, to include more patients in young adulthood as well, to cover the transition phase. The research protocol was approved by the Medical Ethics Committee of the Erasmus MC and confirmed by the ethical boards of all participating hospitals. The study was registered with ClinicalTrials.gov as study number NCT02265588.

After having provided written informed consent, patients (and parents) completed validated psychological instruments at 2 points in time (see Outcome measures). At baseline, patients completed online questionnaires (at home) and a clinical interview (by phone) (no longer than 2 weeks before the start of the PASCET-PI). The immediate post(-treatment) assessment was similar to the baseline and was performed approximately 3 months after baseline, no later than 2 weeks after completing the PASCET-PI. Timing and method of assessments were the same in the experimental and control group.

## Recruitment (see also Figure 1)

### Step 1: Inclusion baseline screening

Included for baseline screening for symptoms of anxiety and depression were adolescents and young adults aged 10-25 years with a confirmed diagnosis of IBD (Crohn's disease, ulcerative colitis or inflammatory bowel disease unclassified). Between October 2014 and October 2016, patients were consecutively recruited from the pediatric or (pediatric) gastroenterology departments of 2 academic hospitals and 4 community hospitals. The centers were medium sized to large hospitals from mixed rural and urban regions. Parents participated for all patients aged 17 years or younger, parental participation for patients aged 18-20 was voluntary. *Exclusion* criteria were 1) intellectual disability, 2) current treatment for mental health problems (pharmacological and/or psychological), 3) insufficient mastery of the Dutch language, 4) a diagnosis of selective mutism, bipolar disorder, schizophrenia/psychotic disorder, autism spectrum disorders, obsessive-compulsive disorder, posttraumatic or acute stress-disorder, or substance use disorder (parent- or self-reported or from medical file), 5) CBT in the past year (at least 8 sessions), and 6) participation in another interventional study, all assessed by the treating physician using medical files (unless otherwise specified).

### Step 2: Inclusion RCT

Only youth with subclinical anxiety and/or depressive symptoms were included in the RCT. Patients with clinical anxiety and/or depression were excluded since we deemed it unethical to randomize them.

Subclinical anxiety and/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/or depression (see below). For anxiety the Screen for Child Anxiety Related Emotional Disorders (SCARED; 10-20 years; cutoff ≥26 for boys and ≥30 for girls) [19] and the Hospital Anxiety and Depression Scale – Anxiety Scale (HADS-A; 21-25 years; cutoff ≥8) [20] were used. For depression the Child Depression Inventory (CDI; 10-17 years; cutoff ≥13) [21] and the Beck Depression Inventory – second edition (BDI-II; 18-25 years; cutoff ≥14) [22] were used.

Clinical anxiety and/or depression was defined as follows: for patients who scored on or above the cutoffs for elevated symptoms of anxiety and/or depression, the psychologist-investigator (LS) administered a clinical interview. The Anxiety Disorders Interview Schedule for Children (ADIS-C) [23] was delivered by telephone to patients, and if applicable, parents. In the ADIS-C, if a patient meets criteria for a clinical disorder a Clinician's Severity Rating (CSR, a 0-8 rating of symptom severity and functional impairment) is assigned by the interviewer. In addition, severity of anxiety and/or depressive symptoms was rated by the interviewer using age-appropriate rating scales. For anxiety the Pediatric Anxiety Rating Scale (PARS; 10-20 years; cutoff ≥18) [24] and Hamilton Anxiety Rating Scale (HAM-A; 21-25 years; cutoff ≥15) [25, 26] were used. For depression the Child Depression Rating Scale Revised (CDRS-R; 10-12 years; cutoff ≥40) [27], Adolescent Depression Rating Scale (ADRS; 13-20 years; cutoff ≥20) [28], and the Hamilton Depression Rating Scale (HAM-D; 21-25 years; cutoff ≥17) [29, 30] were used. If patients met criteria for an anxiety or depressive disorder on the ADIS-C (i.e. a CSR of at least 4) and score equal to or above the clinical cutoff on the rating scale this indicates a clinical anxiety or depressive disorder. These patients were excluded and received immediate referral to mental health care. Within the group of patients included in the RCT (all with subclinical anxiety and/or depressive symptoms, n = 70) a subdivision was made based on the ADIS-C. If patients had one or more CSR's of at least 4 (but scored below the cutoff on either the CDRS, ADRS, HAM-D, PARS or HAM-A) they were considered 'high' subclinical, if not they were considered 'low' subclinical.

## Randomization

Patients with subclinical anxiety and/or depressive symptoms (but not clinical anxiety and/or depression) were randomized to PASCET-PI and CAU versus CAU alone, with a ratio of 1:1 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 one of the investigators (GB). To prevent drop-out, before randomization it was thoroughly checked with the patients whether they would be motivated enough to complete the

CBT. For example, they were asked about their motivation and concerns regarding traveling and time investment, or regarding discussing private information.

## Intervention

The PASCET-PI is a disease-specific CBT protocol, developed for adolescents with IBD and depression. Disease-specific components encompass the illness narrative (i.e. perceptions and experience of having IBD), disease-specific psycho-education, techniques for pain and immune functioning, social skills training and emphasis on IBD related cognitions and behavior [12]. Parents receive psycho-education about coaching their child to cope with IBD.

In the current study the PASCET-PI contained ten weekly individual sessions, delivered in three months. Conform the protocol, six of these sessions were face-to-face, the remaining 4 sessions were by phone at a pre-arranged moment (to advance adherence and lower the treatment burden). In addition, 3 family sessions (for patients and their parents) were held (only for patients ≤ 20 years), and following the weekly sessions, 3 monthly individual booster sessions were held by telephone (this was after the immediate post[-treatment] assessment). As the original PASCET-PI was developed for depression, therapists were instructed how to make the exercises more anxiety-tailored, an anxiety hierarchy and step-by-step exercise was added, and an extra anxiety hand-out was provided to the patients. For patients 21-25 years of age the practice book was made more age-appropriate. See Van den Brink & Stapersma et al. [31] or Appendix 1 for a more detailed description of this Dutch modification of the PASCET-PI. The therapy was provided by all licensed (healthcare/CBT) psychologists, who received onsite training from the developer (EMS) and performed the therapy in their own hospital or center. To ensure treatment integrity, monthly supervision was provided by EMWJU (clinical psychologist/professor) and audiotaped sessions were rated by EMWJU and five master level Psychology students. Of all sessions, 30% was rated on adherence by at least one rater, and of that 30% half was evaluated by at least 2 raters (i.e. 15% of all sessions). Audiotapes were randomly selected to be rated by two of the raters. However, which pair of two raters rated the sessions varied strongly, so there were too few standardized pairs of raters to use for example intraclass correlation [32]. Therefore, interrater agreement was globally calculated using Pearson's correlation between two data columns with 1) all first ratings and 2) all second ratings for all patients and sessions combined. CAU consisted of regular medical appointments with the (pediatric) gastroenterologist every 3 months, consisting of a 15 minute consultation discussing overall wellbeing, disease activity, results of diagnostics tests, medication use, and future diagnostic/treatment plans.

## Outcome measures (online questionnaires)

**Demographic data** were assessed with a general questionnaire, based on a semi-structured interview [33]. Socioeconomic status was based on occupational level from parents or, if they lived on their own, patients themselves. It was divided into low, middle, and high [34]. Ethnicity was based on mother's country of birth or if the mother was born in the Netherlands, the father's country of birth [35]. Disease characteristics were extracted from the 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). It contains five subscales: general anxiety disorder, separation anxiety disorder, specific phobia, panic disorder, and social phobia [19, 36]. The anxiety scale of the HADS has 7-items with 4 response categories (0-3, total score 0-21) [20]. Internal consistency was .86 and .92 for the SCARED and .54 and .77 for the HADS-A at baseline and follow-up, respectively (Cronbach's $\alpha$).

**Symptoms of depression** were assessed using the CDI (for 10-17 years) and the BDI-II (for 18-25 years) self-report symptom scales. The CDI has 27-items with 3 response categories (0-2, total score 0-54) [21]. The BDI-II has 21-items with 4 response categories (0-3, total score 0-63) [22]. Internal consistency was .70 and .77 for the CDI and .54 and .83 for the BDI-II at baseline and follow-up, respectively.

**Health-related quality of life** was assessed with the self-reports IMPACT-III (10-20 years) and Inflammatory Bowel Disease Questionnaire (IBDQ; 21-25 years). The IMPACT-III has 35 items, scored 1-5 (total score 35-175) [37]. The IBDQ contains 32 items, scored 1-5 (total score 32-160) [38]. A higher score of both instruments indicates better quality of life. Internal consistency was .86 and .89 for the IMPACT-III and .71 and .92 for the IBDQ at baseline and follow-up, respectively.

**Clinical disease activity** was assessed with four validated clinical disease activity measures. For patients of 10-20 years with CD the short Pediatric Crohn's Disease Activity Index (sPCDAI) [39] was used, whereas for patients with UC and IBD-U the Pediatric Ulcerative Colitis Activity Index was used (PUCAI) [40]. For patients of 21-25 years with CD the Crohn's Disease Activity Index (CDAI) [41] was used, whereas for patients with UC and IBD-U the partial Mayo score [42] was used. All indices were scored by the physician during the medical visit and provide four categories of clinical disease activity: remission, mild, moderate, and severe.

**Social validity** questions were included in the online questionnaire to gain insight in how the patients in the CBT group (and if applicable parents) evaluated the PASCET-PI. For this study we chose to assess three relevant aspects of social validity: satisfaction, usefulness, and recommendation. Patients and/or parents awarded 3 items with 0-10 points (0 = "Not at all" to 10 = "Very much") regarding 1) their satisfaction with

the protocol, 2) how useful it was for them, and 3) whether they would recommend it to other patients.

## Blinding

The interviewer (LS) and treating physicians were blinded for the result of randomization (they were not informed and had no access to files containing this information). Patients could not be blinded. They were explicitly asked not to discuss the group they were randomized into with their physician.

## Statistical analysis

Descriptive statistics were computed for demographic and disease characteristics. Independent t-tests and chi-square tests were used to assess differences between these variables in the two groups at baseline. An intention-to-treat principle was applied in the analyses.

For each participant we calculated a Reliable Change Index (RCI) [43] value for anxiety and depression (but not for HRQOL, since no data on test-retest reliability was available for the HRQOL instruments, which is necessary to calculate the RCI). By calculating RCI's, we were able to combine all participants in one analysis. The RCI is calculated using the standard error of measurement (SEM) of the pretest and the test-retest reliability of the instrument. The RCI can have three possible values: reliably improved, no reliable change, and reliably deteriorated. See Appendix 2 for the details of calculating the RCI variable. A chi-square test was used to compare the RCI values between the two groups, using complete cases (n = 68). For exploratory analyses we first used six linear mixed models (which take into account missing data) to compare change between the groups from baseline to directly after CBT for anxiety (SCARED or HADS-A), depression (CDI or BDI-II), and HRQOL (IMPACT-III or IBDQ). Time, group (PASCET-PI vs. CAU) and the interaction between time and group were included as fixed factors. We repeated these linear mixed models in subgroups to examine the influence of gender, and disease type. The influence of age is incorporated in the first set of linear mixed models, as the questionnaires for the specific age-group were used. Using an Identity covariance structure, random intercepts were estimated for each participant. No random slopes could be specified, because we only had two time points. Restricted maximum likelihood (REML) was applied as estimation method. A *p*-value of less than .05 was considered statistically significant. Reported Cohen's d's represent the effect size between groups at follow-up. For the SCARED, HADS-A, CDI, and BDI-II a negative effect size is in favor of CBT, for the IMPACT-III and IBDQ a positive effect size is in favor of CBT. Data were analyzed using SPSS version 21.

### Sample size and power

Considering literature regarding effectiveness of CBT for anxiety and depressive symptoms in youth without a somatic disease, as well as earlier studies of CBT in youth with IBD [9], we expected medium to large effects on anxiety symptoms [44] and medium effects for depressive symptoms [45]. This corresponds to $\varphi$ >0.40 for anxiety symptoms, and to $\varphi$ >0.30 for depressive symptoms. For the chi-square tests for anxiety and depressive symptoms this means that a total of 70 patients provides us with sufficient power for the anxiety outcomes (>85%) and with medium power for the depression outcomes (>60%).

## RESULTS

### Demographic, disease and intervention characteristics

Figure 1 displays the patient flow throughout the study. In total, 70 patients were randomized (10-20 years n = 50, 21-25 years n = 20). In Table 1 demographic and disease characteristics are displayed for both groups. No significant differences were found between the PASCET-PI group and the CAU group on demographics (e.g. gender, age) and disease characteristics (disease type, duration, activity), neither as to whether patients were included based on anxiety, depression or both.

Regarding treatment integrity, in the PASCET-PI group 33 (89.2%) patients followed all 10 treatment sessions, 1 patient (2.7%) followed 8 sessions, 1 patients (2.7%) followed 5 sessions, 1 patient (2.7%) followed 3 sessions and 1 patient (2.7%) followed 1 session. The mean number of treatment sessions followed was 9.38. In the 21 patients of whom parents participated as well, 76.2% of the parents followed all three family sessions. The mean number of family sessions was 2.57. In all sessions at least 75%, and in 75% of the sessions at least 80% of the required topics were discussed, indicating good adherence to the protocol (i.e. treatment integrity). A global estimation of interrater agreement, over all sessions and patients combined, was calculated. Treatment adherence ratings correlated .41 between the 6 raters [46]. No patients in the control group sought mental health care and no study-related adverse events occurred during the trial.

### Effect of disease-specific CBT on symptoms of depression and anxiety, HRQOL

As some cells in the cross-tabulation were smaller than 5, a Fisher's exact test was performed. In the primary analysis, RCI values did not differ between the two groups for both anxiety ($\chi^2$ (2) = 1.656, $p$ = .465, $\varphi$ = .159) and depression ($\chi^2$ (2) = 1.648, $p$ =

.523, φ = .161), see Table 2. Overall, patients in both groups either remained stable or improved in their symptoms of anxiety and depression.

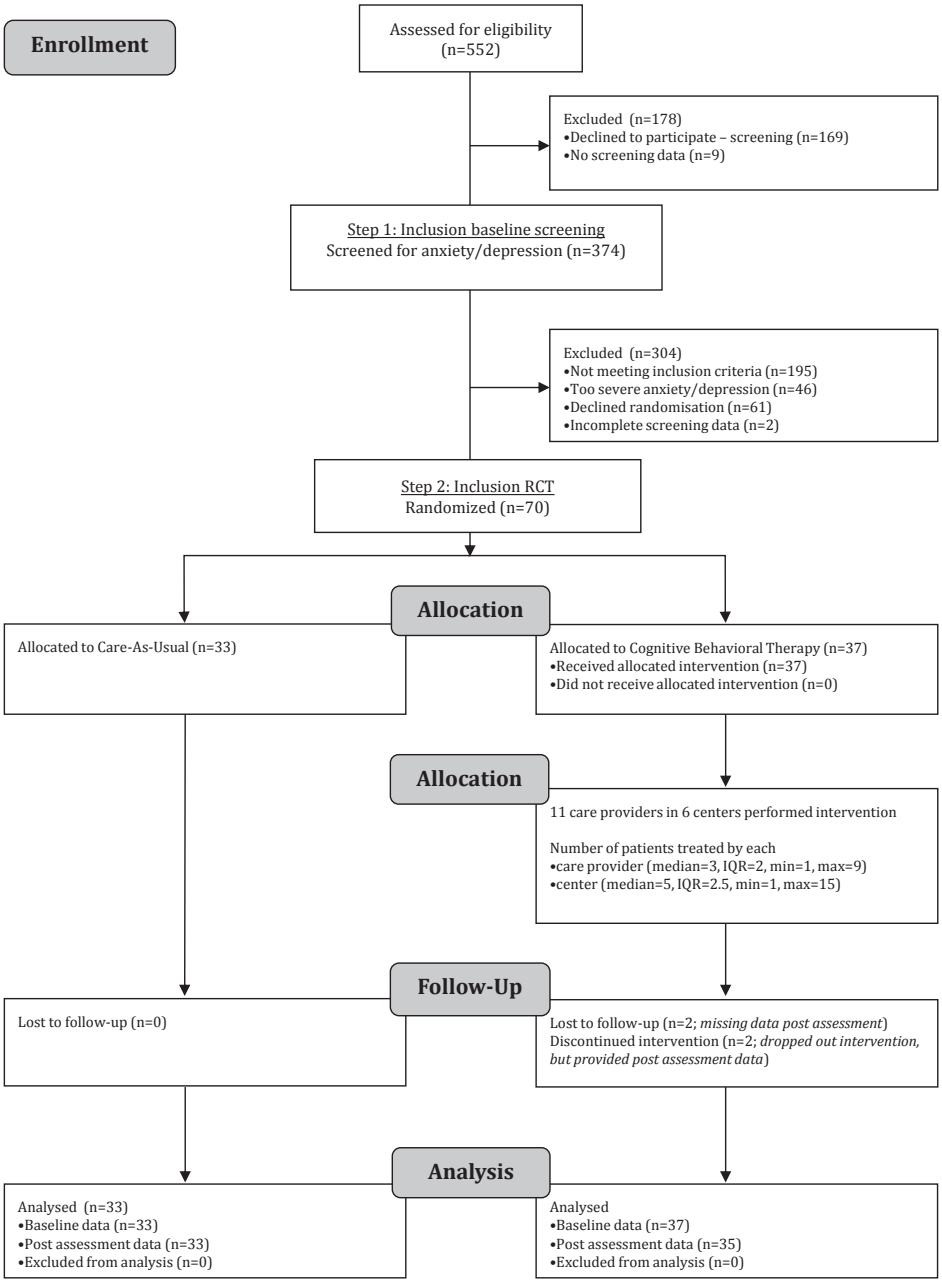


**Figure 1** | CONSORT study flow chart
Abbreviations: RCT= randomized controlled trial; IQR= inter quartile range

**Table 1** | *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) | |
| Disease duration, median, years | 2.59 | 1.17 | .039[d] |

**Table 1** | *Baseline demographic and disease characteristics (continued)*

| | PASCET-PI group (n=37) | CAU group (n=33) | *p value* |
|---|---|---|---|
| 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] |

***Note***: all demographic and disease characteristics were not significantly different between groups, except disease duration

***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 | * 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)

**Table 2** | *Crosstabulation RCI of symptoms of anxiety and depression versus group*

| | No reliable change | Reliable increase of score / deterioration | Reliable decrease of score / improvement | Total |
|---|---|---|---|---|
| RCI categories anxiety (SCARED or HADS-A) | | | | |
| CAU | 20 (60.6%) | 0 (0%) | 13 (39.4%) | 33 |
| CBT | 17 (48.6%) | 1 (2.9%) | 17 (48.6%) | 35 |
| $\chi^2$ =1.656, df = 2, $p$ = .465, $\phi$ = .159 (95%BI 0.00-0.36). Numbers in parentheses indicate row percentages | | | | |
| RCI categories depression (CDI or BDI-II) | | | | |
| CAU | 14 (42.4%) | 1 (3.0%) | 18 (54.5%) | 33 |
| CBT | 14 (40.0%) | 4 (11.4%) | 17 (48.6%) | 35 |
| $\chi^2$ =1.648, df = 2, $p$ = .523, $\phi$ = .161 (95%BI 0.00-0.37). Numbers in parentheses indicate row percentages | | | | |

In the exploratory analyses (see Table 3) the same pattern was seen. No significant time-group interaction effect was found for anxiety (SCARED n=50: $t$(47.460) = -0.639, $p$ = .526, $d$ = -0.15; HADS-A n=20: $t$(16.047) = 0.976, $p$ = .343, $d$ = -0.06), depression (CDI n=35: $t$(32.004) = -1.272, $p$ = .212, $d$ = -0,11; BDI-II n=35: $t$(30.739) = -0.363, $p$ = .719, $d$ = -0.47), and HRQOL (IMPACT-III n=50: $t$(45.363) = 1.033, $p$ = .315, $d$ = 0.23; IBDQ n=20: $t$(18.124) = -0.539, $p$ = .597, $d$ = 0.44). For the SCARED ($t$(48.059) = -5.709, $p$ < .001), HADS-A ($t$(16.431) = -4.375, $p$ < .001), the BDI-II ($t$(31.236) = -4.778, $p$ < .001), the IMPACT-III ($t$(45.849) = 4.847, $p$ < .001), and the IBDQ ($t$(18.738) = 2.367, $p$ < .05) the effect of time was significant, for the CDI this was not the case ($t$(32.525) = -1.554, $p$

= .130). These findings show that, after three months, all patients improved in their symptoms of anxiety and depression, as well as in their HRQOL. Even when these analyses were carried out only in patients who showed relatively 'high' subclinical problems ('high' n=40 vs. 'low' n=30), no group differences were found on the anxiety and depression outcomes (data not shown).

## Influence of age, gender, and disease type on effect of disease specific CBT on anxiety and depression

In exploratory analyses for the four separate age groups (classified by the four age-attuned questionnaires: SCARED [10-20 years], HADS [21-25 years], CDI [10-17 years], BDI-II [18-25 years)] no differences were found between the groups as to the change in anxiety, depression, or HRQOL. As we did not find group differences in all four age groups, an age effect seems absent. We explored the possible influence of gender and disease type on the effect of the PASCET-PI by conducting linear mixed model analyses separately in subgroups (male vs. female and CD vs. UC & IBD-U). Overall, none of the subgroup analyses showed a difference between two groups on either anxiety, depression, or HRQOL, except for a significant lower score on the BDI-II in the CAU group (n=6) than in the CBT group (n=3) for the subgroup analysis in males (data not shown). Therefore, gender and disease type do not seem to influence the effect of CBT.

## Social validity

With respect to satisfaction, patients reported a mean of 7.82 (out of 10), whereas parents reported a mean of 7.50 (out of 10). Mean scores of patients and parents for usefulness were 6.82 and 6.06 (out of 10), respectively. Furthermore, patients reported a mean of 6.96 (out of 10) for recommending it to other patients, and parents reported a mean of 7.25 (out of 10). These results indicate that, in general, patients and their parents evaluated the PASCET-PI positively.

**Table 3** | *Estimated Marginal Means at Baseline and after 3 months for Anxiety, Depression and Health-Related Quality of Life*

| Variable | Baseline | | 3 Months | *p* (time effect) | *p* (time x group) | Cohen's *d* (95%CI) (after 3 months) |
|---|---|---|---|---|---|---|
| SCARED (0-138) | Mean (SE) | | Mean (SE) | | | |
| CBT | 36.2 (2.7) | → | 22.9 (2.6) | < .001 | | |
| CAU | 40.5 (2.8) | → | 25.0 (2.9) | | | |
| CBT vs. CAU | | | | | .526 | -0.15 (-1.02-0.71) |
| HADS-A (0-14) | | | | | | |
| CBT | 9.9 (0.7) | → | 7.1 (0.7) | < .001 | | |
| CAU | 9.1 (0.8) | → | 7.3 (0.8) | | | |

**Table 3** | *Estimated Marginal Means at Baseline and after 3 months for Anxiety, Depression and Health-Related Quality of Life (continued)*

| Variable | Baseline | 3 Months | *p* (time effect) | *p* (time x group) | Cohen's *d* (95%CI) (after 3 months) |
|---|---|---|---|---|---|
| CBT vs. CAU | | | | .343 | -0.06 (-1.49-1.37) |
| CDI (0-54) | | | | | |
| CBT | 8.5 (1.1) | → 7.2 (1.1) | .130 | | |
| CAU | 10.8 (1.2) | → 7.7 (1.2) | | | |
| CBT vs. CAU | | | | .212 | -0.11 (-1.11-1.02) |
| BDI-II (0-63) | | | | | |
| CBT | 11.3 (1.1) | → 5.9 (1.1) | < .001 | | |
| CAU | 14.2 (1.2) | → 8.2 (1.2) | | | |
| CBT vs. CAU | | | | .719 | -0.47 (-1.51-0.58) |
| IMPACT-III (35-175) | | | | | |
| CBT | 137.1 (2.8) | → 148.1 (2.8) | < .001 | | |
| CAU | 137.4 (2.9) | → 144.9 (3.0) | | | |
| CBT vs. CAU | | | | .315 | 0.23 (-1.28-0.49) |
| IBDQ (32-224) | | | | | |
| CBT | 164.6 (5.8) | → 179.6 (5.8) | < .001 | | |
| CAU | 161.6 (6.4) | → 171.2 (6.7) | | | |
| CBT vs. CAU | | | | .597 | 0.44 (-2.02-0.77) |

***Note***. For the SCARED, HADS-A, CDI, and BDI-II a negative Cohen's *d* favors CBT, for the IMPACT-III and IBDQ a positive Cohen's *d* favors CBT.

## DISCUSSION

The current study, which had very low attrition (< 3%), tested the effect of a disease-specific CBT compared to CAU in reducing subclinical anxiety and/or depressive symptoms and in improving HRQOL, in adolescents and young adults with IBD. At the immediate post(-treatment) assessment disease-specific CBT added to standard medical care did not perform better than standard medical care. Overall, both the PASCET-PI and CAU group significantly improved over time, on all three outcomes, 3 months after baseline (i.e. at the immediate post[-treatment] assessment). Furthermore, in subgroup analyses we did not find indications for differences between age groups, boys versus girls, nor between CD and UC/IBD-U regarding the effect of the PASCET-PI on anxiety, depression, or HRQOL. Our results are in contrast to results of earlier trials with positive findings of CBT treatment for youth with IBD [9], but are in accordance with some of the evidence from studies in adults with IBD [47]. There are several explanations for our findings.

First, just by participating in the study, patients in the CAU group did not exactly receive standard medical care. They were psychologically assessed at two points in time with questionnaires and interviews. This is not done in routine practice and therefore it provided additional exposure to attention from professionals. Usually, only if psychological problems are obvious, the medical team refers patients for mental health care. CAU was chosen as comparison condition, because it resembles the current care for youth with IBD in our institute best. However, mere participation in the trial may have had a positive effect on all patients due to increased awareness and (unintended) psychoeducation. It has been described before that merely answering questions or participate in a trial can influence behavior or emotions. For example, McCambridge [48] recently described that the 'question-behavior effect' can occur in randomized trials. Moreover, Arrindell [49] has described the re-test effect: in patients with psychiatric problems mean scores of psychopathology often decrease at follow-up (without any formal intervention). A first assessment can heighten awareness of anxious or depressive symptoms, which can cause an respondent to try to deal with these symptoms (by talking more about it or try to think different) or lead to more introspection or self-monitoring [49]. The awareness caused by receiving information about the study and receiving the psychological assessment may have contributed to the fact that all patients improved. It can be perceived as some form of support, like in the control conditions of earlier trials in youth with IBD [9, 14].

Second, the overall patient group had a low disease burden, both psychologically as well as somatically. Included patients experienced only subclinical anxiety and/or depressive symptoms, as randomization was not ethical for patients with clinical mental health disorders. We mainly included patients in clinical remission, because for patients with severe disease activity adherence to the CBT protocol might have been complex. For the subclinical anxiety and/or depressive symptoms mere participation may have been enough to improve. This raises the question: which IBD-patients should receive psychological treatment? When we analyzed those patients with the highest levels of subclinical anxiety and/or depressive symptoms still no differences between CBT and CAU were observed. However, a recent trial showed a significant effect of CBT compared to a waiting list on QOL, anxiety, and depression in adult IBD patients, of whom 70% met criteria for a *psychiatric disorder* [50]. This implies that IBD patients with severe psychological problems can actually benefit from CBT. Furthermore, for adolescents with IBD, when compared to supportive therapy, CBT has been shown to improve somatic depressive symptoms as well as clinical disease activity and ESR (Erythrocyte Sedimentation Rate), but only in patients with CD and moderate clinical disease activity [51]. This suggests that patients with active disease can benefit from CBT. For these patients, however, sessions should be delivered with great flexibility, as they may not be able to adhere to weekly 'live' sessions.

Third, the PASCET-PI may not be suited enough to improve subclinical anxiety and/or depressive symptoms. However, an earlier study using the original PASCET-PI protocol in a group of patients selected on *elevated* depression, did find an effect on these subclinical depressive symptoms, and also on comorbid anxiety disorders [12]. In our trial patients experienced more anxiety symptoms than depressive symptoms, which can have influenced the results. Nevertheless, CBT is the most evidence-based psychological therapy for both anxiety and depression [11]. In general, CBT techniques do have an effect on both anxiety and depressive symptoms, with even higher effect sizes found for anxiety than for depression [52]. This implies that PASCET-PI may be effective, as to both anxiety and depressive symptoms. In adults with IBD, mixed results are found with respect to the effectiveness of CBT on psychological as well as somatic symptoms [47, 53]. Several recommendations are made [17, 47] to focus on patients with for example decreased HRQOL or experiencing psychological problems and to take into account high attrition rates in power and sample size calculations. In our trial these recommendations were covered by selecting patients on anxiety and/or depression and by having very low attrition. The mixed findings in IBD are consistent with mixed findings on the effect of preventive CBT programs for subclinical anxiety and/or depression in youth [54]. Since our patients experienced subclinical psychological and somatic symptoms, the treatment can be considered as preventive (for the development of clinical disorders). Further studies are needed to examine this type of preventive effects, especially in patients with IBD, as psychological problems can also affect the disease course [55, 56].



Fourth, although a sample size of 70 participants should be large enough for the expected effect sizes for CBT on anxiety and/or depression, perhaps we would have found a significant group difference with a larger sample size. Originally, to take into account possible attrition, we aimed to enroll 100 patients [31], which we could not achieve. Revised power calculations still indicated that we had sufficient power to investigate the effect of the PASCET-PI, using n = 70. With this sample size one would expect to see at least a trend towards a difference between the two groups, but this was not the case. Moreover, compared to earlier trials, a strength of the present study was the very low attrition rate and that almost all (95%) patients completed disease-specific CBT.

Fifth, it may be possible that the effect of the PASCET-PI sustains on the longer-term, whereas the effect of the control group diminishes over time. The course of IBD can be fluctuating, and perhaps the knowledge and skills taught in the PASCET-PI can be more useful when patients suffer from more disease activity or flares during a longer period of follow-up. Patients themselves often expressed that this was a motivation to participate in the therapy ("I have no complaints now, but the CBT skills can be

useful in the future, when I have a flare"). Data on longer follow-up assessments will be available for analyses later.

In summary, strengths of the current study are that we included patients with a broad and clinical relevant age, with both anxiety and/or depressive symptoms, and that our study had very low attrition. Moreover, no patients in the control group sought mental health care. Furthermore, since our study sites encompass both rural and urban hospitals, this strengthens the generalizability and external validity of our findings. Although the age-specific instruments were most appropriate for the patients in our study, statistically it was a limitation that using different instruments made it difficult to combine all patients in one analysis and that we could perform the linear mixed models only in subgroups. Originally the study was sufficiently powered to analyze mean symptom change of anxiety and depression. Due to the fact that finally multiple instruments had to be used to cover the age-range, this was not possible. However, a revised power calculation for the chi-square analyses with the reliable change index indicated that we had enough power with the total of 70 patients in the RCT. Another limitation was the relatively small sample size. Therefore, our results should be interpreted with caution. We recommend screening for anxiety and/or depressive symptoms in youth with IBD, as these symptoms can affect disease course [55, 56], and health-related quality of life [57]. Subclinical symptoms may develop into more severe psychological disorders which even have a greater impact [58, 59]. CBT may be more effective in patients with more severe psychological symptoms or more IBD disease activity. This, however, should be examined in studies with a different design (i.e. not with standard medical care as comparison condition). Based on our clinical experience, we consider PASCET-PI as suited also for patients with more severe IBD symptoms, but with great flexibility in delivery (over the phone or in the hospital when patients are hospitalized). Yet, future research is needed to find out how the PASCET-PI or CBT can be best delivered to those patients, which patients with IBD benefit most from psychological treatment, but also how the long-term course of disease activity is associated to the long-term course of anxiety/depression.

In conclusion, in our RCT all patients improved in their symptoms of anxiety and depression, and their HRQOL over time (3 months). At the immediate post-treatment assessment, we found no additional effect for a disease-specific CBT on improving subclinical anxiety and depressive symptoms or HRQOL in adolescents and young adults with IBD, when compared to CAU. We hypothesize that the awareness the study elicited and the possible (unintended educational) support provided may have had a strong positive effect on all patients. CBT could be beneficial for patients with more severe psychological symptoms or IBD patients with clinical disease activity.

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## APPENDIX 1. OUTLINE OF THE PASCET-PI [12, 31]

**APPENDIX 1** | Outline of the PASCET-PI [12, 31]

| Session number | Content of session |
|---|---|
| Session 1<br>*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<br>*Live (60 min)* | Mood monitoring, explaining link between feelings, thoughts and behaviors, discussing feeling good and feeling bad, problem-solving |
| Session 3<br>*By telephone (30 min)* | Link between behavior and feelings: **A**ctivities to feel better |
| Session 4<br>*Live (60 min)* | Be **C**alm and Confident: relaxation exercises |
| Session 5<br>*Live (60 min)* | Be Calm and **C**onfident: positive self versus negative self, training social skills |
| Session 6<br>*By telephone (30 min)* | **T**alents: developing talents and skills makes you feel better |
| Session 7<br>*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<br>*By telephone (30 min)* | **H**elp from a friend, **I**dentify the 'Silver Lining', and **N**o replaying bad thoughts |
| Session 9<br>*By telephone (30 min)* | **K**eep trying – Don't give up, making several plans to use the **ACT** & **THINK** skills |
| Session 10<br>*Live (60 min)* | Quiz on **ACT** & **THINK** model, discussing use of **ACT** & **THINK** skills in the future, updating illness narrative |
| Booster 1<br>*By telephone (30 min)* | Several plans to use the **ACT** & **THINK** skills, updating illness narrative, personalizing **ACT** & **THINK** skills |
| Booster 2<br>*By telephone (30 min)* | Several plans to use the **ACT** & **THINK** skills, updating illness narrative, personalizing **ACT** & **THINK** skills |
| Booster 3<br>*By telephone (30 min)* | Several plans to use the **ACT** & **THINK** skills, updating illness narrative, personalizing **ACT** & **THINK** skills |
| Family 1<br>*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<br>*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<br>*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.

## 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 [36]| $S_1$ = 13.389| $S_{diff}$ = 8.253
- HADS-A (21-25 years): $r_{xx}$ = .89 [60] | $S_1$ = 2.373| $S_{diff}$ = 1.113
- CDI (10-17 years): $r_{xx}$ = .86 [21]| $S_1$ = 4.648| $S_{diff}$ = 2.459
- BDI-II (18-25 years): $r_{xx}$ = .93 [22] | $S_1$ = 4.381| $S_{diff}$ = 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.

# 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

Luuk Stapersma, Gertrude van den Brink, Jan van der Ende, Eva M. Szigethy, Michael Groeneweg, Frederieke H. de Bruijne, Manon H.J. Hillegers, Johanna C. Escher, Elisabeth M.W.J. Utens

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## 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 $\varphi$ >0.40 and $\varphi$ >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%, $\beta$ = 0.14) and medium power for the depression outcomes (>60%, $\beta$ = 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.

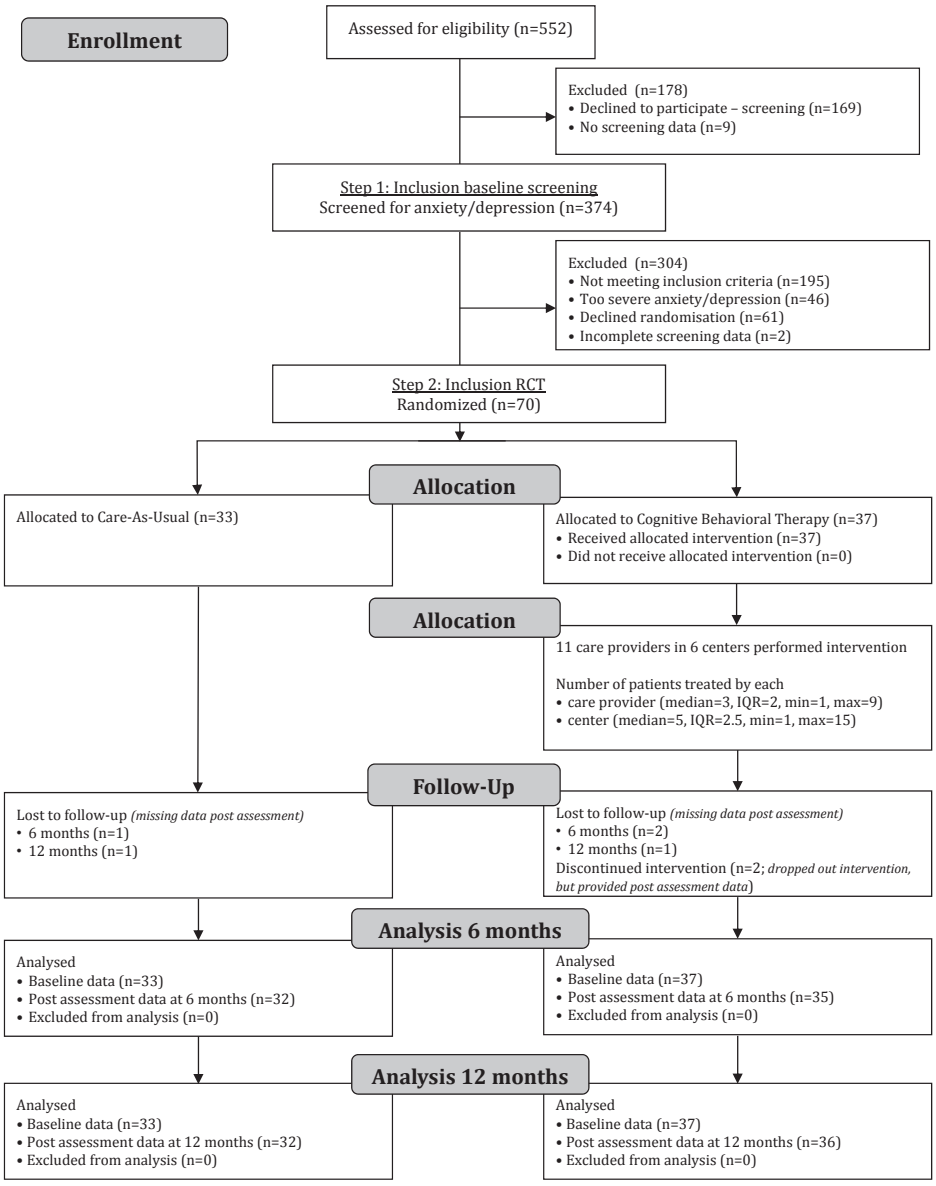


**Figure 1** | CONSORT study flow chart
Abbreviations: RCT= randomized controlled trial; IQR= inter quartile range

## 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 ($\chi^2$ (1) = .226, $p$ = .801) and depression ($\chi^2$ (1) = 2.680, $p$ = .141) after 6 months did not differ between the groups, and neither did the RCI values for anxiety ($\chi^2$ (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 ($\chi^2$ (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 ($\chi^2$ (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 |
| $\chi^2$ = .226, $p$ = .801, $\phi$ = -.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 |
| $\chi^2$= 2.680, $p$ = .141, $\phi$ = .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 |
| $\chi^2$= .337, $p$ = .626, $\phi$ = .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 |
| $\chi^2$= 5.460, $p$ = .026, $\phi$ = .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 ($\chi^2$ (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.

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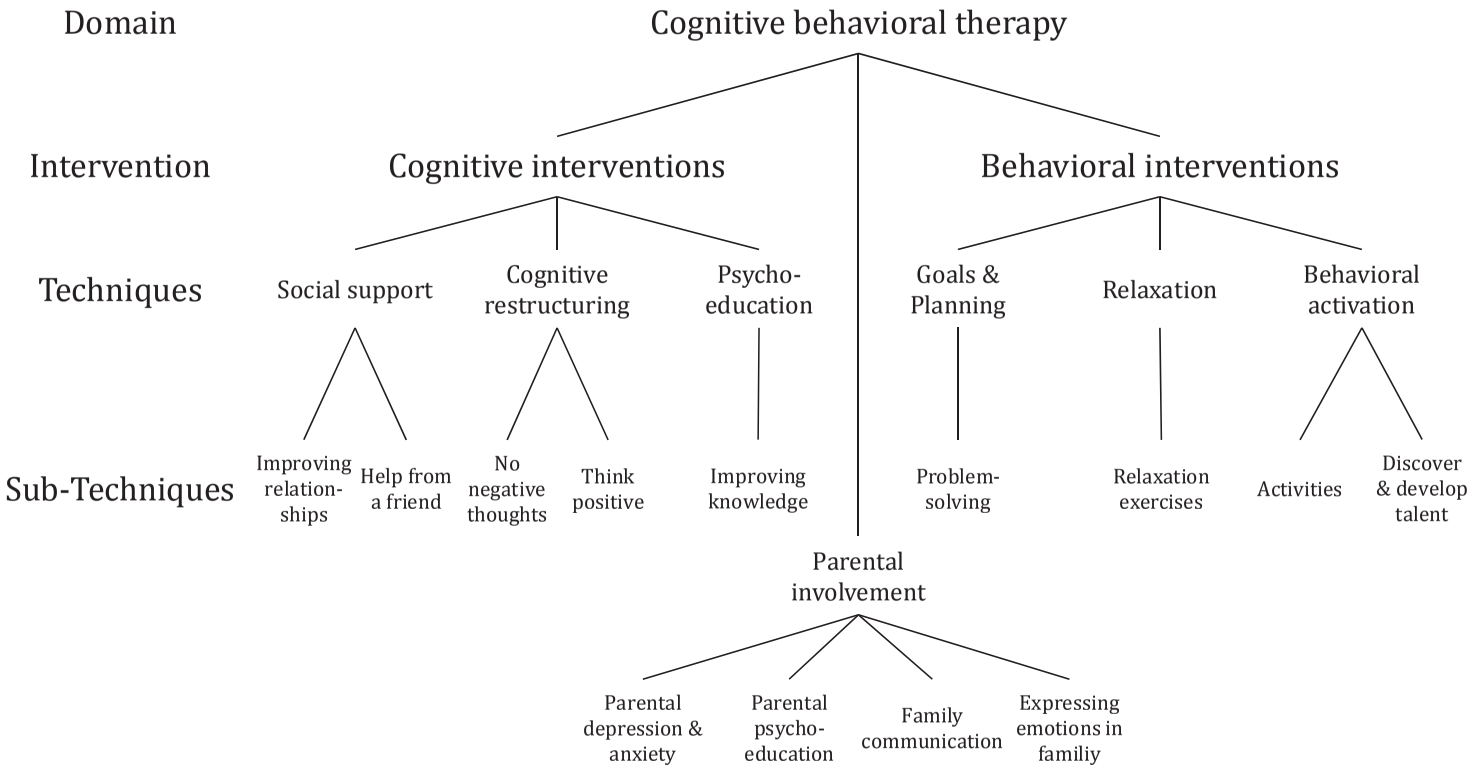
## APPENDIX 1. OUTLINE OF THE PASCET-PI [29, 30] AND TREE DIAGRAM

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

| Session number | Content of session |
|---|---|
| Session 1<br>*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<br>*Live (60 min)* | Mood monitoring, explaining link between feelings, thoughts and behaviors, discussing feeling good and feeling bad, problem-solving |
| Session 3<br>*By telephone (30 min)* | Link between behavior and feelings: **A**ctivities to feel better |
| Session 4<br>*Live (60 min)* | Be **C**alm and Confident: relaxation exercises |
| Session 5<br>*Live (60 min)* | Be Calm and **C**onfident: positive self versus negative self, training social skills |
| Session 6<br>*By telephone (30 min)* | **T**alents: developing talents and skills makes you feel better |
| Session 7<br>*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<br>*By telephone (30 min)* | **H**elp from a friend, **I**dentify the 'Silver Lining', and **N**o replaying bad thoughts |
| Session 9<br>*By telephone (30 min)* | **K**eep trying – Don't give up, making several plans to use the **ACT** & **THINK** skills |
| Session 10<br>*Live (60 min)* | Quiz on **ACT** & **THINK** model, discussing use of **ACT** & **THINK** skills in the future, updating illness narrative |
| Booster 1<br>*By telephone (30 min)* | Several plans to use the **ACT** & **THINK** skills, updating illness narrative, personalizing **ACT** & **THINK** skills |
| Booster 2<br>*By telephone (30 min)* | Several plans to use the **ACT** & **THINK** skills, updating illness narrative, personalizing **ACT** & **THINK** skills |
| Booster 3<br>*By telephone (30 min)* | Several plans to use the **ACT** & **THINK** skills, updating illness narrative, personalizing **ACT** & **THINK** skills |
| Family 1<br>*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<br>*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<br>*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
Cognitive behavioral therapy
Intervention
Cognitive interventions
Behavioral interventions
Techniques
Social support
Cognitive restructuring
Psycho-education
Goals & Planning
Relaxation
Behavioral activation
Sub-Techniques
Improving relation-ships
Help from a friend
No negative thoughts
Think positive
Improving knowledge
Problem-solving
Relaxation exercises
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)

# General discussion

## GENERAL DISCUSSION

### Aims of the present thesis and main results

Young patients with inflammatory bowel disease (IBD) are facing a lifelong disorder that is characterized by episodes of severe clinical symptoms, often accompanied by psychological problems such as anxiety and depression. Currently, there is no cure for IBD, and treatment is aimed at maintenance of remission while maximizing quality of life. Besides medical treatment, focus on the psychological aspects of this disease is essential. Therefore, the aims of this thesis were 1) to investigate the psychological problems in these patients (aged 10-25 years), and 2) to test the effectiveness of a disease-specific cognitive behavioral therapy (CBT) to treat subclinical anxiety and depressive symptoms.

Firstly, in our systematic review and meta-analysis in children and adolescents with IBD (10-18 years of age), we found pooled prevalence rates of 16.4% for anxiety symptoms, 4.2% for anxiety disorders, 15.0% for depressive symptoms, and 3.4% for depressive disorders (**see Chapter 2**). These rates are lower than in adults [1]. However, our results should be interpreted with caution, since varying instruments and cutoffs were used in the included studies.

Secondly, we studied a large baseline cohort of youth with IBD (n=374, 10-25 years of age, the sample of the baseline assessment of the randomized controlled trial (RCT), thus including patients with and without anxiety and/or depression). Almost half of the cohort experienced elevated symptoms of anxiety and/or depression (**see Chapter 4**). Subclinical symptoms were found in 23.6% and clinical symptoms were found 12.4% of the patients. Having active disease, as well as female gender, and shorter disease duration were associated with higher anxiety and/or depressive symptoms. We also demonstrated in this baseline cohort that, added to the influence of demographic and disease factors, illness perceptions and depression were associated with health-related quality of life (HRQOL; **see Chapter 5**). More negative illness perceptions and more depression were associated with lower HRQOL. Only for youth with UC/IBD-U, anxiety was associated with HRQOL as well. This implies that these psychological factors should be targeted in the treatment of youth with IBD.

Thirdly, we performed an RCT to test the effectiveness of a disease-specific CBT in two groups (CBT versus care-as-usual [CAU]). The overall results showed that patients in both groups improved significantly on their subclinical anxiety symptoms, depressive symptoms, HRQOL, as well as in social functioning, coping, and illness perceptions over the course of 12 months (**see Chapter 6 and 7**). When comparing the outcomes between groups, we found no differences in any of the outcomes between the CBT group and the CAU group. This raised the question as to which patients with IBD would benefit the most from CBT and in what format and dose CBT should be de-

livered. The results of our study concerning the medical outcomes of disease-specific CBT are in line with this, as no effect on the clinical disease activity was found over the course of 12 months (**see Appendix B**).

The abovementioned findings will be discussed more extensively below.

## Psychological aspects of IBD in youth

### Anxiety and depression in youth with IBD

Several studies have found high prevalence rates for anxiety (39-50%) and depression (+/- 25%) separately in youth with IBD [2-5], including a higher risk for anxiety and depressive disorders (hazard ratios of respectively 2.28 and 1.74) [6]. In contrast, other studies reported low prevalence rates ranging from 0-8% [7, 8]. To provide more insight into the combination of IBD and anxiety/depression, we performed a systematic review and meta-analysis in children and adolescents with IBD. The results of the meta-analysis were quite surprising, as we found that (especially symptoms of) anxiety and depression were quite prevalent in these patients (pooled prevalence rates of 16.4% for anxiety symptoms, 4.2% for anxiety disorders, 15.0% for depressive symptoms, and 3.4% for depressive disorders). However, these rates are not as high as one might expect based on earlier studies, summarized in a meta-analysis in adults with IBD [1], showing a pooled prevalence rate of 35.1% for anxiety symptoms, 20.7% for anxiety disorders, 21.6% for depressive symptoms, and 15.2% for depressive disorders.

In our baseline cohort of youth (age 10-25 years) with IBD, we found that almost half of the patients experienced at least some anxiety and/or depression [9], and **Chapter 4**. More specifically, 28.3% of the patients reported to have elevated anxiety symptoms, 2.9% reported to have elevated depressive symptoms, and 15.8% reported to have both.

There are several explanations for the mixed findings with respect to the combination of IBD and anxiety/depression in youth. These explanations concern 1) disease factors (most importantly clinical disease activity, but also disease duration, age at diagnosis, disease type, and medication use), 2) demographic factors (gender and socioeconomic status) and 3) how anxiety and depression are assessed in youth with IBD.

#### 1) Disease factors

*Clinical disease activity*

Firstly, clinical disease activity is an important factor to consider. IBD has a fluctuating course, which means that the severity of inflammation (with increased activation of pro-inflammatory cytokines) and resulting clinical symptoms will vary over time. This fluctuating course can have an influence on the presence of anxiety and depression. However, both evidence supporting and opposing this explanation has been found. For example, in our meta-analysis we found that the higher the proportion of patients

with active disease in a study, the higher the prevalence of depressive symptoms. In addition, we found that active disease (defined as having mild, moderate, or severe clinical disease activity) was associated with anxiety and depressive symptoms. This is also found in other studies in youth [4, 10, 11], as well as in adults [12].

However, patients in clinical remission still can experience anxiety and/or depressive symptoms [13-15], as we also found in our baseline cohort in which approximately 75% of the patients was in clinical remission [9] and **Chapter 4**. This implies that it is important to consider anxiety and/or depression in all IBD patients; not only in those with active disease, but also in those with less disease activity. Interestingly, the recent study of Gracie et al. [16] provided evidence for the proposed bidirectional relationship between IBD activity and anxiety and/or depression. Patients with clinical disease activity at baseline had an almost 6-fold higher risk for a later elevated anxiety score, and abnormal anxiety and depression at baseline were associated with several indicators of increased clinical disease activity. Obviously, these results stress the importance of taking into account clinical disease activity when investigating anxiety and depression.

*Other disease factors*

Secondly, other disease factors can play a role in the presence of anxiety and/or depression. There is some evidence that in patients with IBD, disease duration can influence anxiety and/or depression [13] and HRQOL [17]. We also found this in our baseline cohort [9] and **Chapter 4**, i.e. shorter disease duration associated with more anxiety/depression. In contrast, a review did not find an association between disease duration and anxiety and/or depression [11]. The studies in this review included patients with well-established IBD, with a mean disease duration of 1.2-5.4 years. It is possible that disease duration has some effect on the presence of anxiety and/or depression, for example in patients that recently have been diagnosed.

Furthermore, age at diagnosis is related to disease duration. However, independent of the disease duration, evidence has been reported that an older age at diagnosis (during adolescence) was associated with more depressive symptoms [2, 18]. This may have to do with the fact that being confronted with a diagnosis of a chronic disease such as IBD, can be harder for adolescents than for younger children, since adolescence is period with many changes, which can make the patient more susceptible for psychological problems.

In addition, the influence of disease type (CD versus UC) has been studied extensively. In their review, Brooks et al. did not find an association between disease type and depressive symptoms [11]. In our meta-analysis, we neither found an association between the proportion of patients with CD and the prevalence of depressive symptoms [19] / **Chapter 2**. However, the results of both studies should be interpreted with

caution. The studies included in the review of Brooks et al. were not powered specifically to detect the influence of disease type on the presence of anxiety and depression [11]. Moreover, in our meta-analysis there was a substantial amount of heterogeneity between studies [19] / **Chapter 2**. In adults, on the other hand, a meta-analysis did show that patients with CD had a higher prevalence of depressive symptoms than patients with UC [1]. It may be that for youth, disease type indeed has no effect and depression. That is, having a chronic illness such as IBD in adolescence can have an impact, regardless of with type of IBD. An alternative explanation is that, in youth, there is insufficient data available yet to draw strong conclusions about the effect of disease type on the presence of anxiety and depression.

Moreover, medication use can influence anxiety and depression in youth with IBD. Although we did not find an association between medication use and the presence of anxiety and/or depression [9] / **Chapter 4**, the review of Brooks et al. [11] reported that 4 out of 5 studies showed an association between corticosteroid use and anxiety and depression. In contrast, the use of biologicals (e.g. infliximab or adalimumab, anti-tumor necrosis factor [TNF] $\alpha$) was not associated with anxiety and depression in three studies [10, 20, 21]. Finally, abdominal pain has been related to the presence of anxiety and depression [22, 23]. The review of Sweeney et al. [22] suggests to focus on anxiety and depression in psychological treatment for youth with IBD, but also on pain-specific emotions, cognitions, and behaviors.

**2) Demographic factors**

Besides the abovementioned disease factors, some other factors may also play a role when discussing anxiety and depression in youth with IBD. Firstly, following the gender differences in anxiety and depression in the general population [24], gender has also been studied in youth with IBD. Three studies did not find an association between gender and anxiety and/or depression [11]. However, in our own baseline cohort being female was associated with more anxiety and depression [9] / **Chapter 4**. In children with IBD, a large study by Loftus et al. in anxiety and depressive disorders, found that teenage girls had a higher risk for anxiety disorders, and boys younger than 12 years had a higher risk of depressive disorders [6].

Secondly, mixed findings are reported with respect to the association between socioeconomic status (SES) and anxiety and depression. In youth with IBD, Clark et al. [10] found that SES was a strong predictor of depression, but they only included infliximab exposure, clinical disease activity and SES in their regression model. Other studies in adults with IBD found an association between lower income and more depressive symptoms [25, 26]. For Gold et al. conclusions are limited, because also a group of patients with functional gastrointestinal symptoms was included. Two other studies did not find an association between SES and anxiety and depression symptoms

[27, 28]. In our own baseline cohort, with several other demographic and disease factors taken into account, SES was not associated with anxiety and depression as well [9] / **Chapter 4**.

**3) Assessment of anxiety and depression in youth with IBD**

Lastly, the way anxiety, and more importantly depression, are assessed is important when studying these psychological problems in youth with IBD. There is considerable overlap in IBD symptoms and symptoms of depression: weight loss/gain, sleep disturbance, psychomotor agitation/slowing, and fatigue/low energy, and reduced appetite. This is reflected in the often used CDI and BDI-II depression questionnaires. Thompson et al. [29] found a 3-factor structure of the CDI in a large cohort of pediatric patients with IBD, called 'mood', ' behavioral/emotional', and 'somatic', with the latter factor containing the symptoms that overlap between IBD and depression. Furthermore, within a large sample of adolescents with IBD and depressive symptoms several profiles have been identified, including a profile characterized by somatic symptoms (severe fatigue, appetite change, decreased motor activity) [21]. However, another study found that these somatic symptoms did not differentiate between youth with more clinical disease activity and youth experiencing non-somatic symptoms of depression [30]. Hence, there is ongoing debate about whether to include or exclude items that refer to somatic symptoms in the screening for depression in youth with IBD [31]. Recently, in adults, evidence was found for an association between clinical disease activity and affective-cognitive depressive symptoms (with somatic depressive symptoms left out of the questionnaire) [32]. This indicates that the comorbidity between IBD and depression is not solely the result of the somatic symptoms that are often assessed. Therefore, including the somatic symptoms in screening instruments for depression provides extra information and does not seem to lead to an overestimation of the depressive symptoms.

**Other psychological factors of IBD in youth**

Anxiety and depression are the most studied psychological problems in youth with IBD. Nevertheless, other psychological factors are studied in these patients as well.

Firstly, several studies found that youth with IBD have a lower HRQOL when compared to healthy peers [33, 34].

Secondly, coping also may play a role in the psychological outcomes of patients with IBD. Children with IBD have been shown to use more avoidant coping than healthy controls [35]. In general, however, youth with IBD do not differ in their coping compared to controls [36]. On the other hand, large adult studies showed that patients with IBD used avoidant coping more often than controls [36]. With respect to the

effect of coping on outcomes and adjustment some studies do find an association [e.g. 37], whereas others do not [e.g. 38].

Thirdly, regarding illness perceptions, few studies have been conducted in youth with IBD [11]. In adults, studies showed that illness perceptions were associated with anxiety and depression [39], and with HRQOL [38, 40]. Recently, Van Tilburg et al. [41] also found evidence for the effect of pain beliefs on patient-reported symptoms, and disability, when controlling for coping, anxiety, depression, and clinical disease activity.

Fourthly, symptoms of IBD can affect the social functioning of youth with IBD. Indeed, a meta-analysis indicated that youth with IBD have worse social functioning compared to healthy controls [42]. In fact, onset of IBD during adolescence is associated with worse social functioning [43], probably due to increasing responsibilities in school and jobs.

### Interrelationships between disease and psychological factors

Previous research has shown that there is a complex interplay between psychological factors in patients with IBD, especially in how they influence disease outcomes. In adults, clinical disease activity, illness perceptions, coping, and anxiety and depression are associated with HRQOL [e.g. 38, 39, 44]. More specifically, in youth, anxiety/depression have been shown to mediate the relationship between clinical disease activity and HRQOL [45]. Recently, disability (as disease outcome) was found to be predicted by a latent construct 'psychological factors', consisting of anxiety, depression, pain beliefs, and coping [41].

However, most studies only examined the unique influence of one or two psychological factors on HRQOL. In our study we investigated the combined influence of these factors on HRQOL. Adjusted for the influence of demographic and disease factors, illness perceptions and depression were associated with HRQOL, whereas anxiety was only in youth with UC/IBD-U coping and was not at all [46] / **Chapter 5**. This suggests 1) that at least illness perceptions and depression should be the focus of psychological interventions for youth with IBD and 2) that not only anxiety/depression but also HRQOL should be considered as disease outcome.

## Disease-specific CBT for youth with IBD

Findings in adults with IBD are mixed with respect psychological treatment for patients with IBD. For treatment focused on anxiety, depression, and HRQOL both positive and negative findings are reported, but for pain, fatigue, and medication adherence the results are promising [47]. However, the difference between the included patients may be an explanation for the inconclusive results, since several studies included all patients with IBD, regardless of the presence of psychological problems

or low HRQOL. Recently, several studies found that CBT was effective in improving anxiety, depression and HRQOL, in adults selected on having elevated symptoms of anxiety, depression or a low HRQOL [48, 49]. With respect to the effect of CBT on disease outcomes, in general no effects are reported [50, 51].

In youth, promising findings have been reported [52, 53]. Recently, CBT was found to be effective in improving depression [54] and HRQOL [55]. Furthermore, Szigethy et al. [54] reported that CBT outperformed supportive non-directive therapy in patients with CD and moderate clinical disease activity. Levy et al. [55] found no effects of their 3-session CBT on anxiety and depression in youth with IBD. In our own RCT, we tried to avoid limitations of the previous studies. Firstly, studies often focused only on depression. Since anxiety and depression are highly comorbid [56], we focused on both simultaneously. Secondly, the Levy et al. study [57] included all children and adolescents. As described above in adults, CBT seems to be more effective in patients with elevated symptoms of anxiety and depression or low HRQOL. Therefore, we only selected patients with elevated anxiety and/or depressive symptoms. Thirdly, we used a full-protocol of disease-specific CBT, since Levy et al. [55] mentioned that their 3-session therapy may have been too short.

In spite of these methodological considerations, we did not find any differences between the disease-specific CBT group and the CAU group in improving anxiety, depression, HRQOL, neither in improving social functioning, coping, negative illness perceptions, and sleep problems [57,58] / **Chapter 6 & Chapter 7**.

Our results, and that of earlier RCT's into the effect of CBT for psychological outcomes in youth with IBD, may be explained by several factors. Firstly, and most importantly, mere participating in the study may have elicited awareness for anxiety and depression in these patients. They received informed consent forms, discussed these with their physician and one of the investigators, filled out questionnaires on psychological problems, and received a psychiatric interview. For both groups this may have been sufficient to improve from their subclinical anxiety and/or depression. It has been described before that merely answering questions or participating in a trial can influence behavior and emotions. McCambridge [59] described this 'question-behavior effect' that can occur in RCT's. Moreover, Arrindell [60] described the re-test effect: mean scores of psychopathology often decrease without any formal intervention, perhaps because the first assessment can heighten awareness, which in turn can influence an individual's behaviors and emotions. This awareness can be perceived as some form of educational support, like in the control condition of earlier trials in youth with IBD [54, 55].

Secondly, in our study patients experienced relatively low disease burden, psychologically as well as somatically. Youth were included with subclinical anxiety and/or depression, since we were interested in the effect of the disease-specific CBT to

prevent clinical anxiety and/or depression, and because randomization of youth with clinical anxiety and/or depression to a CAU control group without any mental health care is not ethical. Next, approximately three-quarters of the patients had disease in remission and the remainder of the patients had mild disease activity. Hence, for patients with this low disease burden, participation may have been enough to improve on their subclinical anxiety and/or depression.

Other explanations for our findings can be provided as well. Thirdly, the disease-specific CBT that we investigated was originally developed for and has been found effective in improving depression. Therefore, the therapy may not have been focused enough on anxiety, and the other psychological outcomes such as social functioning, coping, and illness perceptions. However, we adapted the PASCET-PI to also target anxiety symptoms. In addition, anxiety and depression are highly related, and CBT has been found effective for both type of emotional problems, with even higher effect sizes for anxiety than for depression [61].

Fourthly, CBT showed to have additional effects, for example on coping [62] and illness perceptions [63]. Together, these studies imply that our disease-specific CBT could have been able to improve anxiety, coping, and illness perceptions. However, this CBT protocol may have had insufficient focus on these outcomes.

## Strengths and limitations

Several strengths and limitations have been described in the Discussion sections of the previous chapters. Therefore, below the most important will be mentioned.

For our cohort, that provided cross-sectional baseline data, strengths were that the sample was mixed, since we included patients from 6 hospitals (academic and non-academic) and from mixed regions in the Netherlands (large cities vs. smaller cities) and that we systematically and consecutively screened all available patients, using validated and age-attuned questionnaires and a psychiatric interview.

These strengths also apply to the RCT. Furthermore, and specifically for the RCT, we had very low attrition during the follow-up assessments and we had a thorough check of treatment integrity (i.e. whether the treatment was provided as intended). The treatment integrity results were positive, indicating that the therapy was delivered as intended. Almost 90% of the patients in the CBT groups received all 10 sessions and in all provided sessions at least 75% of the topics was discussed. Another important strength of our RCT was that we aimed at improving both anxiety and depressive symptoms, since these are highly comorbid [56]. Finally, we used standard medical care as comparison condition, as this, in general, resembles the care-as-usual for these patients best. In addition, other comparison conditions (e.g. attention placebo, waitlist-control) were not feasible, because a long follow-up was needed to be able to

examine flares during follow-up, which is an important medical outcome in youth with IBD.

## Future research

Our results and that of earlier studies have implications for future research into psychological problems and psychological treatment in youth with IBD.

### Future research – psychological problems in IBD

Most importantly, we do not exactly know yet how psychological problems and IBD are related. Although there is evidence that there is a bidirectional relationship [16], it is still unclear to what extent, what this means for the medical and psychological treatment, and when psychological interventions should be provided. Therefore, anxiety and depression should be assessed regularly and repeatedly and thus more frequently than in most studies (that have several months between different assessments). Since IBD has a fluctuating course, it is possible that anxiety and depression fluctuate as well in these patients. Reed-Knight et al. [64] demonstrated that emotional and behavioral problems were relatively stable in newly as well as in previously diagnosed youth, with 6 months between the two assessments. However, no other studies have been conducted in youth with IBD to examine the course of anxiety and depression. Yet is unknown how anxiety and depression can fluctuate per week or month. With more regular assessments we can learn more about how clinical disease activity impacts anxiety and/or depression, and vice versa, especially in youth with IBD. Some studies on the bidirectionality of the relationship between clinical disease activity and anxiety/depression have been conducted in adults [e.g. 16], but no such study has been conducted in IBD youth. Most studies in youth with IBD had a cross-sectional design, but future studies should be longitudinal, so more information comes available about causality and the course of psychopathology and IBD fluctuations.

Furthermore, to be able to assess of anxiety and depression regularly, as part of standard care, short screening questionnaires for these problems should be validated in youth with IBD. Currently, studies often use the CDI for assessing depression symptoms and the SCARED for assessing anxiety symptoms. Although these instruments are well validated and often used in research into anxiety and depression, they are lengthy (e.g. 20+ items), which limits their potential as screening instrument during a regular medical visit or to be administered, for example, every week. In adults, Bernstein et al. [65] compared several screening instruments for anxiety and depression. They included the Patient Health Questionnaire (PHQ-9; depression, 9 items), and the thereof derived PHQ-2 (depression, 2 items), Hospital Anxiety and Depression (HADS; anxiety, 7 items; depression, 7 items), Kessler Distress Scale (Kessler-6; depression, 5 items of 6 items in total), Patient-Reported Outcomes Measurement Information

System Emotional Distress Depression Short-Form 8a (PROMIS Depression; 8 items), Patient-Reported Outcomes Measurement Information System Anxiety Disorder Short-Form 8a (PROMIS Anxiety; 8 items), Generalized Anxiety Disorder 7-item Scale (GAD-7; anxiety, 7 items), and Overall Anxiety and Severity Impairment Scale (OASIS; anxiety, 5 items). All performed adequately as screening tool for anxiety and depression (compared to a semi-structured psychiatric interview), although the depression instruments performed better than the anxiety instruments. Such studies should be conducted in youth with IBD as well. However, for youth, less short screening instruments are available than for adults, so new instruments may be needed, since anxiety and depression may present differently in youth than in adults [66, 67]. Another possibility to regularly assess anxiety and depression is Ecological Momentary Assessment (EMA) or Experience Sampling Method (ESM). These methods often use a smartphone application to collect data using short screenings instruments or individual questions, several times a day or week. EMA/ESM has been successfully used in chronic pain research [68] and in adolescents, to study for example emotional states [69] or coping and mood [70].

Next, our results stress the importance of other psychological factors in youth with IBD as well. HRQOL has been studied extensively and these patients often have a lower HRQOL than healthy youth [34]. We found that illness perceptions are associated with HRQOL [46]. This may imply that changing negative illness perceptions improves HRQOL. It seems important to consider illness perceptions in youth with IBD, especially in psychological interventions for these patients. In adults, some studies have been performed stressing the importance of illness perceptions in the care for patients with IBD [e.g. 37, 44]. However, in youth with IBD, studies are scarce. We do not know yet what specific illness perceptions youth with IBD have, how these can impact outcomes such as HRQOL, and how these should be part of psychological interventions. Future research, therefore, should provide more insight in illness perceptions in youth with IBD. In our study, we used the Brief Illness Perceptions Questionnaire (BIPQ), but the full IPQ provides more detailed information about several types of illness perceptions.

Other psychological factors may also be important. Sleep problems are often present in youth with IBD, although we only examined these in the RCT and not in our baseline cohort. Sleep problems can influence clinical disease activity, but also anxiety and depression [71, 72]. Therefore, when considering anxiety and depression in youth with IBD, attention has to be given to sleep problems as well. Future studies can shed light on how sleep problems are related to anxiety and depression, and whether treating sleep problems can influence the disease course or the presence of anxiety and depression. Similarly, parental factors can influence anxiety and depression, especially parental anxiety and depression or stress [45, 73]. Hence, it seems important

to also be aware of parental mental health, when assessing and treating anxiety and/or depression in youth IBD.

Finally, anxiety and depression should also be assessed as outcome parameters in drug trials, in addition to quality of life. On one hand because anxiety and depression can influence the disease course [74]. On the other hand, it has been shown that anxiety and/or depression can lower treatment adherence in adolescents with IBD [75], which can impact the outcomes of trials testing the effectiveness of IBD medication. Moreover, corticosteroids can impact anxiety and depression and depression can be a side effect of biologicals [11], so trials that investigate the effect of corticosteroids or biologicals may be stronger if they also take into account anxiety and depression.

**Future research – for disease specific CBT for youth with IBD**

With respect to psychological treatment for youth with IBD, future research should provide information on several topics. Since anxiety and depression are the most important psychological problems in these patients, CBT has been investigated the most. However, it is not clear yet which patients should be provided with CBT. CBT seems beneficial for treating severe depressive symptoms and HRQOL, but was equally effective as SNDT [54]. Furthermore, Levy et al. [55] showed that 3-session CBT improved HRQOL, but not anxiety and depression. Our own results indicate that CBT has no additional effect to standard medical care in improving anxiety, depression, and HRQOL. Studies differed in the patients they included (patients with subclinical anxiety and/or depressive symptoms, patients with severe depression, all youth with IBD). Selecting patients based on the presence of anxiety and/or depression or low HRQOL seems important. Patients with severe clinical anxiety or depression will benefit from psychological treatment, such as CBT. However, within patients with subclinical anxiety and/or depression, there may be a subgroup of patients that can benefit from psychological treatment as well. For example, those with active disease or those with negative illness perceptions. Future studies may include both patients with both severe clinical as well as subclinical anxiety and/or depression. As smaller effects can be expected for subclinical symptoms, sample sizes should be sufficiently large to be able to detect these effect as well.

Furthermore, future studies should focus on which type or format of CBT is most appropriate for treating anxiety and depression, and for improving HRQOL. For example, CBT in a group format has been shown to have positive effects on parent-reported anxiety and depression in children with a chronic illness [76] or on coping and HRQOL in a small pilot trial of adolescents with IBD [77]. In addition, more evidence is needed on with how much flexibility CBT can provided. In the studies of Szigethy et al. [51, 53] and in our own RCT [57, 58], a part of the sessions was delivered via the telephone.

More research is needed to examine, for example, whether all sessions can be delivered via the telephone or online using the computer or a smartphone.

Next, to investigate the bidirectional relationship between clinical disease activity and anxiety/depression during treatment, future studies should include assessments between sessions. In that way, studies are able to examine the effects of changes in anxiety and/or depression on changes in clinical disease activity and vice versa. This type of design also provides the opportunity to investigate other moderators of the treatment effects (e.g. changes in illness perceptions).

## Clinical implications and Recommendations

- Systematic and repeated screening for anxiety and depression during medical visits in youth with IBD is important, preferably every three months, but at least yearly.
- For the screening of anxiety and depression (in youth with IBD), cross-cultural instruments, covering a broad age-range and with appropriate cutoffs should be used, to reduce the current heterogeneity between studies.
- Patients with subclinical levels of anxiety and/or depression should be monitored for their mental health by their treating professionals (either by their physician or by an affiliated psychologist of the gastroenterology department). This monitoring may be sufficient to prevent the development of an anxiety or depressive disorder. If not, they should receive a short preventive psychological treatment.
- Patients with clinical anxiety and/or depression should receive psychological treatment, either by a medical psychologist with knowledge of IBD or by referral to a child and adolescent psychiatrist.
- If patients experience severe or clinical anxiety and/or depression they should receive psychological treatment. In case of a clinical relapse of IBD, timing of treatment should be tailored to the patient's wishes and possibilities. Preferably, the treatment is provided by a medical psychologist with knowledge of IBD.
- Professionals working with youth with IBD should be aware of not only anxiety and/or depression, but also of possible negative illness perceptions.

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# Appendix A

## Editorial: Anxiety And Depression In Inflammatory Bowel Disease

A. Mikocka-Walus, S.R. Knowles

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Anxiety and depression are common comorbidities in patients with inflammatory bowel disease (IBD), with 19% of patients reporting symptoms of anxiety and 21% of depression, as compared to 9% and 13%, respectively, in healthy controls [1]. Anxiety and depression have been associated with clinical recurrence in adults with IBD [2]. Bidirectionality of IBD and mood disorders has also been proposed in adults, with IBD activity at baseline associated with an almost six-fold increase in future risk for anxiety, and anxiety at baseline (in quiescent IBD) linked to future flares, steroid prescriptions and escalation of therapy [3]. Approximately 25% of IBD cases are diagnosed in paediatric populations [4], with 19% of incident cases occurring in the first decade of life [5], and poorer outcomes in those with early onset IBD [6]. While paediatric IBD is now becoming fairly common, much less systematic knowledge is available on anxiety and depression in children with IBD than in adults. The excellent systematic review with meta-analysis by Stapersma et al. is therefore timely [7].

Analysing 28 studies (n = 8107) published between 1994-2017, they7 showed the pooled prevalence of anxiety symptoms to be 16.4% (95% CI: 6.8%-27.3%), of anxiety disorders to be 4.2% (95%CI: 3.6%-4.8%), of depressive symptoms to be 15.0% (95% CI: 6.4%-24.8%), and of depressive disorders to be 3.4% (95% CI: 0%-9.3%). Except for anxiety disorders, significant heterogeneity was noted among the studies, and there were fewer studies reporting disorders as opposed to symptoms, which is consistent with previous systematic reviews [1, 8].

Reporting anxiety/depression symptoms and disorders separately is a strength of the present review. The differences between the two are frequently ignored both in practice and in academic papers. Symptoms are derived from screening measures such as the Child Depression Inventory, while disorders are typically established during a psychological or psychiatric interview, which is more costly and time-consuming, and thus less often used in research. Symptoms are common but, as shown [7], are not disorders in most cases. This is a reassuring finding for clinicians. Nevertheless, the symptoms of anxiety and depression are a sign that there is a need for psychological support and, if this can be provided, there is a good chance they will not escalate to a diagnosable psychological disorder.

As the rates of anxiety and depression are lower in children than in adults [1, 7, 8], pediatric IBD clinics may be ideally situated to provide biopsychosocial integrated care which could offer support not only for IBD symptoms and non-intestinal inflammatory issues but also, holistically, for overall wellbeing. Studies on psychological therapy,

while limited in number, show higher efficacy in children with IBD than adults [9], further supporting early psychological interventions in IBD. While the impact of anxiety/depression on dis- ease course in pediatric IBD was outside the scope of the recent review [7], it sends an important message to clinicians and policymakers working in IBD: it is time to go beyond treating the bowel in our approaches to IBD care.

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## Editorial: Anxiety And Depression In Inflammatory Bowel Disease - Authors' Reply

Gertrude van den Brink, Luuk Stapersma, Eva M. Szigethy, Elisabeth M.W.J. Utens, Johanna C. Escher

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We thank Mikocka-Walus & Knowles [1] for their editorial about our systematic review and meta-analysis on anxiety and depression in children and adolescents with inflammatory bowel disease (IBD) [2]. Indeed, anxiety and depression are common in IBD, and the bidirectional relationship between anxiety/depression and intestinal inflammation can be explained in terms of the "brain-gut-axis" [3, 4]. In adult (and less so in pediatric) IBD, the association between anxiety/depression and clinical recurrence of IBD has been confirmed [5, 6]. In almost 25% of the patients, IBD presents in childhood or adolescence with a disease course often more severe compared to adults [7, 8]. In addition, adolescence is a challenging life phase with many biological and psychosocial changes. IBD disrupts normal psychosocial development, and increases the vulnerability to developing anxiety/depression. Furthermore, it is known that anxiety/depression in adolescence is associated with anxiety/depression in adulthood [9, 10], affecting quality of life, work participation and socioeconomic status [11] with subsequently high societal costs [12].

There are several ways to integrate psychosocial support in the care for (pediatric) IBD patients. First, for early detection, patients should be regularly screened for anxiety/depressive symptoms. In our Dutch cohort we systematically screened 374 IBD patients, aged 10-25 years, and found that 47% suffered from symptoms of anxiety and/or depression, with the highest prevalence of anxiety [13], and females and patients with active disease having the highest risk. Ideally, mental health screening is done routinely in the outpatient clinic using a short and easy-to-use screening tool. Second, we fully agree with Mikocka-Walus and Knowles that in case of elevated symptoms, a psychiatric interview should check if symptoms are mild/subclinical or severe as in a clinical disorder. It is important to make this difference in order to determine the best treatment strategy. Third, mental health specialists should be part of the multidisciplinary IBD team for young IBD patients, to evaluate the outcome of screening and provide psychosocial care if necessary.

In pediatric IBD, Szigethy et al. found promising results of two psychological therapies in obtaining remission of clinical depression (cognitive behavioral therapy [CBT]: 67.8%, and supportive non-directive therapy: 63.2%) [14]. However, in our recently published multicenter trial we did not find an additional effect of CBT over care-as-

usual in improving subclinical anxiety and depressive symptoms in 10-25-year-old IBD patients directly post treatment [15], as patients in both groups improved. Whether psychosocial interventions also have an effect on inflammatory disease course remains questionable. In conclusion, future studies investigating anxiety and depression in paediatric IBD should use validated instruments cross-culturally, and, importantly, with similar cutoffs. For patients with subclinical anxiety/depression, screening and monitoring may be sufficient to prevent their development into disorders, but this group could also benefit from e-health (internet-CBT) interventions. Patients with clinical anxiety/depression should be referred for CBT. Future research will unravel the "dose" and modality of CBT that should be provided to patients with (sub)clinical anxiety/depression and the long-term effects of CBT on the course of disease.

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Appendix B

# 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

Gertrude van den Brink, Luuk Stapersma, Anna S. Bom, Dimitris Rizopoulos, C. Janneke van der Woude, Rogier J.L. Stuyt, Daniëlle M. Hendriks, Joyce A.T. van der Burg, Ruud Beukers, Thea A. Korpershoek, Sabine D.M. Theuns-Valks, Elisabeth M.W.J. Utens, Johanna C. Escher

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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.

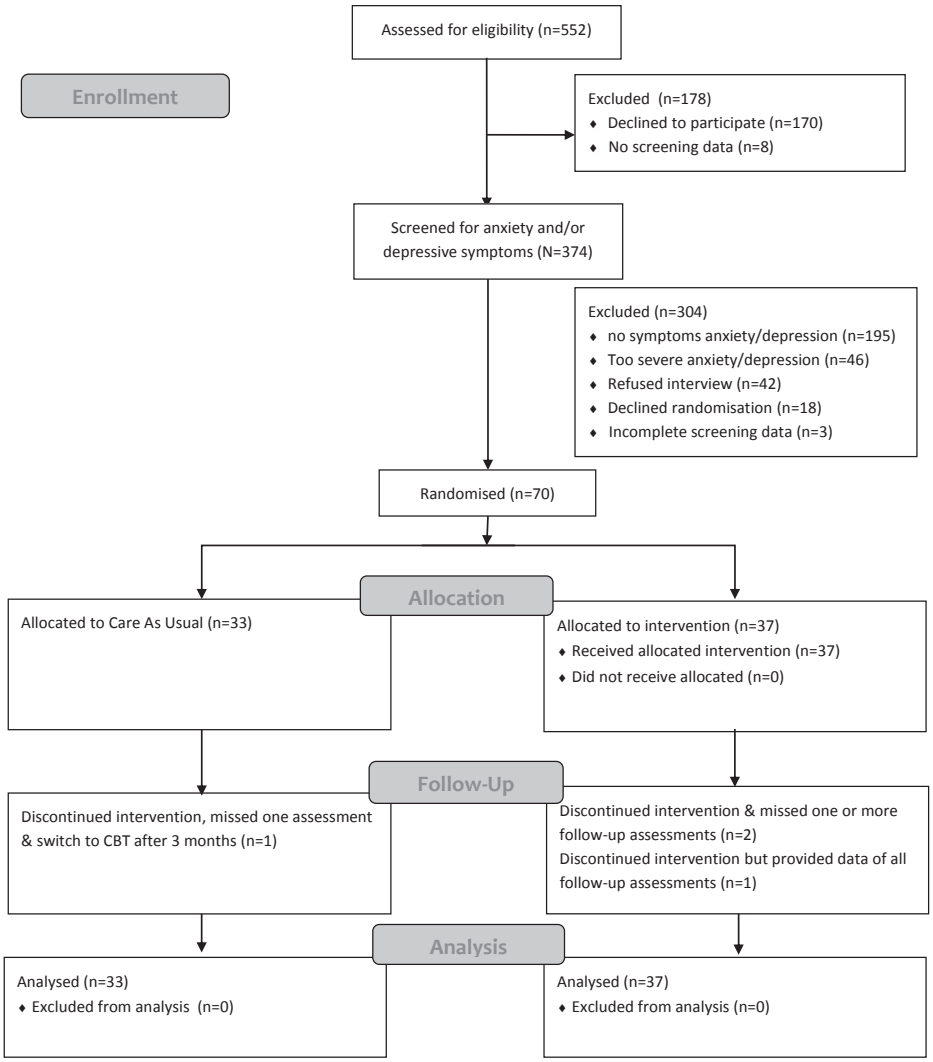


**Figure 1** | CONSORT study flow chart
Abbreviations: CBT= cognitive behavioral therapy

## 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%).

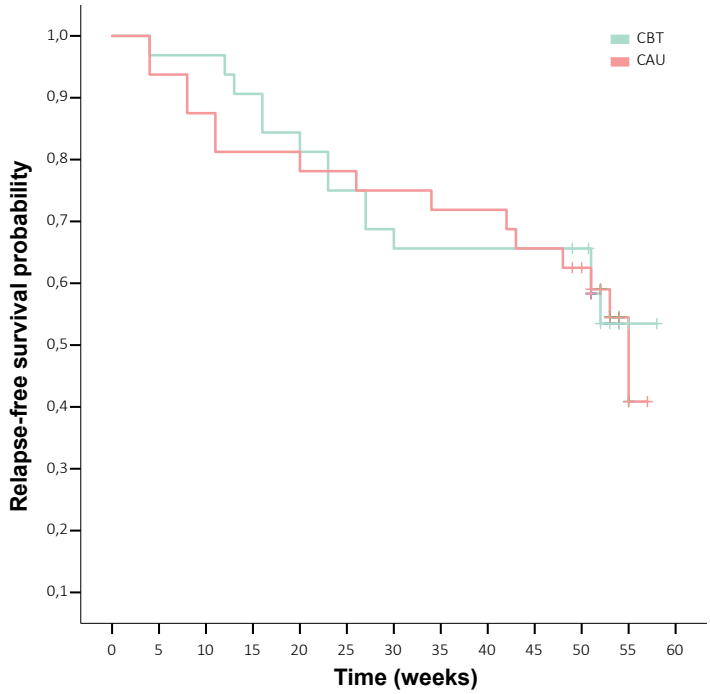


**Figure 2** | Survival curve time to first flare
Abbreviations: CBT= cognitive behavioral therapy + care-as-usual; CAU= care-as-usual

## 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).

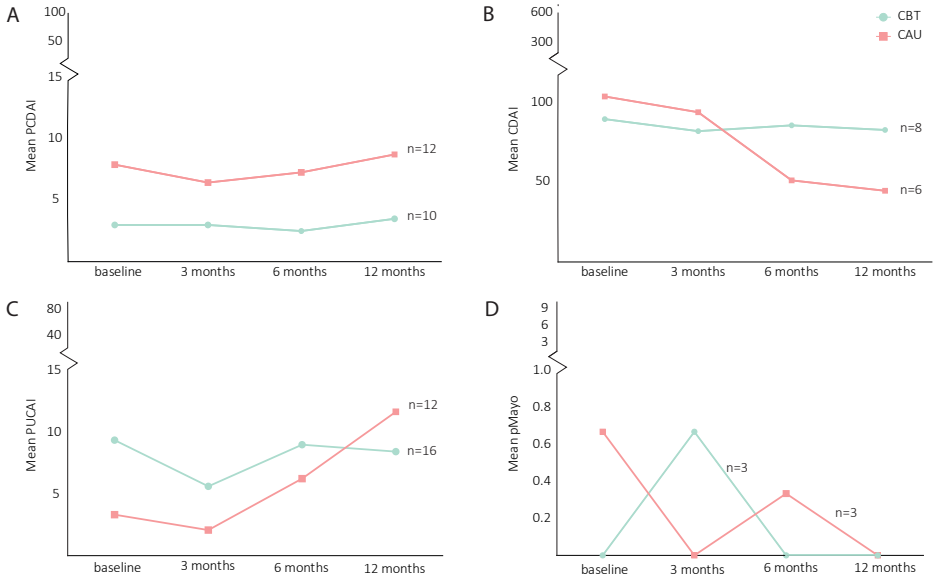


**Figure 3** | Raw means of clinical disease activity scores over time
Abbreviations: PUCAI= Pediatric Ulcerative Colitis Activity Index; pMayo= partial Mayo; PCDAI= Pediatric Crohn's Disease Activity Index; CDAI= Crohn's Disease Activity Index; CBT= cognitive behavioral therapy; CAU= care-as-usual

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).

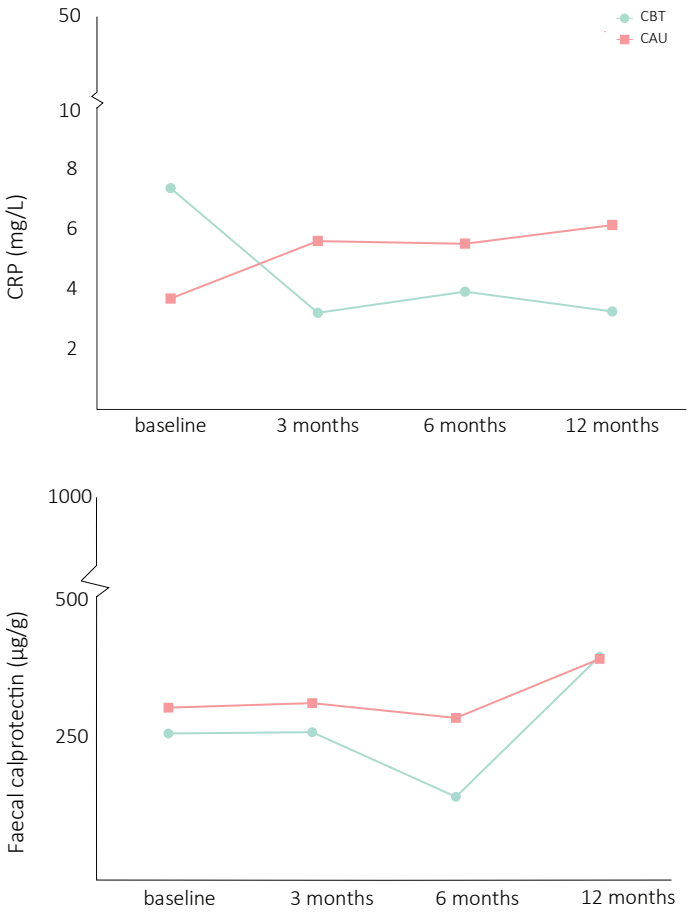
**Step 2: S''**

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

# Summary

In this thesis several studies are described, investigating anxiety and depression in youth with inflammatory bowel disease (IBD), including outcomes of a randomized controlled trial (RCT) testing the effectiveness of a disease-specific cognitive behavioral therapy (CBT) for these patients.

In **Chapter 1**, the general introduction describes the background of the present studies. IBD has two main types; Crohn's disease (CD) and ulcerative colitis (UC). Approximately 25% of all patients receives the diagnosis of IBD before they are 18 years of age, and for patients up to 25 years of age this is +/- 35%. The last decade more attention has been given to the psychological aspects of IBD. Youth with IBD have a lower health-related quality of life (HRQOL) than healthy peers, but the most studied psychological problems are anxiety and depression. In general, youth with IBD have a high risk for anxiety and/or depression. The association between inflammation and anxiety/depression may be explained by the brain-gut axis. Inflammation can affect the brain and induce anxiety and/or depression. On the other hand, increased anxiety and/or depression can increase inflammation. In this way a vicious circle arises in which inflammation and anxiety/depression negatively influence each other, to an increasing extent. Psychological problems such as anxiety and/or depression can have serious consequences. They can influence the disease course, can lower medication adherence, and can negatively impact HRQOL. The brain-gut axis implies that treating anxiety and/or depression may also improve the disease course. There is evidence that a disease-specific CBT can improve depressive symptoms, HRQOL, and school attendance. However, earlier studies focused on either anxiety or depression, or did not select youth on the presence of any psychological problems. Therefore, this study was designed to investigate anxiety and depression in youth with IBD, and to test the effectiveness of a disease-specific CBT on both subclinical anxiety and depressive symptoms, HRQOL and other psychological outcomes (social functioning, coping, illness perceptions, and sleep problems).

In **Chapter 2**, the results are described of a systematic review and meta-analysis into the prevalence rates of anxiety and depression in pediatric IBD. Previous studies showed varying prevalence rates from 0% - 50%; most studies found relatively high prevalence rates. For our review, we identified 28 studies (N = 8107, mean age: 14.3 years). Pooled prevalence estimates were 16.4% (95% confidence interval [CI] 6.8%-27.3%) for anxiety symptoms and 4.2% (95% CI 3.6%-4.8%) for anxiety disorders. Pooled prevalence estimates were 15.0% (95% CI 6.4%-24.8%) for depressive symptoms and 3.4% (95% CI 0%-9.3%) for depressive disorders. Meta-regression showed no influence of disease type or gender on all prevalence rates, but studies with a higher percentage of active disease showed a higher rate of depressive symptoms. Our results should be interpreted with caution, due to varying instruments/cutoffs to assess symptoms, and because only a few studies investigated disorders. We recommend to use the same

instruments, cross-culturally, to gain a better insight into the prevalence rates for anxiety and depression in pediatric IBD, and into the underlying mechanisms.

**Chapter 3** describes the study protocol of a RCT to test the effectiveness of a disease-specific CBT for youth with IBD and subclinical anxiety and/or depression. Youth with IBD were screened for symptoms of anxiety and depression (baseline cohort, N = 374, 10-25 years). Those with elevated scores received a psychiatric interview. Patients with subclinical (and not clinical) anxiety and/or depression were randomly assigned to medical care-as-usual (CAU) or CAU plus disease-specific CBT. The main outcomes were 1) reduction of subclinical anxiety and/or depressive symptoms and 2) sustained remission for 12 months. Secondary outcomes were health-related quality of life (HRQOL) and psychosocial functioning, and we assessed inflammatory cytokines in peripheral blood mononuclear cells, and whole blood RNA expression profiles.

In **Chapter 4**, several disease factors were examined as risk factors for anxiety and depression in youth with IBD. Since youth with IBD are at risk for anxiety and depression, this study aimed to (1) describe the prevalence and severity of anxiety and depressive symptoms in the large baseline cohort of young IBD patients, and (2) identify demographic and disease risk factors for anxiety and depression. Youth with IBD (N = 374, 10-25 years) were screened for anxiety and depression. Patients with elevated scores for anxiety and/or depression received a psychiatric diagnostic interview. Demographic and disease characteristics were retrieved from medical charts. Three-quarters of patients had IBD in remission. Subclinical anxiety/depressive symptoms were present in 35.2%, and clinical symptoms in 12.4% of patients. Elevated symptoms of either anxiety (28.3%), depression (2.9%) or both (15.8%) were found and did not differ between adolescents (10-17 years) and young adults (18-25 years).

Using multiple logistic regression analyses, we found that having active disease and being female was significantly associated with elevated depressive symptoms, whereas being female and having shorter disease duration was significantly associated with elevated anxiety/depressive symptoms. Therefore, it is recommended to screen youth with IBD for psychological problems, such as anxiety and depression. Female patients and those with active disease are the most vulnerable.

In **Chapter 5**, we examined the associations of demographic, disease and psychological factors with HRQOL. Previous studies mainly investigated the unique contribution of one or two factors to HRQOL. However, combining all factors simultaneously in one study provides more insight. Data were collected on clinical disease activity, illness perceptions, coping, anxiety, depression, and HRQOL in our baseline cohort consisting of 262 youth (age 10-20 years, 46.6% male). Multiple linear regression analyses were performed in two disease type groups separately (CD, UC/IBD-U). Illness perceptions and depression were significantly associated with HRQOL, whereas anxiety only was in youth with UC/IBD-U and coping was not at all. In both disease type groups, more

negative illness perceptions and more depression were associated with lower HRQOL. Therefore it is important to pay attention to these psychological factors in the medical care for youth with IBD, and in psychological interventions for these patients.

**Chapter 6** presents the direct post-treatment results of the RCT, testing the effectiveness of a disease-specific CBT (CBT group: N = 37 vs. CAU group: N = 33). At post-treatment, the group that received 3 months of disease-specific CBT did not differ from the control group. In both groups a similar proportion of patients remained stable, improved or deteriorated on their symptoms of anxiety and depression. Exploratory linear mixed models showed that, in general, patients in both groups improved on their anxiety and depressive symptoms, as well as in their HRQOL, regardless of age, gender, and disease type. This may be explained by the awareness created for psychological problems in both groups by merely participating in the study or by the low burden of disease that patients experienced.

In **Chapter 7**, we discuss the results of the RCT 6 and 12 months after the baseline assessment. Not only did we test the effect of the disease specific CBT on anxiety, depression, and HRQOL, but also on social functioning, coping, illness perceptions, and sleep problems. The results were comparable with the direct post-treatment results described in Chapter 6. In the CBT group and the CAU group a similar proportion of patients remained stable, improved or deteriorated on their symptoms of anxiety and depression. Again, in exploratory linear mixed models, patients in both groups improved on their psychological outcomes, 6 and 12 months after baseline. Participating in the study may have created awareness that was sufficient for these patients with subclinical anxiety and/or depression to improve. CBT may be more useful for patients with severe anxiety/depression or those with active disease.

Finally, **Chapter 8** provided a general discussion, with a discussion of the main findings and conclusions, and recommendations for future research and clinical practice. Although several studies reported high prevalence rates of anxiety and depression in youth with IBD, our meta-analysis showed pooled prevalence rates of 16.4% for anxiety symptoms, 4.2% for anxiety disorders, 15.0% for depressive symptoms, and 3.4% for depressive disorders. These prevalence rates are lower than those are found in adults. In our large cohort of youth with IBD, we found that 35.2% of the patients had subclinical symptoms of anxiety/depression, and that 12.4% had severe clinical symptoms of anxiety/depression. Furthermore, having active disease, being female, and having shorter disease duration were associated with higher anxiety/depressive symptoms. In addition, we demonstrated in our cohort that, added to the influence of demographic and disease factors, more negative illness perceptions and more depression were associated with lower HRQOL. The results of the RCT showed that all patients improved on their anxiety symptoms, depressive symptoms, HRQOL, as well

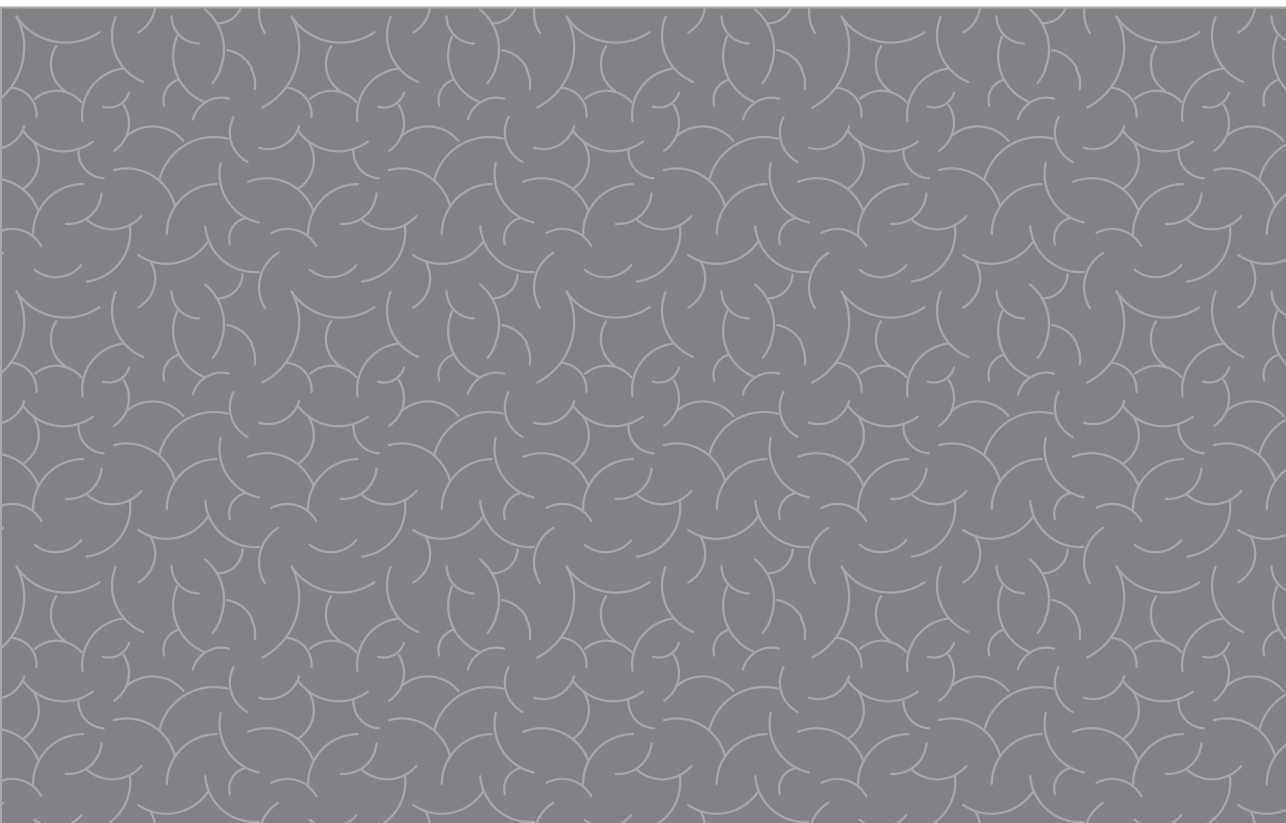
as on their social functioning, coping, and illness perceptions over the course of 12 months. We found no differences between the CBT group and the CAU group.

This is the first European study screening a large cohort of youth with IBD on subclinical and clinical anxiety and depression. Another strength of the current research is that our cohort was mixed (academic versus community, and urban versus rural hospitals). Moreover, we systematically screened all available youth with IBD with validated, and age-attuned questionnaires and a psychiatric interview. Strengths of our RCT were that we had very low attrition, that treatment integrity was checked carefully, but most importantly that we aimed at improving both anxiety and depression simultaneously.

Future research is needed to examine how anxiety/depression and inflammation are related, by using more regular assessments of both the psychological symptoms and the clinical disease activity. For this purpose, short (disease-specific) screening instruments for anxiety and depression should be validated in youth with IBD. With respect to psychological treatment for youth with IBD and anxiety/depression, studies should examine which patients should be treated with psychological treatment, what format should be used, and with what treatment dose. In addition, future longitudinal studies should use more intermediate assessments to be able to test the bidirectionality of the relationship between anxiety/depression and inflammation and to test possible moderators of treatment effects.

Recommendations for clinical practice are that youth with IBD should be screened systematically for anxiety and depression, and that patients with severe anxiety/depression should receive psychological treatment by psychologists with expertise with the disease. Preferably, parents should be engaged in the treatment, to optimally coach their children in coping with IBD. For patients with subclinical anxiety and/or depression, monitoring might be sufficient to prevent that these symptoms develop into clinical disorders and have an even larger impact on the disease course.

# Samenvatting



In dit proefschrift worden verschillende studies beschreven naar angst en depressie bij jongeren met inflammatoire darmziekten (*inflammatory bowel disease*; IBD), inclusief studies naar de effectiviteit van een ziekte-specifieke cognitieve gedragstherapie (CGT).

In **Hoofdstuk 1** wordt een algemene inleiding gegeven met de achtergrond van de studies. IBD heeft twee hoofdtypen, namelijk de Ziekte van Crohn (ZvK) en colitis ulcerosa (CU). Ongeveer 25% van de patiënten krijgt de diagnose voordat ze 18 jaar zijn en voor patiënten onder de 25 jaar is dit ongeveer 35%. De laatste jaren wordt steeds meer aandacht geschonken aan de psychologische aspecten van IBD. Jongeren met IBD hebben een lagere gezondheid gerelateerde kwaliteit van leven (*health-related quality of life*; HRQOL) dan gezonde jongeren. De meest onderzochte psychologische problemen bij jongeren met IBD zijn angst en depressie. Over het algemeen hebben jongeren met IBD een groter risico op het hebben van angst en/of depressie. Het veelvuldig samen voorkomen van angst/depressie met IBD kan mogelijk worden verklaard door de zogenoemde brein-darm as (of de *brain-gut axis*), waarmee het brein en de darmen met elkaar communiceren. Ontstekingen (oftewel inflammatie) in de darmen kunnen het brein beïnvloeden en zo leiden tot angst en depressie. Anderzijds kunnen angst en depressie een toename van inflammatie veroorzaken. Op deze manier ontstaat een vicieuze cirkel, waarin inflammatie en angst/depressie elkaar negatief beïnvloeden, in toenemende mate. Angst en depressie kunnen ernstige gevolgen hebben voor jongeren met IBD. Deze psychologische problemen kunnen het ziektebeloop negatief beïnvloeden, medicatietrouw verminderen en een lagere HRQOL veroorzaken. De *brain-gut axis* impliceert dat het behandelen van angst en depressie er mogelijk ook voor kan zorgen dat het ziektebeloop kan verbeteren. Er zijn aanwijzingen dat een ziekte-specifieke CGT depressieve symptomen kan verminderen, en HRQOL en de aanwezigheid op school kan verbeteren. De eerdere studies hadden echter als nadeel dat er apart naar angst of depressie werd gekeken of dat patiënten niet werden geselecteerd op eventueel aanwezige angst- en depressieve symptomen. Daarom was deze studie ontworpen om onderzoek te doen naar angst en depressie bij jongeren met IBD en om de effectiviteit te onderzoeken van een ziekte-specifieke CGT op én angst- én depressieve symptomen.

In **Hoofdstuk 2** beschrijven we de resultaten van een systematische review en meta-analyse naar hoe vaak angst en depressie bij kinderen en adolescenten met IBD voorkomen, oftewel wat de prevalentie hiervan is. Hierbij zijn systematisch alle beschikbare studies verzameld (op een dergelijke manier dat een ander dezelfde studies zou vinden) om een algemene conclusie daarover te trekken. Eerder onderzoek vond sterk uiteenlopende prevalenties van 0% tot 50%, hoewel er toch veel onderzoeken hoge prevalenties vonden. Uit onze zoektocht kwamen 28 studies (N = 8107, gemiddelde leeftijd van de patiënten: 14.3 jaar). De gepoolde (ofwel samengevatte)

prevalenties waren 16.4% (met een 95% Betrouwbaarheidsinterval [BI] van 6.8%-27.3%) voor angstsymptomen en 4.2% (met een 95%BI van 3.6%-4.8%) voor angststoornissen. De gepoolde (oftewel samengevatte) prevalenties waren 15.0% (met een 95%BI van 6.4%-24.8%) voor depressieve symptomen en 3.4% (met een 95%BI van 0%-9.3%) voor depressieve stoornissen. Met meta-regressie analyses kan je bekijken of bepaalde factoren nog invloed hebben op de samengevatte prevalenties. Hieruit bleek dat het ziektetype of geslacht geen invloed had, maar dat onderzoeken met relatief meer patiënten met actieve ziekte hogere prevalenties vonden van depressieve symptomen. Echter, deze resultaten moeten met voorzichtigheid worden geïnterpreteerd. De studies verschilden namelijk zeer sterk in welke instrumenten ze gebruikten en welke cutoff waarden ze hanteerden voor het bepalen van angst- of depressieve symptomen. Ook waren er maar weinig studies die onderzochten hoeveel angst- en depressieve stoornissen er voorkomen bij kinderen en adolescenten met IBD. We maken ons daarom ook sterk dat in vervolgonderzoek dezelfde vragenlijsten met vergelijkbare cutoff waarden gebruikt worden in verschillende landen en culturen. Op die manier kunnen we beter inzicht krijgen in hoe vaak angst en depressie voorkomen bij kinderen en adolescenten met IBD en welke factoren daarmee samenhangen.

**Hoofdstuk 3** is een beschrijving van de onderzoeksopzet van de RCT om de effectiviteit te onderzoeken van een ziekte-specifieke CGT voor jongeren met IBD en subklinische angst- en/of depressieklachten. Jongeren met IBD kunnen angst- en depressieve klachten ervaren. De relatie tussen IBD en angst en depressie kan mogelijk verklaard worden door de *brein-darm as*. Deze as houdt in dat het brein en de darmen met elkaar communiceren. Dit betekent dat het behandelen van angst en depressie de ontstekingen in de darmen kan verminderen en daarmee het ziektebeloop kan verbeteren. Jongeren met IBD worden gescreend met vragenlijsten voor symptomen van angst en depressie. Bij degenen met verhoogde angst en depressie werd een psychiatrisch interview afgenomen. Patiënten met verhoogde angst en/of depressie, maar niet met klinische angst en/of depressie, werden willekeurig verdeeld over twee groepen. De ene groep krijgt de standaard medische zorg van de (kinder-)MDL-arts, de andere groep krijgt de standaard medische zorg plus een ziekte-specifieke CGT. De belangrijkste uitkomsten zijn 1) het verminderen van angst en depressieve symptomen en 2) het in remissie blijven van de IBD gedurende 12 maanden. Andere uitkomsten zijn HRQOL en psychosociaal functioneren. Daarnaast onderzoeken we ook ontstekingsstoffen (cytokinen) en RNA expressie profielen in het bloed.

In **Hoofdstuk 4** onderzochten we risicofactoren voor het hebben van angst en/of depressie bij jongeren met IBD. Aangezien deze patiënten een verhoogd risico hebben op angst en/of depressie, wilden we met deze studie 1) onderzoeken hoe vaak angst en depressie voorkomen bij jongeren met IBD en 2) er achter komen welke demografische en ziektefactoren een risico geven op angst en depressie. Jongeren met IBD (N

= 374, 10-25 jaar oud) werden met vragenlijsten gescreend op angst en depressie. Bij patiënten met verhoogde scores werd een psychiatrisch interview afgenomen. Demografische en ziektefactoren werden gehaald uit de medische dossiers van de patiënten. Driekwart van de patiënten had IBD in remissie (dus weinig tot geen ontstekingen in de darmen). Milde angst en/of depressie werd gevonden in 35.2% van de patiënten, ernstige angst en/of depressie werd gevonden bij 12.4%. Meer specifiek vonden we bij 28.3% verhoogde angstklachten, bij 2.9% verhoogde depressieve klachten en bij 15.8% beiden. Deze aantallen verschilden niet tussen adolescenten (10-17 jaar oud) en jongvolwassenen (18-25 jaar oud). Met multipele logistische regressieanalyses vonden we dat het hebben van een actieve IBD en vrouw zijn significant gerelateerd waren aan depressieve symptomen. Vrouw zijn en korter geleden de diagnose IBD hebben gekregen waren significant gerelateerd aan angst en/of depressieve symptomen. Het is daarom belangrijk om jongeren met IBD te screenen op psychologische problemen, zoals angst en depressie. Vrouwelijke patiënten en degenen met een actieve IBD zijn het meest kwetsbaar.

In **Hoofdstuk 5** deden we onderzoek naar de onderlinge verbanden van demografische, ziekte- en psychologische factoren met HRQOL. Eerder onderzoek keek meestal naar individuele verbanden en combineerde dan één of twee factoren met HRQOL. Het is echter sterker om alle factoren in één keer te onderzoeken, zodat je rekening houdt met de onderlinge samenhang tussen deze factoren. We verzamelden data over de ziekteactiviteit, ziektepercepties, coping stijlen, angst, depressie en HRQOL in 262 jongeren met IBD (10-20 jaar oud, waarvan 46.6% mannelijk). Multipele lineaire regressieanalyses werden toegepast in twee aparte groepen voor elk ziektetype (één groep voor ZvK en één groep voor CU en IBD-ongeclassificeerd; IBD-U). Ziektepercepties en depressie waren significant gerelateerd met HRQOL, terwijl dit niet het geval was voor coping stijlen. Angst was alleen bij jongeren met CU/IBD-U gerelateerd aan HRQOL. In beide ziektetype groepen waren meer negatieve ziektepercepties en meer depressie gerelateerd aan een lagere HRQOL. Het is daarom belangrijk om deze psychologische factoren aandacht te geven in de medische zorg voor jongeren met IBD en om deze factoren aan te pakken in psychologische behandelingen voor deze patiënten. Daarmee lijkt hun HRQOL verbeterd te kunnen worden.

**Hoofdstuk 6** was een beschrijving van de resultaten van de directe nameting van de RCT. De groep die 3 maanden lang een ziekte-specifieke CGT kreeg verschilde niet van de controle groep die alleen de standaard medische zorg kreeg. In beide groepen zat een vergelijkbaar aantal patiënten dat stabiel bleef wat angst en depressie betreft. Daarnaast zat er in beide groepen een vergelijkbaar aantal patiënten van wie de angst- en depressieklachten afnamen. Exploratieve lineaire *mixed models* lieten zien dat de patiënten over het algemeen allemaal vooruitgingen op het gebied van angst, depressie, maar ook in hun HRQOL. Leeftijd, geslacht en ziektetype hadden hier geen

invloed op. Deze resultaten kunnen mogelijk verklaard worden door de bewustwording die bij patiënten in beide groepen gecreëerd werd doordat ze deelnamen aan het onderzoek. Een andere factor die een rol speelde is dat de patiënten weinig ziektelast ervoeren, wat betreft hun IBD en wat betreft hun angst- en depressieklachten.

In **Hoofdstuk 7** gaven we de resultaten van de RCT na 6 en 12 maanden na de eerste meting. We onderzochten hierbij verschillende psychologische uitkomsten. We keken niet alleen naar het effect van de ziekte-specifieke CGT op angst, depressie en HRQOL (zoals in Hoofdstuk 6), maar ook op sociaal functioneren, coping stijlen, ziektepercepties, en slaapproblemen. De resultaten waren vergelijkbaar met die uit Hoofdstuk 6. In beide groepen zat een vergelijkbaar aantal patiënten dat stabiel bleef of vooruitging in hun angst- en depressieklachten. Wederom wezen exploratieve lineaire *mixed models* erop dat patiënten in beiden groepen vooruitgingen in hun psychologische uitkomsten, 6 en 12 maanden na de eerste meting.

Tot slot gaven we in **Hoofdstuk 8** een algemene discussie, waarin we alle belangrijkste uitkomsten bespraken en conclusies en aanbevelingen gaven voor vervolgonderzoek en voor de klinische praktijk. Ondanks dat verschillende eerdere onderzoeken hoge prevalenties vonden van angst en depressie bij jongeren met IBD, kwamen de volgende prevalenties uit onze meta-analyse: 16.4% voor angstsymptomen, 4.2% voor angststoornissen, 15.0% voor depressieve symptomen en 3.4% voor depressieve stoornissen. Deze prevalenties zijn lager dan de prevalenties die gevonden zijn volwassenen met IBD. In onze eigen grote groep met jongeren met IBD vonden we dat 35.2% milde angst- of depressieklachten had en dat dit 12.4% was voor ernstige angst- en depressieklachten. We vonden ook dat een actieve IBD, vrouw zijn en korter geleden de diagnose IBD hebben gehad risicofactoren zijn voor het hebben van angst en/of depressie. Daarnaast vonden we in onze groep dat meer negatieve ziektepercepties en meer depressie samenhangen met een lagere HRQOL, bovenop de invloed van demografische en ziekte factoren, zoals leeftijd, geslacht, sociaal economische status, ziektetype en ziekteactiviteit. De RCT leerde ons dat alle patiënten verbeterden in hun angst- en depressiesymptomen, hun HRQOL, maar ook op het gebied van hun sociaal functioneren, coping stijlen en ziektepercepties gedurende 12 maanden follow-up.

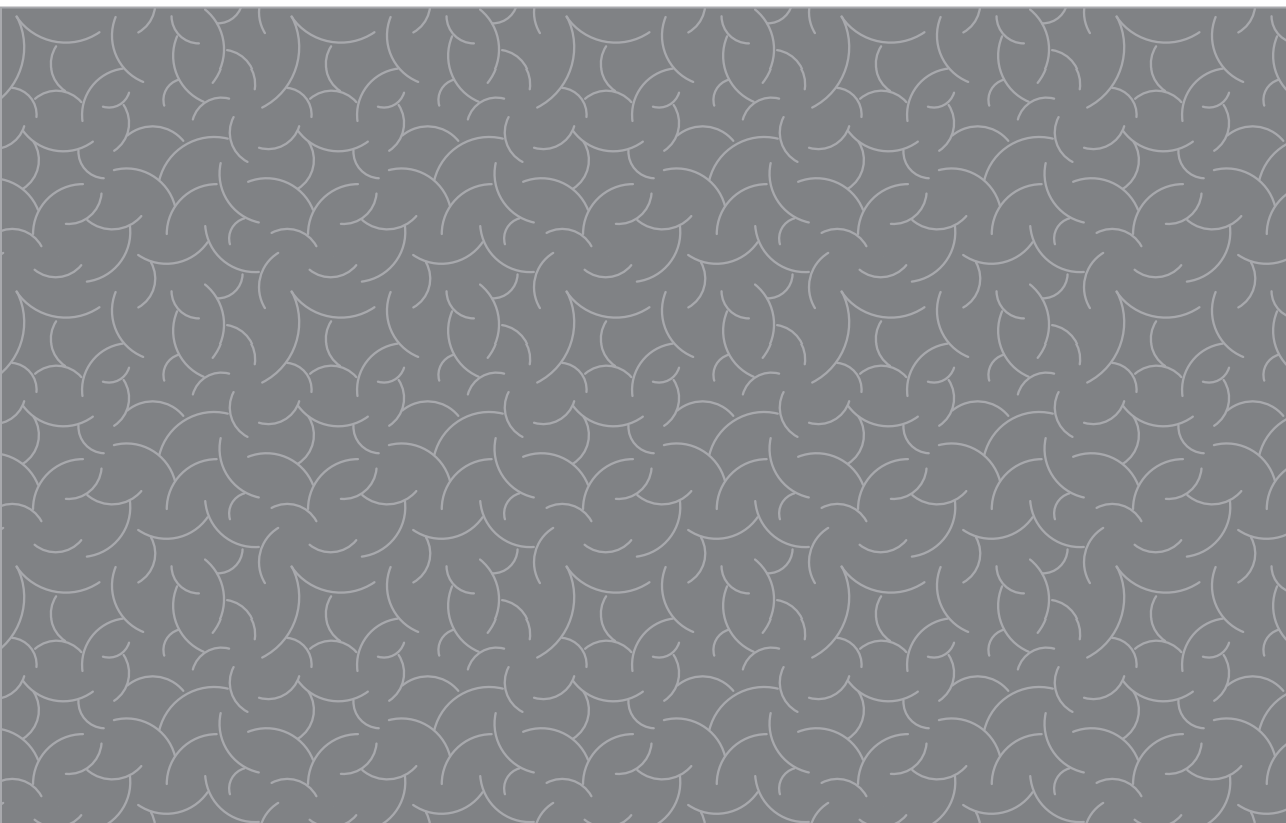
Dit onderzoek had verschillende sterke punten. In onze grote groep patiënten (374 deelnemers die één meting meededen) waren verschillende typen patiënten vertegenwoordigd. Enerzijds, omdat universitaire en perifere ziekenhuizen meededen. Anderzijds bevonden de ziekenhuizen zich in meer stedelijke gebieden en meer landelijke gebieden. Alle patiënten werden systematisch onderzocht met vragenlijsten, maar ook met een psychiatrisch interview. Voor onze RCT geldt dat sterke punten waren dat er zeer weinig patiënten stopten met de behandeling, dat we grondig hebben onderzocht of de behandeling daadwerkelijk is uitgevoerd zoals van te voren bedacht

was (behandelintegriteit genaamd) en dat ons doel was om èn angst èn depressie aan te pakken, aangezien deze veelvuldig samen voor komen.

Toekomstig onderzoek is nodig om nog beter uit te vinden hoe angst en depressie samenhangen met ontstekingen in de darmen. Hiervoor is het belangrijk dat de angst en depressie, maar ook de ziekteactiviteit veel regelmatiger gemeten worden dan in de meeste onderzoeken word gedaan, bijvoorbeeld wekelijks of maandelijks in plaats van om de drie of meer maanden. Om dit onderzoek te kunnen doen moeten korte screeningsinstrumenten voor angst en depressie gevalideerd worden in jongeren met IBD. Verder zouden studies naar psychologische behandeling van jongeren met IBD moeten uitvinden welke patiënten het meest geholpen zijn met psychologische behandeling en hoe deze het beste gegeven kan worden. Dit kan bijvoorbeeld slechts een aantal sessies zijn of door sessies online of telefonisch te doen. Daarnaast is het goed als onderzoeken naar de effecten van psychologische behandelingen tussenmetingen doen om zo inzicht te krijgen in hoe de wederkerige relatie tussen angst/depressie en ontstekingen in de darmen eruit ziet als je behandeling geeft. Ook kunnen zo factoren worden ontdekt die het succes van een behandeling kunnen voorspellen (zogenoemde moderatoren).

Voor de klinisch praktijk is het belangrijk dat jongeren met IBD systematisch gescreend worden op angst en depressie. Degenen met ernstige angst en/of depressie kunnen dan psychologische behandeling, zoals CGT, krijgen. Patiënten met milde angst en/of depressieklachten hebben er mogelijk voldoende aan dat deze klachten in de gaten worden gehouden, zodat de klachten niet erger worden en een grote invloed hebben op de darmontsteking.

List of publications
PhD portfolio
Curriculum vitae
Dankwoord



## LIST OF PUBLICATIONS

*van den Brink G, ***Stapersma L**, El Marroun H, Henrichs J, Szigethy EM, Utens EMWJ, Escher JC. Effectiveness of disease-specific cognitive-behavioural therapy on depression, anxiety, quality of life and the clinical course of disease in adolescents with inflammatory bowel disease: study protocol of a multicentre randomised controlled trial (HAPPY-IBD). BMJ Open Gastroenterology. 2016;3(1):e000071. doi:10.1136/bmjgast-2015-000071

**Stapersma L**, van den Brink G, van der Ende J, Szigethy EM, Beukers R, Korpershoek TA, Theuns-Valks SDM, Hillegers MHJ, Escher JC, Utens EMWJ. Effectiveness of Disease-Specific Cognitive Behavioral Therapy on Anxiety, Depression, and Quality of Life in Youth With Inflammatory Bowel Disease: A Randomized Controlled Trial. Journal of Pediatric Psychology. 2018;43(9):967-80. doi:5025052 [pii]

van den Brink G, **Stapersma L**, Vlug LE, Rizopoulos D, Bodelier AG, van Wering H, Hurkmans PCWM, Stuyt RJL, Hendriks DM, van der Burg JAT, Utens EMWJ, Escher JC. Clinical disease activity is associated with anxiety and depressive symptoms in adolescents and young adults with inflammatory bowel disease. Alimentary Pharmacolology and Therapeutics. 2018;48(3):358-69. doi:10.1111/apt.14832

***Stapersma L**, *van den Brink G, Szigethy EM, **Escher JC, **Utens EMWJ. Systematic review with meta-analysis: anxiety and depression in children and adolescents with inflammatory bowel disease. Alimentary Pharmacolology and Therapeutics. 2018;48(5):496-506. doi:10.1111/apt.14865

***Stapersma L**, *van den Brink G, Szigethy EM, **Escher JC, **Utens EMWJ. Editorial: anxiety and depression in inflammatory bowel disease – authors' reply. Alimentary Pharmacolology and Therapeutics. 2018;48(6):687-688. doi:10.1111/apt.14928

Utens EMWJ, **Stapersma L**, van der Mheen M, van Dalen M, Dessens A. Depressie en angst bij kinderen en jongeren met een lichamelijke aandoening: screening en behandeling. Tijdschrift Kinder- en Jeugdpsychotherapie. 2019;46(1).

van den Brink G, **Stapersma L**, Bom AS, Rizopoulos D, van der Woude CJ, Stuyt, RJL, Hendriks DM, van der Burg JAT, Beukers R, Korpershoek TA, Theuns-Valks SDM, Utens EMWJ, Escher JC. 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. Inflammatory Bowel Diseases; 2019; izz073. doi:10.1093/ibd/izz073

Dekkers FHW, Go ATJI, **Stapersma L**, Eggink AJ, Utens EMWJ. Termination of pregnancy for fetal anomalies: Parents' preferences for psychosocial care. Prenatal Diagnosis; 2019; 1-13. doi:10.1002/pd.5464

**Stapersma L**, van den Brink G, van der Ende J, Szigethy EM, Bodelier A, Van Wering HM, Hurkmans PCWM, Escher JC, Utens, EMWJ. Illness perceptions and depression are associated with health-related quality of life in youth with inflammatory bowel disease. International Journal of Behavioral Medicine; 2019, 1-12. doi:10.1007/s12529-019-09791-6

**Stapersma L**, van den Brink G, van der Ende J, Szigethy EM, Groeneweg M, de Bruijne FH, Hillegers MHJ, Escher JC, Utens EMWJ. Psychological outcomes of a cognitive behavioral therapy for youth with inflammatory bowel disease: results of a randomized controlled trial at 6 and 12 months follow-up. (In revision for Journal of Clinical Psychology in Medical Settings).

Van den Brink G, Costes LMM, Tindemans I, **Stapersma L**, Rizopoulos D, van der Woude CJ, Raatgreep HRC, Utens EMWJ, Samsom JN, Escher JC. Plasma protein profiles associated with anxiety and/or depressive symptoms in young IBD patients and the effect of cognitive behavioral therapy. (Submitted to Inflammatory Bowel Diseases)

## PHD PORTFOLIO

| Name PhD student | Luuk Stapersma |
|---|---|
| Research School | Netherlands Institue for Health Sciencs (NIHES) |
| Erasmus MC Department | Child and Adolescent Psychiatry/Psychology |
| PhD Period | April 2014 – August 2018 |
| Promotor(s) | Prof. dr. E.M.W.J. Utens, prof. dr. J.C. Escher, prof. dr. M.H.J. Hillegers |

| | Year | Workload (ECTS) |
|---|---|---|
| **PhD training activities** | | |
| **General academic skills** | | |
| EndNote and PubMed | 2014 | 1 |
| Basic course for clinical investigators (BROK®) | 2014 | 1 |
| BROK® Herregistratie | 2018 | 0.2 |
| Integrity in Science (Erasmus MC) | 2015 | 0.3 |
| Course Consultation center for Patient Oriented research (CPO, Erasmus MC) | 2015 | 0.3 |
| Biomedical English Writing and Communication | 2016-2017 | 4 |
| **Research skills** | | |
| Biostatistics for Clinicians (EWP22) | 2015 | 0.7 |
| Psychology in Medicine (MP01) | 2015 | 1.4 |
| Principles of Research in Medicine (ESP01) | 2015 | 0.7 |
| Regression Analysis (ESP09) | 2015 | 1.9 |
| Clinical Trials (ESP14) | 2015 | 0.7 |
| Causal Mediation Analysis (ESP69) | 2015 | 0.7 |
| Psychopharmacology (MP03) | 2016 | 1.4 |
| Repeated Measurements (CE08) | 2016 | 1.4 |
| Preventing Failed Interventions in Behavioral Research (MP05) | 2016 | 1.4 |
| Psychiatric Epidemiology (EP12) | 2018 | 1.1 |
| **Specific skills** | | |
| Basiskwalifitcatie Onderwijs (BKO, Erasmus MC) | | |
| Teach the Teacher I | 2014 | 0.7 |
| Individual guidance | 2015 | 0.15 |
| Lectures | 2015 | 0.3 |
| **Presentations** | | |
| NVvP Voorjaarscongres April 10, 2014, Maastricht, The Netherlands (Discussion group) | 2014 | 0.2 |

| | Year | Workload (ECTS) |
|---|---|---|
| Research meetings Child and Psychiatry/Psychology, Erasmus MC (3 orals) | 2014-2016 | 0.2 |
| Clinical and Research meetings Pediatric Psychology (1 orals) | 2014 | 0.1 |
| Sophia Research Days, Erasmus MC (2 orals) | 2017-2018 | 0.2 |
| Clinical Psychology, Erasmus University Rotterdam (EUR) (1 oral) | 2017 | 0.1 |
| pIBD Conference, September 13-16, 2017, Barcelona, Spain (1 poster) | 2017 | 0.2 |
| VGCt Najaarscongres, November 8, 2017 Veldhoven, The Netherlands (1 oral) | 2017 | 0.2 |
| Research meetings Pediatric Psychology (1 oral) | 2018 | 0.1 |
| Colloquium Child and Adolescent Psychiatry/Psychology (1 oral) | 2018 | 0.1 |
| EPPC, September 20-21, 2018, Ghent, Belgium (1 oral) | 2018 | 0.2 |
| VGCt Najaarscongres, November 8, 2018, Veldhoven, The Netherlands (1 workshop) | 2018 | 0.2 |
| | | |
| **Conferences** | | |
| NVvP Voorjaarscongres April 10, 2014, Maastricht, The Netherlands | 2014 | 0.3 |
| Sophia Research Days, Erasmus MC | 2014-2018 | 0.45 |
| Dutch-UK Pediatric Psychology Conference, Amsterdam, The Netherlands | 2014 | 0.3 |
| ESPRi Symposium, Erasmus MC | 2014, 2015 | 0.4 |
| Symposium Dubbeloratie Van der Woude & Escher, Erasmus MC | 2015 | 0.15 |
| Congress Research Integrity, Erasmus MC | 2015 | 0.3 |
| KNICR Symposium, Erasmus MC | 2016 | 0.1 |
| Child Development Conference, University of Amsterdam | 2016 | 0.2 |
| Afscheidssymposium prof.dr. F.C. Verhulst | 2017 | 0.3 |
| Symposium 'Het psychisch kwetsbare kind', AMC – De Bascule | 2017 | 0.3 |
| VGCt Najaarscongres, November 8, 2017 Veldhoven, The Netherlands | 2017 | 0.3 |
| EPPC, September 20-21, 2018, Ghent, Belgium | 2018 | 0.6 |
| VGCt Najaarscongres, November 8, 2018, Veldhoven, The Netherlands | 2018 | 0.3 |
| | | |
| **Workshops, meetings and seminars** | | |
| Research meetings Child and Psychiatry/Psychology, Erasmus MC | 2014-2018 | 2 |
| Clinical and Research meetings Pediatric Psychology, Erasmus MC | 2014-2018 | 1.5 |
| Research meetings Pediatric Psychology, Erasmus MC | 2014-2018 | 1 |
| Colloquium Child and Psychiatry/Psychology, Erasmus MC | 2014-2018 | 1 |
| 'How to Publish a World Class Paper', Erasmus University Rotterdam | 2015 | 0.15 |
| 'How to Present your Poster', Erasmus MC | 2015 | 0.1 |

| | Year | Workload (ECTS) |
|---|---|---|
| PhD Lectures, Erasmus MC | 2015 | 0.1 |
| Workshop Grant Writing, Erasmus MC | 2015 | 0.1 |
| PhD Day, Erasmus MC | 2015-2017 | 0.45 |
| Science Café Child and Psychiatry/Psychology, Erasmus MC | 2016-2018 | 1 |
| Inventarisatiebijeenkomst Zorginstituut | 2016 | 0.15 |
| | | |
| **Teaching activities** | | |
| **Master's Thesis Supervision** | | |
| M. van den Heuvel (Child and Adolescent Psychology, Leiden University) | 2014-2015 | 3.0 |
| *Sleep problems impact quality of life and feelings of anxiety and depression in Dutch adolescents with inflammatory bowel disease* | | |
| L. van den Berg (Clinical Child and Adolescent Psychology, Erasmus University Rotterdam) | 2015 | 3.0 |
| *Cognitive coping and its relation with anxiety, depression, and quality of life in adolescents with inflammatory bowel disease* | | |
| N. Akbas (Clinical Child and Adolescent Psychology, Erasmus University Rotterdam) | 2015-2016 | 3.0 |
| *Verhoogd angstklachten en een verslechterde kwaliteit van leven bij kinderen en jongeren met inflammatory bowel disease* | | |
| R. Gutlich (Clinical Child and Adolescent Psychology, Erasmus University Rotterdam) | 2016 | 3.0 |
| *Kwaliteit van leven bij kinderen en adolescenten met IBD* | | |
| D. Ormskerk (Clinical Child and Adolescent Psychology, Erasmus University Rotterdam) | 2017 | 3.0 |
| *De invloed van ouderlijke stress en familie functioneren, op kinderen en adolescenten met inflammatoire darmziekten* | | |
| | | |
| **Other teaching activities** | | |
| Supervising 2nd year medical students, Erasmus University Rotterdam "Writing a systematic review" | 2015-2017 | 2.1 |
| Supervising 3rd year medical students, Erasmus University Rotterdam | 2015-2019 | 2.0 |
| Lecture IBD in children, Tilburg University | 2015 | 0.15 |
| Lecture Minor Medical Psychology, Erasmus MC | 2015-2016 | 0.3 |
| Training PASCET-PI (CBT) | 2015-2016 | 0.3 |
| Lecture Anxiety disorders, OCD and tic disorders, VUmc | 2019 | 0.15 |
| **Clinical activities** | | |
| PASCET-PI (CBT) Training prof.dr. E. Szigethy | 2014 | 0.6 |
| SCREEN patient demonstration, outpatient clinic Child and Adolescent Psychiatry/Psychology, Erasmus MC | 2014 | 0.2 |

| | Year | Workload (ECTS) |
|---|---|---|
| Practical WISC-III-NL Child and Adolescent Psychology, Erasmus University Rotterdam | 2014-2015 | 0.3 |
| CHIP Parent Workshop | 2016-2017 | 0.2 |
| Psychologist outpatient clinic Child and Adolescent Psychiatry/ Psychology, Erasmus MC | 2017-present | |
| Training ADOS-2 | 2018 | 2 |
| Training WISC-V | 2019 | 0.3 |
| **Other activities** | | |
| Organization committee Science Café Rotterdam, Bibliotheek Rotterdam | 2015-2018 | |
| Coordination of Research meetings Child and Psychiatry/ Psychology, Erasmus MC | 2015-2016 | |
| Organization of monthly Science Café Child and Adolescent Psychiatry/Psychology, Erasmus MC | 2016-present | |
| Reviewing articles (Journal of Crohn and Colitis, Journal of Psychosomatic Research, Journal of Clinical Psychology in Medical Settings) | 2018-present | |