# 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*

## 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.

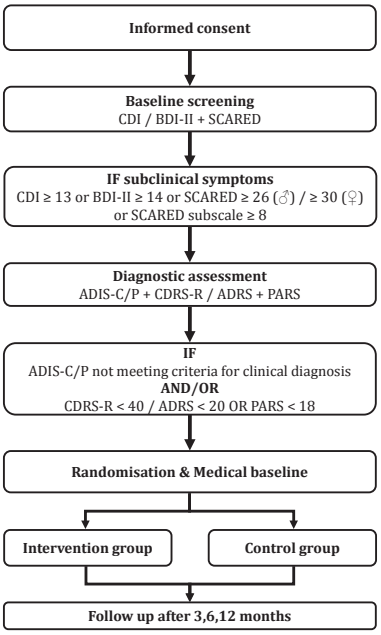


**Figure 1** | Flow chart study design
Abbreviations: CDI= Child Depression Inventory; BDI-II= Beck Depression Inventory – Second Edition; SCARED= Screen for Child Anxiety Related Emotional Disorders; ADIS-C/P= Anxiety Disorders Interview Schedule - Child and Parent Version; CDRS-R= Child Depression 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-1β, 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 $\beta = 0.05$ 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.

## REFERENCES


1. Baumgart DC, Bernstein CN, Abbas Z, Colombel JF, Day AS, D'Haens G, et al. IBD Around the world: comparing the epidemiology, diagnosis, and treatment: proceedings of the World Digestive Health Day 2010–Inflammatory Bowel Disease Task Force meeting. Inflamm Bowel Dis. 2011;17(2):639-44.
2. Greenley RN, Hommel KA, Nebel J, Raboin T, Li SH, Simpson P, et al. A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. Journal of pediatric psychology. 2010;35(8):857-69.
3. Griffiths AM. Specificities of inflammatory bowel disease in childhood. Best practice & research Clinical gastroenterology. 2004;18(3):509-23.
4. Rabizadeh S, Dubinsky M. Update in pediatric inflammatory bowel disease. Rheumatic diseases clinics of North America. 2013;39(4):789-99.
5. Engelmann G, Erhard D, Petersen M, Parzer P, Schlarb AA, Resch F, et al. Health-related quality of life in adolescents with inflammatory bowel disease depends on disease activity and psychiatric comorbidity. Child Psychiatry Hum Dev. 2015;46(2):300-7.
6. Lynch T, Spence D. A qualitative study of youth living with Crohn disease. Gastroenterol Nurs. 2008;31(3):224-30; quiz 31-2.
7. Kilroy S, Nolan E, Sarma KM. Quality of life and level of anxiety in youths with inflammatory bowel disease in Ireland. J Pediatr Gastroenterol Nutr. 2011;53(3):275-9.
8. Ross SC, Strachan J, Russell RK, Wilson SL. Psychosocial functioning and health-related quality of life in paediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2011;53(5):480-8.
9. Karwowski CA, Keljo D, Szigethy E. Strategies to improve quality of life in adolescents with inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(11):1755-64.
10. Mackner LM, Greenley RN, Szigethy E, Herzer M, Deer K, Hommel KA. Psychosocial issues in pediatric inflammatory bowel disease: report of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2013;56(4):449-58.
11. Szigethy E, Craig AE, Iobst EA, Grand RJ, Keljo D, DeMaso D, et al. Profile of depression in adolescents with inflammatory bowel disease: implications for treatment. Inflamm Bowel Dis. 2009;15(1):69-74.
12. Szigethy E, McLafferty L, Goyal A. Inflammatory bowel disease. Pediatric clinics of North America. 2011;58(4):903-20, x-xi.
13. Burke P, Meyer V, Kocoshis S, Orenstein DM, Chandra R, Nord DJ, et al. Depression and anxiety in pediatric inflammatory bowel disease and cystic fibrosis. J Am Acad Child Adolesc Psychiatry. 1989;28(6):948-51.
14. Burke PM, Neigut D, Kocoshis S, Chandra R, Sauer J. Correlates of depression in new onset pediatric inflammatory bowel disease. Child Psychiatry Hum Dev. 1994;24(4):275-83.
15. Clark JG, Srinath AI, Youk AO, Kirshner MA, McCarthy FN, Keljo DJ, et al. Predictors of depression in youth with Crohn disease. J Pediatr Gastroenterol Nutr. 2014;58(5):569-73.
16. Reigada LC, Bruzzese JM, Benkov KJ, Levy J, Waxman AR, Petkova E, et al. Illness-specific anxiety: implications for functioning and utilization of medical services in adolescents with inflam-

matory bowel disease. Journal for specialists in pediatric nursing : JSPN. 2011;16(3):207-15.
17. Szigethy E, Kenney E, Carpenter J, Hardy DM, Fairclough D, Bousvaros A, et al. Cognitive-behavioral therapy for adolescents with inflammatory bowel disease and subsyndromal depression. J Am Acad Child Adolesc Psychiatry. 2007;46(10):1290-8.
18. Szigethy E, Levy-Warren A, Whitton S, Bousvaros A, Gauvreau K, Leichtner AM, et al. Depressive symptoms and inflammatory bowel disease in children and adolescents: a cross-sectional study. J Pediatr Gastroenterol Nutr. 2004;39(4):395-403.
19. Reigada LC, Hoogendoorn CJ, Walsh LC, Lai J, Szigethy E, Cohen BH, et al. Anxiety symptoms and disease severity in children and adolescents with crohn disease. J Pediatr Gastroenterol Nutr. 2015;60(1):30-5.
20. Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. Depress Anxiety. 2001;14(2):67-78.
21. Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Andrews JM, Holtmann GJ. Controversies surrounding the comorbidity of depression and anxiety in inflammatory bowel disease patients: a literature review. Inflamm Bowel Dis. 2007;13(2):225-34.
22. Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. Arch Gen Psychiatry. 2009;66(7):764-72.
23. Thompson RD, Craig A, Crawford EA, Fairclough D, Gonzalez-Heydrich J, Bousvaros A, et al. Longitudinal results of cognitive behavioral treatment for youths with inflammatory bowel disease and depressive symptoms. Journal of clinical psychology in medical settings. 2012;19(3):329-37.
24. Loftus EV, Jr., Guerin A, Yu AP, Wu EQ, Yang M, Chao J, et al. Increased risks of developing anxiety and depression in young patients with Crohn's disease. Am J Gastroenterol. 2011;106(9):1670-7.
25. Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. Gastroenterology. 2013;144(1):36-49.
26. Goodhand JR, Wahed M, Mawdsley JE, Farmer AD, Aziz Q, Rampton DS. Mood disorders in inflammatory bowel disease: relation to diagnosis, disease activity, perceived stress, and other factors. Inflamm Bowel Dis. 2012;18(12):2301-9.
27. Bennebroek Evertsz F, Thijssens NA, Stokkers PC, Grootenhuis MA, Bockting CL, Nieuwkerk PT, et al. Do Inflammatory Bowel Disease patients with anxiety and depressive symptoms receive the care they need? Journal of Crohn's & Colitis. 2012;6(1):68-76.
28. Panara AJ, Yarur AJ, Rieders B, Proksell S, Deshpande AR, Abreu MT, et al. The incidence and risk factors for developing depression after being diagnosed with inflammatory bowel disease: a cohort study. Aliment Pharm Ther. 2014;39(8):802-10.
29. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. Inflamm Bowel Dis. 2009;15(7):1105-18.
30. Mittermaier C, Dejaco C, Waldhoer T, Oefferlbauer-Ernst A, Miehsler W, Beier M, et al. Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. Psychosomatic medicine. 2004;66(1):79-84.
31. Nahon S, Lahmek P, Durance C, Olympie A, Lesgourgues B, Colombel JF, et al. Risk factors of anxiety and depression

in inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(11):2086-91.
32. Keethy D, Mrakotsky C, Szigethy E. Pediatric inflammatory bowel disease and depression: treatment implications. Curr Opin Pediatr. 2014;26(5):561-7.
33. Simren M, Axelsson J, Gillberg R, Abrahamsson H, Svedlund J, Bjornsson ES. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. Am J Gastroenterol. 2002;97(2):389-96.
34. Engstrom I. Inflammatory bowel disease in children and adolescents: mental health and family functioning. J Pediatr Gastroenterol Nutr. 1999;28(4):S28-33.
35. Gray WN, Graef DM, Schuman SS, Janicke DM, Hommel KA. Parenting stress in pediatric IBD: relations with child psychopathology, family functioning, and disease severity. J Dev Behav Pediatr. 2013;34(4):237-44.
36. Fuller-Thomson E, Sulman J. Depression and inflammatory bowel disease: findings from two nationally representative Canadian surveys. Inflamm Bowel Dis. 2006;12(8):697-707.
37. Mackner LM, Crandall WV. Psychological factors affecting pediatric inflammatory bowel disease. Curr Opin Pediatr. 2007;19(5):548-52.
38. Szigethy EM, Youk AO, Benhayon D, Fairclough D, Newara MC, Kirshner MA, et al. Depression Subtypes in Pediatric Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr. 2013.
39. Reed-Knight B, Lobato D, Hagin S, McQuaid EL, Seifer R, Kopel SJ, et al. Depressive symptoms in youth with inflammatory bowel disease compared with a community sample. Inflamm Bowel Dis. 2014;20(4):614-21.
40. Bernstein CN, Singh S, Graff LA, Walker JR, Miller N, Cheang M. A prospective population-based study of triggers of symptomatic flares in IBD. Am J Gastroenterol. 2010;105(9):1994-2002.
41. Bitton A, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. Gut. 2008;57(10):1386-92.
42. Bitton A, Sewitch MJ, Peppercorn MA, de BEMD, Shah S, Ransil B, et al. Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. Am J Gastroenterol. 2003;98(10):2203-8.
43. Levenstein S, Prantera C, Varvo V, Scribano ML, Andreoli A, Luzi C, et al. Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. Am J Gastroenterol. 2000;95(5):1213-20.
44. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. Gut. 2005;54(10):1481-91.
45. Srinath AI, Goyal A, Zimmerman LA, Newara MC, Kirshner MA, McCarthy FN, et al. Predictors of abdominal pain in depressed pediatric inflammatory bowel disease patients. Inflamm Bowel Dis. 2014;20(8):1329-40.
46. Ryan JL, Mellon MW, Junger KW, Hente EA, Denson LA, Saeed SA, et al. The clinical utility of health-related quality of life screening in a pediatric inflammatory bowel disease clinic. Inflamm Bowel Dis. 2013;19(12):2666-72.
47. Gray WN, Denson LA, Baldassano RN, Hommel KA. Treatment adherence in adolescents with inflammatory bowel disease: the collective impact of barriers to adherence and anxiety/depressive symptoms. Journal of pediatric psychology. 2012;37(3):282-91.
48. O'Donovan A. Inflammation and depression: unraveling the complex interplay in inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2014;58(5):541-2.

49. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends in immunology. 2006;27(1):24-31.
50. Mawdsley JE, Rampton DS. The role of psychological stress in inflammatory bowel disease. Neuroimmunomodulation. 2006;13(5-6):327-36.
51. Reber SO. Stress and animal models of inflammatory bowel disease–an update on the role of the hypothalamo-pituitary-adrenal axis. Psychoneuroendocrinology. 2012;37(1):1-19.
52. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychological bulletin. 2014;140(3):774-815.
53. Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC medicine. 2013;11:129.
54. Schmidt HD, Shelton RC, Duman RS. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2011;36(12):2375-94.
55. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosomatic medicine. 2009;71(2):171-86.
56. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67(5):446-57.
57. Vogelzangs N, Beekman AT, de Jonge P, Penninx BW. Anxiety disorders and inflammation in a large adult cohort. Transl Psychiatry. 2013;3:e249.
58. Hou R, Baldwin DS. A neuroimmunological perspective on anxiety disorders. Human psychopharmacology. 2012;27(1):6-14.
59. Salim S, Chugh G, Asghar M. Inflammation in anxiety. Advances in protein chemistry and structural biology. 2012;88:1-25.
60. Hoge EA, Brandstetter K, Moshier S, Pollack MH, Wong KK, Simon NM. Broad Spectrum of Cytokine Abnormalities in Panic Disorder and Posttraumatic Stress Disorder. Depress Anxiety. 2009;26(5):447-55.
61. Szigethy E, Weisz JR, Findling RL. Cognitive-Behavior Therapy for Children and Adolescents. Arlington: American Psychiatric Publishing; 2012. p. 331-78.
62. Thompson RD, Delaney P, Flores I, Szigethy E. Cognitive-behavioral therapy for children with comorbid physical illness. Child and adolescent psychiatric clinics of North America. 2011;20(2):329-48.
63. Szigethy E, Whitton SW, Levy-Warren A, DeMaso DR, Weisz J, Beardslee WR. Cognitive-behavioral therapy for depression in adolescents with inflammatory bowel disease: a pilot study. J Am Acad Child Adolesc Psychiatry. 2004;43(12):1469-77.
64. Szigethy E, Bujoreanu SI, Youk AO, Weisz J, Benhayon D, Fairclough D, et al. Randomized efficacy trial of two psychotherapies for depression in youth with inflammatory bowel disease. J Am Acad Child Adolesc Psychiatry. 2014;53(7):726-35.
65. Reigada LC, Benkov KJ, Bruzzese JM, Hoogendoorn C, Szigethy E, Briggie A, et al. Integrating illness concerns into cognitive behavioral therapy for children and adolescents with inflammatory bowel disease and co-occurring anxiety. Journal for specialists in pediatric nursing : JSPN. 2013;18(2):133-43.
66. Timbremont B, Brat C, Roelofs J. Handleiding Children's Depression In-

ventory (herziene versie). Amsterdam, NL: Pearson, 2008.
67. van der Does AJW. BDI-II-NL. Handleiding. De Nederlandse versie van de Beck Depression Inventory. Lisse, NL: Harcourt Test Publishers, 2002.
68. Muris PB, D.; Hale, W.; Birmaher, B.; Mayer, B. Vragenlijst over angst en bang zijn bij kinderen en adolescenten. Handleiding bij gereviseerde Nederlandse versie van de Screen for Child Anxiety Related Disorders. Amsterdam, NL: Boom, 2007.
69. Bodden DH, Bogels SM, Muris P. The diagnostic utility of the Screen for Child Anxiety Related Emotional Disorders-71 (SCARED-71). Behav Res Ther. 2009;47(5):418-25.
70. Siebelink BM, Treffers PDA. Anxiety Disorders Interview Schedule for DSM-IV-Child version, ADIS-C Handleiding. Amsterdam: Harcourt Test Publishers; 2001.
71. Silverman WK, Albano AM. Anxiety Disorders Interview Schedule for DSM-IV Child Version, Child Interview Schedule. San Antonio. The Psychological Corporation; 1996.
72. Poznanski EO, Mokros H. Children's Depression Rating Scale Revised (CDRS-R). Los Angeles Western Psychological Services; 1996.
73. Revah-Levy A, Birmaher B, Gasquet I, Falissard B. The Adolescent Depression Rating Scale (ADRS): a validation study. BMC Psychiatry. 2007;7:2.
74. The Pediatric Anxiety Rating Scale (PARS): development and psychometric properties. J Am Acad Child Adolesc Psychiatry. 2002;41(9):1061-9.
75. Ginsburg GS, Keeton CP, Drazdowski TK, Riddle MA. The Utility of Clinicians Ratings of Anxiety Using the Pediatric Anxiety Rating Scale (PARS). Child Youth Care For. 2011;40(2):93-105.
76. Vogels T, Verrips GHW, Koopman HM, Theunissen NCM, Fekkes M, Kamphuis RP. Child Quality of Life Questionnaire (TACQOL). Manual parent and child form. . Leiden, NL: LUMC-TNO; 1999.
77. Bruil J, Fekkes M, Vogels T, Verrips GHW. TAAQOL Manual. Leiden, NL: Leiden Center for Child Health and Pediatrics LUMC-TNO; 2004.
78. Loonen HJ, Grootenhuis MA, Last BF, de Haan RJ, Bouquet J, Derkx BH. Measuring quality of life in children with inflammatory bowel disease: the impact-II (NL). Qual Life Res. 2002;11(1):47-56.
79. Liber JM, Van Lang NDJ, Treffers PDA. Confirmatory factor analysis of the Dutch version of the Social Skills Rating System:. Curium, Academic Center for Child and Adolescent Psychiatry, LUMC 2006.
80. Achenbach TM, Rescorla LA. Manual for the ASEBA school-age forms & profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2001.
81. Achenbach TM, Rescorla LA. Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2003.
82. Utens EMWJ, van Rijen EHM, Erdman RAM, Verhulst FC. Rotterdam's Kwaliteit van Leven Interview. Erasmus MC Rotterdam, Netherlands. Department of Child and Adolescent Psychiatry and Psychology, 2000.
83. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res. 2006;60(6):631-7.
84. Garnefski NK, V.;Spinhoven, P. CERQ: Manual for the use of the Cognitive Emotion Regulation Questionnaire. A questionnaire for measuring cognitive coping strategies. Leiderdorp, NL.: Datec V.O.F.; 2007.

85. Owens JA, Spirito A, McGuinn M, Nobile C. Sleep habits and sleep disturbance in elementary school-aged children. J Dev Behav Pediatr. 2000;21(1):27-36.
86. Beurs E, Van Dyck R, Marquenie LA, Lange A, Blonk RWB. De DASS: een vragenlijst voor het meten van depressie, angst en stress. Gedragstherapie. 2001;34:35-53.
87. Tuinman MA, Gazendam-Donofrio SM, Hoekstra-Weebers JE. Screening and referral for psychosocial distress in oncologic practice: use of the Distress Thermometer. Cancer. 2008;113(4):870-8.
88. Epstein NB, Baldwin LM, Bishop DS. The McMaster family assessment device. Journal of Marital and Family Therapy 9, (2), 171-180 1983.
89. Weisz JR, Thurber CA, Sweeney L, Proffitt VD, LeGagnoux GL. Brief treatment of mild-to-moderate child depression using primary and secondary control enhancement training. J Consult Clin Psychol. 1997;65(4):703-7.
90. Hyams JS, Ferry GD, Mandel FS, Grybosski JD, Kibort PM, Kirschner BS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr. 1991;12(4):439-47.
91. Turner D, Griffiths AM, Walters TD, Seah T, Markowitz J, Pfefferkorn M, et al. Mathematical weighting of the pediatric Crohn's disease activity index (PCDAI) and comparison with its other short versions. Inflamm Bowel Dis. 2012;18(1):55-62.
92. Turner D, Otley AR, Mack D, Hyams J, de Bruijne J, Uusoue K, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology. 2007;133(2):423-32.
93. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007;132(3):863-73; quiz 1165-6.
94. Utens EM, Verhulst FC, Duivenvoorden HJ, Meijboom FJ, Erdman RA, Hess J. Prediction of behavioural and emotional problems in children and adolescents with operated congenital heart disease. European heart journal. 1998;19(5):801-7.
95. Klein JB, Jacobs RH, Reinecke MA. Cognitive-behavioral therapy for adolescent depression: a meta-analytic investigation of changes in effect-size estimates. J Am Acad Child Adolesc Psychiatry. 2007;46(11):1403-13.
96. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. Psychological bulletin. 2006;132(1):132-49.
97. In-Albon T, Schneider S. Psychotherapy of childhood anxiety disorders: A meta-analysis. Psychotherapy and psychosomatics. 2007;76(1):15-24.
98. Reynolds S, Wilson C, Austin J, Hooper L. Effects of psychotherapy for anxiety in children and adolescents: a meta-analytic review. Clin Psychol Rev. 2012;32(4):251-62.