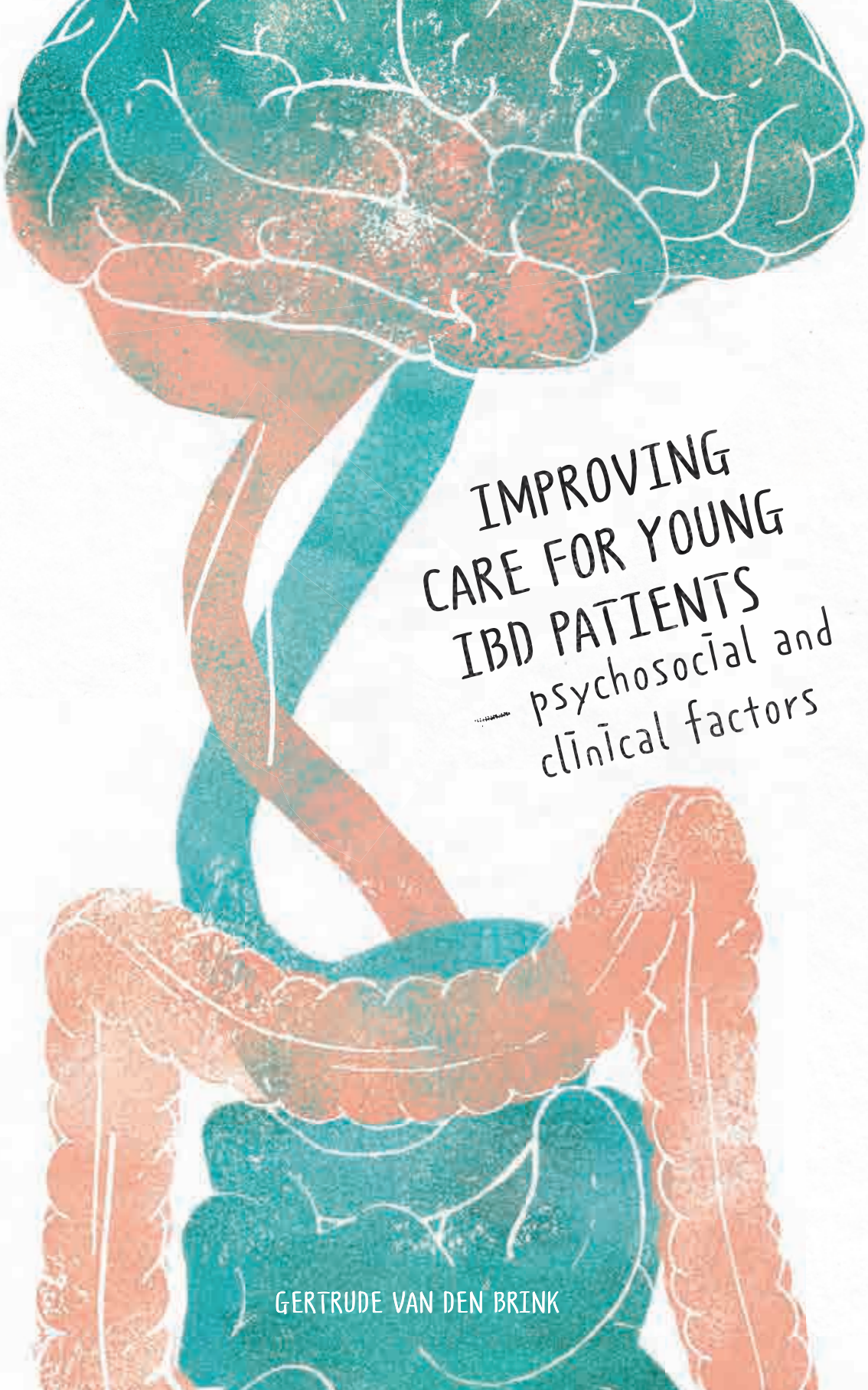

IMPROVING CARE FOR YOUNG IBD PATIENTS

– psychosocial and clinical factors

GERTRUDE VAN DEN BRINK

IMPROVING CARE FOR YOUNG IBD PATIENTS

Psychosocial and clinical factors

Gertrude van den Brink

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IMPROVING CARE FOR YOUNG IBD PATIENTS

Psychosocial and clinical factors

Verbeteren van de zorg voor jonge IBD-patiënten
Psychosociale en klinische factoren

Proefschrift

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Blessed beyond measure

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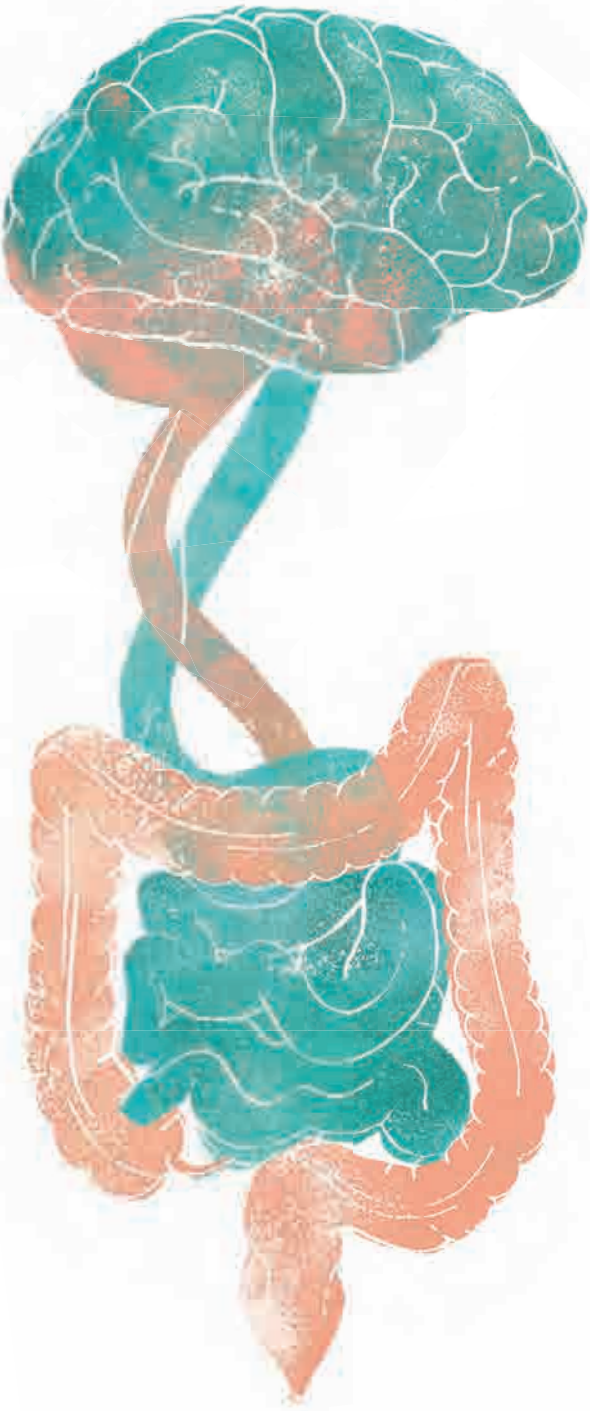

CHAPTER 1

General introduction, aims and outline

GENERAL INTRODUCTION

Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a chronic relapsing inflammatory disorder that affects the gastrointestinal tract in children, adolescents and adults and generally consists of two types: Ulcerative Colitis (UC) and Crohn's disease (CD). The exact aetiology of IBD is unclear, it is believed that a complex interaction of genetics and environmental factors leads to a dysregulated immune response to the commensal intestinal microbiota.[1, 2] Genetic and environmental factors initiate alterations in epithelial barrier function which leads to infiltration of luminal antigens with ultimately inflammation of the bowel wall. When acute intestinal inflammation is not resolved, uncontrolled activation of the mucosal immune system (e.g. Macrophages, Dendritic Cells, T-cells) causes chronic intestinal inflammation which is driven by cytokines (e.g. Tumor Necrosis Factor alpha (TNF-α), Interferon gamma (IFN-γ), Interleukin (IL)-1, IL-1β, IL-6, IL-12, IL-22, IL-17, and IL-23).[2-4]

Worldwide, an increase in the incidence and prevalence of IBD has been observed.[5] For adults with IBD, the highest incidence has been found in Europe and North America (4-8 per 100.000 person years).[5] For paediatric IBD most recent studies show varying incidence rates, from 4.4[6] (France, up to 2011) to 10 per 100.000/year[7] (England, up to 2017). Until recently, it was thought that in up to 25% of patients IBD develops and manifests during childhood[8], with a peak onset in adolescence.[9] A recent study however indicates that the incidence might be lower, around 8%.[6]

Clinical presentation of IBD

UC and CD have overlapping clinical features but are considered separate entities, clinical presentation depends on the site and extent of mucosal inflammation.

CD is characterised by a transmural and granulomatous inflammation involving any part of the gastrointestinal tract (from mouth to anus), often with a non-contiguous pattern (so called skip lesions). Patients with CD mostly suffer from abdominal pain, diarrhoea, decreased appetite and weight loss, but anaemia, perianal disease (abscesses or fistula), growth failure and delayed puberty are also common.[1] Initial symptoms may not be that specific and can contribute to delay in diagnosis.

UC is characterised by continuous mucosal inflammation of the colon, extending from the rectum proximally, without skip lesions or granulomas. Patients with UC suffer mostly from abdominal pain, rectal bleeding, diarrhoea and weight loss.

IBD is not limited to the bowel, up to 30% of patients will develop an extra intestinal manifestation (EIM) during their lifetime, mostly arthritis and skin manifestations.[10 11]

The bowel inflammation in IBD is characterised by episodes of relapse and remission. Literature shows that in general, 30-50 percent of patient has at least one relapse per year[12-14], which can lead to irreversible damage despite chronic medical treatment. There is no cure for IBD, lifelong treatment is focused on mucosal healing (inducing and

maintaining remission) and prevention of disease progression and complications with the least amount of side effects from medication.

Paediatric versus adult onset IBD

Studies have shown several differences between paediatric and adult onset IBD. Paediatric onset IBD is considered to have a more extensive disease location, a more severe phenotype, increased use of immunomodulatory therapy, higher rates of intestinal complications (strictures, colon surgery and perianal disease) and an increased risk of malignancy later in life.[15-18]

PSYCHOSOCIAL PROBLEMS IN YOUNG IBD PATIENTS

Adolescence is known as a life phase with significant psychological, physical and social changes.[19] Suffering from a chronic disease like IBD, poses a threat to a healthy psychosocial development. Throughout life, important milestones and transitions (such as transitioning into adulthood), may give greater challenges for patients with IBD than for healthy peers. Therefore, it is not surprising that adolescent IBD patients frequently experience psychosocial problems, such as reduced social functioning, family problems, school problems and emotional problems.[20, 21] All these problems contribute to a decreased quality of life.[22] Several clinical, psychological and social factors have been associated with psychosocial outcomes and Health Related Quality Of Life (HRQOL) in (young) IBD patients. For example, clinical factors such as active disease, Crohn's disease (compared to UC), corticosteroid treatment and a high hospitalization rate have been associated with a poorer QoL in IBD patients.[23, 24] In addition, psychological and social factors such as anxiety or depression[25, 26], negative illness perceptions[27, 28], maladaptive coping[29], a lack of social support[30], high perceived stress[31] and work disability[24] have also been associated with a lower QoL. As summarized in the biopsychosocial model of health and disease, all the factors mentioned above are interrelated and influence health.[32] For IBD, it is mostly emotional problems, specifically anxiety and depression, that have received much attention in the current literature.

Anxiety and depression

In mental health care, a distinction is made between anxiety and depressive symptoms and anxiety and depression as disorders. Disorders reflect severe symptoms that cause significant impairment in daily life and are diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, using a psychiatric interview. Symptoms are usually measured with self-report questionnaires, and patients with elevated symptoms (who do not meet all criteria of a disorder) suffer from milder (or so-called subclinical) symptoms, but do not experience such a significant impairment in their daily life as patients with a diagnosed disorder. However, both subclinical and clinical symptoms affect health

status and health care use, and subclinical symptoms hold a risk for progression into clinical symptoms.[33]

Symptoms of anxiety and/or depression are often found in paediatric IBD patients. Reported prevalence rates range from 20-50% for anxiety[34-36] and 25-40% for depression.[35, 37, 38] Although some studies report lower rates[39], the prevalence in paediatric IBD seems to be higher compared to other chronic diseases.[40, 41] A systematic review is not yet available, but will be presented in this thesis. For adult IBD patients, a recent systematic review showed pooled prevalence rates of anxiety symptoms of 35.1% and 21.6% for depressive symptoms[42], suggesting that psychological problems persist or arise again in adulthood.[43] As illustrated, many studies investigated anxiety/depressive symptoms in paediatric IBD, but studies investigating anxiety and depressive disorders in IBD are scarce. This can be explained by the time-consuming psychiatric interview which is necessary for diagnosing a psychological disorder.

As in the general population[44, 45], female sex[39, 46, 47] and low socio-economic status[48] have been reported to be risk factors for anxiety and depression. More importantly, psychological symptoms have repeatedly been shown to be associated with active disease.[42, 46, 49-51] In addition, other disease-related factors such as abdominal pain[37, 52], corticosteroid use[53], fatigue[54], extra-intestinal manifestations[47], prior surgery and perianal disease[47, 55], are known to be associated with psychological symptoms in IBD patients

Moreover, psychological symptoms impact patients' lives, they are associated with a higher symptom burden[47], worsening of disease course[56, 57], fatigue[47], school or work absenteeism[58, 59], lower therapy adherence[50], higher health care utilisation[47, 50, 60], more steroid courses and biologic therapy[47], all leading to high societal costs.[61]

Brain-gut axis

The findings above illustrate that psychological symptoms may influence disease course, and vice versa. This bidirectional relationship between IBD and psychological problems has been previously described[62] and can be explained in terms of the hypothetical 'brain-gut'-axis. This axis describes interactions between the central, autonomic, and enteric nerve system, the hypothalamic-pituitary-adrenal (HPA) axis, gut microbiome and mucosal immune system. Through feedback loops, (para)sympathetic signals reach peripheral organs including cells of the immune system. Any kind of (psychological) stress activates the sympathetic system and the HPA-axis, with the release of neurotransmitters, hormones and pro-inflammatory cytokines. Many of these factors have pro-inflammatory properties, but HPA-axis function also serves to limit the effect inflammation by means of the release of cortisol.[63] In IBD patients, all of these processes may lead to increased colonic motility, increased water and ion secretion, increased mucus production, and increased bacterial transfer into the mucosa, all contributing to increased intestinal symptoms.[62, 64] More specifically, the brain-gut axis applied to IBD means that the presence of intestinal inflammation might negatively influence anxiety and/or depression and vice versa: anxiety and/or depression may increase

intestinal inflammation and may trigger a relapse of IBD.[57, 62, 64, 65] Several studies support this by showing an association between clinical disease activity and anxiety[36, 42] and depression.[42, 53] In addition, several longitudinal studies also provide support: in a recent systematic review 5 out of 11 studies reported an association between depression and worsening of disease course.[56, 66] For anxiety, less studies are available, with mixed results.[57, 65, 67-70]

Treatment of anxiety and depression in IBD

In the current international guidelines for paediatric[71, 72] and adult[73-76] patients with IBD, screening for psychological problems is not (yet) part of standard care for IBD patients. Considering that psychological problems are not always recognised in a 10-minute doctor's or nurse's consultation in the outpatient clinic, it is likely that these problems are often missed and remain untreated. To illustrate, Klag et al. (2017) found in a group of 630 adult IBD patients, that half had a high demand for psychological help.[77] In addition, it has been reported that psychological disorders in IBD are undertreated; a study in 231 adult IBD patients showed that only half of the patients with anxiety and/or depressive symptoms indicative of a psychiatric disorder received psychological or psychiatric treatment.[78]

The most effective evidence based psychological treatment for anxiety and/or depression for both children, adolescents and adults, is cognitive behavioural therapy (CBT).[79, 80] CBT has been proven effective in reducing anxiety and depressive symptoms in both paediatric[81, 82] and adult[83] IBD patients. Cognitive behavioural therapy is based on the theoretical rationale that thoughts, feelings, and behaviour are interrelated. CBT aims to change distorted or dysfunctional thinking patterns, in order to improve negative emotions and maladaptive behaviors.[80] In addition, relaxation, and exposure (exercising with difficult situations) are essential elements in CBT. A few studies investigated the efficacy of CBT in IBD patients suffering from anxiety and/or depression.[81, 82, 84, 85] In addition, most of these studies focused only on psychological outcomes (anxiety, depression).[81, 84, 85] Only one study, in paediatric IBD, investigated clinical disease course in IBD patients with depression.[82] This emphasises the need to conduct studies investigating CBT in patients with IBD and anxiety and/or depression, and to study both clinical (medical) and psychological outcomes.

TRANSITION

Next to psychosocial problems, transition to adult care is an important issue in the lives of young adult IBD patients. As IBD is a lifelong disease, all patients will need to undergo transfer of paediatric to adult care. Transfer to the adult gastroenterology department is not always easy. Patients and their parents are frequently reluctant to break the familiar and valued relationship with their paediatrician, and can have a negative perception of adult health care.[86-88] In addition, in many cases parental involvement is high, which can interfere with the development of self-management skills.[87, 89] Furthermore, there are several other

differences between paediatric and adult care that make the transfer to adult health care challenging. For example, in paediatrics, endoscopy is usually done under deep sedation or general anaesthesia, there is more attention for growth and pubertal development, and the outpatient clinic is family-focused and less formal. This in contrast to adult health care, where endoscopy is often performed without deep sedation, where gastroenterologists are not trained to evaluate growth and pubertal development, and focus on adult-oriented topics, such as cancer surveillance and fertility. Furthermore, the organisation of the outpatient clinic in adult care is more formal and physicians often only communicate with the patient (and not the parents).

To help adolescent patients get acquainted with these differences and prepare patients and parents for adult health care, it is advised to have a transition period.[90, 91] Transition is defined as the process of purposeful planned movement of adolescents and young adults with chronic diseases from child centred to adult oriented healthcare systems.[92] In the transition process, both patients, parents and the paediatric and adult gastroenterologist have specific tasks. Patients should learn to be responsible for their own health, acquire (disease) knowledge, autonomy and self-management. Parents need to allow and stimulate their adolescent child's independence. Physicians and nurses should support the transition process, be knowledgeable of adolescents' developmental and health issues and prepare adolescents for the changes that will be encountered in the adult health care system.[86, 93, 94]

Transitional programs are designed to facilitate all these processes[86, 95, 96] and prepare the individual patient for his/her transfer by helping to increase knowledge as well as to reach a higher level of self-management. Although many different models for transitional care have been proposed in IBD, there is no evidence that one particular model is more effective than others.[90] In addition, not all health care providers working with adolescent IBD patients have an IBD transition clinic and transition practices vary greatly between and within countries and continents.[88, 90] However, the importance of transition is emphasised by the fact that studies generally report that adolescent patients lack knowledge about their disease, treatment and also lack self-management.[97-102]

Inadequate transition arrangements have been associated with adverse outcomes across several medical conditions, for example diabetes.[103] In IBD, studies investigating the outcome or impact of structured transition are scarce. The available studies have showed that the lack of a structured transition service negatively impacted adherence[104, 105] and attendance[104, 105], and was associated with a higher hospitalisation and surgery rate.[104] On the other hand, structured transition programmes have been shown to result in better disease related outcomes[106, 107], improved self- and disease knowledge and improved quality of life.[107, 108]

A clear definition of success of transition, or a scoring system measuring success of transition in IBD is not available.[86, 104, 109] Therefore, studies investigating outcome or success of transition are warranted.

AIMS OF THIS THESIS

The general aim of this thesis is to investigate two themes relevant to adolescent and young adult IBD patients: psychosocial problems, especially anxiety and depression, and transition to adult care.

The specific aims of this thesis are:

- To systematically review the scientific international literature with regard to the prevalence of anxiety and/or depression in paediatric and adolescent IBD
- To study the prevalence and risk factors of anxiety and/or depression in Dutch adolescents and young adult patients with IBD
- To investigate the effectiveness of cognitive behavioural therapy on both psychological symptoms and clinical disease course in young IBD patients suffering from mild or subclinical anxiety and/or depressive symptoms
- To identify immunological profiles in IBD patients with anxiety and/or depression, and investigate if these profiles are altered by cognitive behavioural therapy
- To study outcome of transition, especially identifying which factors health care providers and patients find important for success of transition to adult care.

OUTLINE

Part I (Chapters 2-9) has a focus on anxiety and depression in paediatric IBD. In **Chapter 2** a systematic review with a meta-analysis is presented of all studies that have investigated prevalence of anxiety and/or depression in paediatric IBD until December 2017. In **Chapter 3** we present the study protocol of HAPPY-IBD, our multicentre randomised trial investigating the effectiveness of cognitive behavioural therapy (CBT) on psychological outcomes ánd clinical disease course in young IBD patients with subclinical symptoms of anxiety and/or depression. HAPPY-IBD is a collaboration between the department of child psychiatry/psychology and paediatric gastroenterology. Luuk Stapersma, the research psychologist of HAPPY-IBD, is responsible for collecting and analysing all psychological data and is the first author of three articles included in this thesis. In short, HAPPY-IBD is a two-stage study: the first stage is the screening of 374 Dutch adolescents and young adults with IBD on anxiety and/or depression. The second stage is a multicentre randomised controlled trial (RCT) with IBD patients with elevated mild or subclinical symptoms of anxiety and/or depression. In **Chapter 4** we present the first results from stage 1: we show the prevalence and severity of anxiety and/or depressive symptoms in our large cohort of Dutch adolescents and young adults with IBD. In addition, we describe the risk factors found in our cohort for these symptoms. In **Chapter 5** we aimed to clarify the associations between several psychological

factors (illness perceptions, coping, anxiety, depression) and Health Related Quality of Life (HRQOL) in the 374 patients screened in stage 1. In **Chapters 6 and 7,** the short- and long-term results of the disease specific CBT on psychological outcomes, such as anxiety, depression and HRQOL, are presented. **Chapter 8** discusses the effect of CBT on several clinical outcomes: time to relapse, clinical disease activity scores, C-Reactive protein and faecal calprotectin. In **Chapter 9** we aim to explore the brain-gut axis in IBD at a molecular level. We take a first step in unravelling the relationship between anxiety/depression and systemic inflammation in IBD patients. Using a large inflammatory protein panel, we first investigate plasma protein profiles in 45 young IBD patients with and without anxiety and/or depressive symptoms. Secondly, we study whether CBT changes these profiles in a subgroup from the RCT (described in Chapters 3, 6, 7 and 8).

Part II (Chapters 10 and 11) discusses outcomes of transition. In **Chapter 10** we propose a composite score measuring success of transition, and evaluate whether self-efficacy is a predictor of successful transition according to that score. In **Chapter 11** we use a more thorough approach in identifying outcomes reflecting successful transition by asking the opinion of a large expert and patient panel in a multinational Delphi study.

In **Part III (Chapters 12 and 13)**, we discuss our main findings and conclusions and give recommendations for clinical practice and future research in **Chapter 12**. In **Chapter 13** our findings, as described in this thesis, are summarised in English and Dutch.

REFERENCES

1 Rosen MJ, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. *JAMA Pediatr*. 2015;169(11):1053-1060.

2 Peloquin JM, Goel G, Villablanca EJ, Xavier RJ. Mechanisms of Pediatric Inflammatory Bowel Disease. *Annu Rev Immunol*. 2016;34:31-64.

3 Lee SH, Kwon JE, Cho ML. Immunological pathogenesis of inflammatory bowel disease. *Intest Res*. 2018;16(1):26-42.

4 Neurath MF. Cytokines in inflammatory bowel disease. *Nat Rev Immunol*. 2014;14(5):329-342.

5 Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2018;390(10114):2769-2778.

6 Ghione S, Sarter H, Fumery M, et al. Dramatic Increase in Incidence of Ulcerative Colitis and Crohn's Disease (1988-2011): A Population-Based Study of French Adolescents. *Am J Gastroenterol*. 2018;113(2):265-272.

7 Ashton JJ, Cullen M, Afzal NA, Coelho T, Batra A, Beattie RM. Is the incidence of paediatric inflammatory bowel disease still increasing? *Arch Dis Child*. 2018;103(11):1093-1094.

8 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best practice & research Clinical gastroenterology*. Review. 2004;18(3):509-523.

9 Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis*. 2011;17(1):423-439.

10 Duricova D, Sarter H, Savoye G, et al. Impact of Extra-Intestinal Manifestations at Diagnosis on Disease Outcome in Pediatric- and Elderly-Onset Crohn's Disease: A French Population-Based Study. *Inflamm Bowel Dis*. 2019;25(2):394-402.

11 Day AS, Ledder O, Leach ST, Lemberg DA. Crohn's and colitis in children and adolescents. *World J Gastroenterol.* 2012;18(41):5862-5869.

12 Burisch J, Kiudelis G, Kupcinskas L, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut*. 2018 Jan 23. [Epub ahead of print]

13 Martinelli M, Giugliano FP, Russo M, et al. The Changing Face of Pediatric Ulcerative Colitis: A Population-based Cohort Study. *J Pediatr Gastroenterol Nutr*. 2018;66(6):903-908.

14 Vester-Andersen MK, Vind I, Prosberg MV, et al. Hospitalisation, surgical and medical recurrence rates in inflammatory bowel disease 2003-2011-a Danish population-based cohort study. *J Crohns Colitis*. 2014;8(12):1675-1683.

15 Pigneur B, Seksik P, Viola S, et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. *Inflamm Bowel Dis*. 2010;16(6):953-961.

16 Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology*. 2008;135(4):1114-1122.

17 Olen O, Askling J, Sachs MC, et al. Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964-2014. *BMJ*. 2017;358:j3951.

18 Herzog D, Fournier N, Buehr P, et al. Prevalence of intestinal complications in inflammatory bowel disease: a comparison between paediatric-onset and adult-onset patients. *Eur J Gastroenterol Hepatol*. 2017;29(8):926-931.

19 Bousvaros A, Sylvester F, Kugathasan S, et al. Challenges in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2006;12(9):885-913.

20 Greenley RN, Hommel KA, Nebel J, et al. A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. *J Pediatr Psychol*. 2010;35(8):857-869.

21 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):449-458.

22 Knowles SR, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses-Part I. *Inflamm Bowel Dis*. 2018;24(4):742-751.

23 Knowles SR, Keefer L, Wilding H, Hewitt C, Graff LA, Mikocka-Walus A. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses-Part II. *Inflamm Bowel Dis*. 2018;24(5):966-976.

24 van der Have M, van der Aalst KS, Kaptein AA, et al. Determinants of health-related quality of life in Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2014;8(2):93-106.

25 Zhang CK, Hewett J, Hemming J, et al. The influence of depression on quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2013;19(8):1732-1739.

26 Engelmann G, Erhard D, Petersen M, 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):300-307.

27 Rochelle TL, Fidler H. The importance of illness perceptions, quality of life and psychological status in patients with ulcerative colitis and Crohn's disease. *J Health Psychol*. 2013;18(7):972-983.

28 van der Have M, Minderhoud IM, Kaptein AA, et al. Substantial impact of illness perceptions on quality of life in patients with Crohn's disease. *J Crohns Colitis*. 2013;7(8):e292-301.

29 Chao CY, Lemieux C, Restellini S, et al. Maladaptive coping, low self-efficacy and disease activity are associated with poorer patient-reported outcomes in inflammatory bowel disease. *Saudi J Gastroenterol*. 2019;25(3):159-166.

30 Faust AH, Halpern LF, Danoff-Burg S, Cross RK. Psychosocial factors contributing to inflammatory bowel disease activity and health-related quality of life. *Gastroenterol Hepatol (N Y)*. 2012;8(3):173-181.

31 Tabibian A, Tabibian JH, Beckman LJ, Raffals LL, Papadakis KA, Kane SV. Predictors of health-related quality of life and adherence in Crohn's disease and ulcerative colitis: implications for clinical management. *Dig Dis Sci*. 2015;60(5):1366-1374.

32 Engel GL. The clinical application of the biopsychosocial model. *Am J Psychiatry*. 1980;137(5):535-544.

33 Wesselhoeft R, Sorensen MJ, Heiervang ER, Bilenberg N. Subthreshold depression in children and adolescents - a systematic review. *J Affect Disord*. 2013;151(1):7-22.

34 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):275-279.

35 Reigada LC, Bruzzese JM, Benkov KJ, et al. Illness-specific anxiety: implications for functioning and utilization of medical services in adolescents with inflammatory bowel disease. *J Spec Pediatr Nurs*. 2011;16(3):207-215.

36 Reigada LC, Hoogendoorn CJ, Walsh LC, et al. Anxiety symptoms and disease severity in children and adolescents with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2015;60(1):30-35.

37 Srinath AI, Goyal A, Zimmerman LA, et al. Predictors of abdominal pain in depressed pediatric inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2014;20(8):1329-1340.

38 Szigethy E, Levy-Warren A, Whitton S, 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.

39 Walter JG, Kahn SA, Noe JD, Schurman JV, Miller SA, Greenley RN. Feeling Fine: Anxiety and Depressive Symptoms in Youth with Established IBD. *Inflamm Bowel Dis*. 2016;22(2):402-408.

40 Hood KK, Huestis S, Maher A, Butler D, Volkening L, Laffel LM. Depressive symptoms in children and adolescents with type 1 diabetes: association with diabetes-specific characteristics. *Diabetes Care*. 2006;29(6):1389-1391.

41 Duff AJ, Abbott J, Cowperthwaite C, et al. Depression and anxiety in adolescents and adults with cystic fibrosis in the UK: a cross-sectional study. *J Cyst Fibros*. 2014;13(6):745-753.

42 Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review. *J Psychosom Res*. 2016;87:70-80.

43 Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Archives of general psychiatry*. 2009;66(7):764-772.

44 Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. *Front Neuroendocrinol*. 2014;35(3):320-330.

45 Matthews KA, Gallo LC. Psychological perspectives on pathways linking socioeconomic status and physical health. *Annu Rev Psychol*. 2011;62:501-530.

46 Byrne G, Rosenfeld G, Leung Y, et al. Prevalence of Anxiety and Depression in Patients with Inflammatory Bowel Disease. *Can J Gastroenterol Hepatol*. 2017 Nov 29; [Epub ahead of print]

47 Navabi S, Gorrepati VS, Yadav S, et al. Influences and Impact of Anxiety and Depression in the Setting of Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2018;24(11):2303-2308.

48 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):2301-2309.

49 Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. *Inflamm Bowel Dis*. 2016;22(3):752-762.

50 Brooks AJ, Rowse G, Ryder A, Peach EJ, Corfe BM, Lobo AJ. Systematic review: psychological morbidity in young people with inflammatory bowel disease - risk factors and impacts. *Aliment Pharmacol Ther*. 2016;44(1):3-15.

51 Leone D, Gilardi D, Corro BE, et al. Psychological Characteristics of Inflammatory Bowel Disease Patients: A Comparison Between Active and Nonactive Patients. *Inflamm Bowel Dis*. 2019 Jan 30. [Epub ahead of print]

52 Watson KL, Jr., Kim SC, Boyle BM, Saps M. Prevalence and Impact of Functional Abdominal Pain Disorders in Children With Inflammatory Bowel Diseases (IBD-FAPD). *J Pediatr Gastroenterol Nutr*. 2017;65(2):212-217.

53 Clark JG, Srinath AI, Youk AO, et al. Predictors of Depression in Youth With Crohn Disease. *J Pediatr Gastroenterol Nutr*. 2014;58(5):569-573.

54 Marcus SB, Strople JA, Neighbors K, et al. Fatigue and health-related quality of life in pediatric inflammatory bowel disease. *Clinical gastroenterology and hepatology*: 2009;7(5):554-561.

55 Ananthakrishnan AN, Gainer VS, Cai T, et al. Similar risk of depression and anxiety following surgery or hospitalization for Crohn's disease and ulcerative colitis. *Am J Gastroenterol*. 2013;108(4):594-601.

56 Alexakis C, Kumar S, Saxena S, Pollok R. Systematic review with meta-analysis: the impact of a depressive state on disease course in adult inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46(3):225-235.

57 Mikocka-Walus A, Pittet V, Rossel JB, von Kanel R, Swiss IBDCSG. Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol.* 2016;14(6):829-835 e821.

58 Singh H, Nugent Z, Brownell M, Targownik LE, Roos LL, Bernstein CN. Academic Performance among Children with Inflammatory Bowel Disease: A Population-Based Study. *J of pediatrics*. 2015;166(5):1128-1133.

59 De Boer AG, Bennebroek Evertsz F, Stokkers PC, et al. Employment status, difficulties at work and quality of life in inflammatory bowel disease patients. *Eur J Gastroenterol Hepatol*. 2016;28(10):1130-1136.

60 Reigada LC, Satpute A, Hoogendoorn CJ, et al. Patient-reported Anxiety: A Possible Predictor of Pediatric Inflammatory Bowel Disease Health Care Use. *Inflamm Bowel Dis*. 2016;22(9):2127-2133.

61 Burisch J, Jess T, Martinato M, Lakatos PL, EpiCom E. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis*. 2013;7(4):322-337.

62 Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology*. 2013;144(1):36-49.

63 Stasi C, Orlandelli E. Role of the brain-gut axis in the pathophysiology of Crohn's disease. *Dig Dis*. 2008;26(2):156-166.

64 Bernstein CN. Psychological Stress and Depression: Risk Factors for IBD? *Dig Dis*. 2016;34(1-2):58-63.

65 Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain-Gut Interactions in Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2018;154(6):1635-1646 e1633.

66 Kochar B, Barnes EL, Long MD, et al. Depression Is Associated With More Aggressive Inflammatory Bowel Disease. *Am J Gastroenterol*. 2018;113(1):80-85.

67 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.

68 Bitton A, Dobkin PL, Edwardes MD, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut*. 2008;57(10):1386-1392.

69 Bitton A, Sewitch MJ, Peppercorn MA, et al. Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. *Am J Gastroenterol*. 2003;98(10):2203-2208.

70 Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Holtmann GJ, Andrews JM. Does psychological status influence clinical outcomes in patients with inflammatory bowel disease (IBD) and other chronic gastroenterological diseases: an observational cohort prospective study. *Biopsychosoc Med*. 2008;2:11.

71 Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care- an Evidence-Based Guideline from ECCO and ESPGHAN. *J Pediatr Gastroenterol Nutr*. 2018 May 30. [Epub ahead of print]

72 Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis*. 2014;8(10):1179-1207.

73 Gionchetti P, Dignass A, Danese S, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. *J Crohns Colitis*. 2017;11(2):135-149.

74 Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis*. 2017;11(1):3-25.

75 Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis*. 2017;11(6):649-670.

76 Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis*. 2017;11(7):769-784.

77 Klag T, Mazurak N, Fantasia L, et al. High Demand for Psychotherapy in Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2017;23(10):1796-1802.

78 Bennebroek Evertsz F, Thijssens NA, Stokkers PC, et al. Do Inflammatory Bowel Disease patients with anxiety and depressive symptoms receive the care they need? *J Crohns Colitis*. 2012;6(1):68-76.

79 Compton SN, March JS, Brent D, Albano AMt, Weersing R, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. *J Am Acad Child Adolesc Psychiatry*. 2004;43(8):930-959.

80 Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognit Ther Res*. 2012;36(5):427-440.

81 Reigada LC, Benkov KJ, Bruzzese JM, et al. Integrating illness concerns into cognitive behavioral therapy for children and adolescents with inflammatory bowel disease and co-occurring anxiety. *J Spec Pediatr Nurs*. 2013;18(2):133-143.

82 Szigethy E, Bujoreanu SI, Youk AO, 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):726-735.

83 Knowles SR, Monshat K, Castle DJ. The efficacy and methodological challenges of psychotherapy for adults with inflammatory bowel disease: a review. *Inflamm Bowel Dis*. 2013;19(12):2704-2715.

84 Szigethy E, Kenney E, Carpenter J, et al. Cognitive-behavioral therapy for adolescents with inflammatory bowel disease and subsyndromal depression. *J Am Acad Child Adolesc Psychiatry.* 2007;46(10):1290-1298.

85 Bennebroek Evertsz F, Sprangers MAG, Sitnikova K, et al. Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: A multicenter randomized controlled trial. *J Consult Clin Psychol*. 2017;85(9):918-925.

86 Goodhand J, Hedin CR, Croft NM, Lindsay JO. Adolescents with IBD: the importance of structured transition care. *J Crohns Colitis*. 2011;5(6):509-519.

87 Gray WN, Resmini AR, Baker KD, et al. Concerns, Barriers, and Recommendations to Improve Transition from Pediatric to Adult IBD Care: Perspectives of Patients, Parents, and Health Professionals. *Inflamm Bowel Dis*. 2015;21(7):1641-1651.

88 Gray WN, Maddux MH. Current Transition Practices in Pediatric IBD: Findings from a National Survey of Pediatric Providers. *Inflamm Bowel Dis*. 2016;22(2):372-379.

89 Paine CW, Stollon NB, Lucas MS, et al. Barriers and facilitators to successful transition from pediatric to adult inflammatory bowel disease care from the perspectives of providers. *Inflamm Bowel Dis*. 2014;20(11):2083-2091.

90 van Rheenen PF, Aloi M, Biron IA, et al. European Crohn's and Colitis Organisation Topical Review on Transitional Care in Inflammatory Bowel Disease. *J Crohns Colitis*. 2017;11(9):1032-1038.

91 Brooks AJ, Smith PJ, Cohen R, et al. UK guideline on transition of adolescent and young persons with chronic digestive diseases from paediatric to adult care. *Gut*. 2017;66(6):988-1000.

92 Blum RW, Garell D, Hodgman CH, et al. Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine. *J Adolesc Health*. 1993;14(7):570-576.

93 Philpott JR, Kurowski JA. Challenges in Transitional Care in Inflammatory Bowel Disease: A Review of the Current Literature in Transition Readiness and Outcomes. *Inflamm Bowel Dis*. 2019;25(1):45-55.

94 Brooks AJ, Smith PJ, Lindsay JO. Monitoring adolescents and young people with inflammatory bowel disease during transition to adult healthcare. *Frontline Gastroenterol*. 2018;9(1):37-44.

95 Escher JC. Transition from pediatric to adult health care in inflammatory bowel disease. *Dig Dis*. 2009;27(3):382-386.

96 Dabadie A, Troadec F, Heresbach D, Siproudhis L, Pagenault M, Bretagne JF. Transition of patients with inflammatory bowel disease from pediatric to adult care. *Gastroenterol Clin Biol*. 2008;32(5 Pt 1):451-459.

97 Fishman LN, Houtman D, van Groningen J, Arnold J, Ziniel S. Medication knowledge: an initial step in self-management for youth with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2011;53(6):641-645.

98 Benchimol EI, Walters TD, Kaufman M, et al. Assessment of knowledge in adolescents with inflammatory bowel disease using a novel transition tool. *Inflamm Bowel Dis*. 2011;17(5):1131-1137.

99 Sebastian S, Jenkins H, McCartney S, et al. The requirements and barriers to successful transition of adolescents with inflammatory bowel disease: differing perceptions from a survey of adult and paediatric gastroenterologists. *J Crohns Colitis*. 2012;6(8):830-844.

100 van Groningen J, Ziniel S, Arnold J, Fishman LN. When independent healthcare behaviors develop in adolescents with inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18(12):2310-2314.

101 Wright EK, Williams J, Andrews JM, et al. Perspectives of paediatric and adult gastroenterologists on transfer and transition care of adolescents with inflammatory bowel disease. *Intern Med J*. 2014;44(5):490-496.

102 Gumidyala AP, Greenley RN, Plevinsky JM, et al. Moving On: Transition Readiness in Adolescents and Young Adults With IBD. *Inflamm Bowel Dis*. 2018;24(3):482-489.

103 Nakhla M, Daneman D, To T, Paradis G, Guttmann A. Transition to adult care for youths with diabetes mellitus: findings from a Universal Health Care System. *Pediatrics*. 2009;124(6):e1134-1141.

104 Cole R, Ashok D, Razack A, Azaz A, Sebastian S. Evaluation of Outcomes in Adolescent Inflammatory Bowel Disease Patients Following Transfer From Pediatric to Adult Health Care Services: Case for Transition. *J Adolesc Health*. 2015;57(2):212-217.

105 Bollegala N, Brill H, Marshall JK. Resource utilization during pediatric to adult transfer of care in IBD. *J Crohns Colitis*. 2013;7(2):e55-60.

106 Crowley R, Wolfe I, Lock K, McKee M. Improving the transition between paediatric and adult healthcare: a systematic review. *Arch Dis Child*. 2011;96(6):548-553.

107 Mackie AS, Islam S, Magill-Evans J, et al. Healthcare transition for youth with heart disease: a clinical trial. *Heart*. 2014;100(14):1113-1118.

108 McDonagh JE, Southwood TR, Shaw KL, British Society of P, Adolescent R. The impact of a coordinated transitional care programme on adolescents with juvenile idiopathic arthritis. *Rheumatology (Oxford)*. 2007;46(1):161-168.

109 Leung Y, Heyman MB, Mahadevan U. Transitioning the adolescent inflammatory bowel disease patient: guidelines for the adult and pediatric gastroenterologist. *Inflamm Bowel Dis*. 2011;17(10):2169-2173.

PART I

Anxiety and depression in paediatric IBD

CHAPTER 2

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

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EDITORIALS

Anxiety and depression in inflammatory bowel disease
Antonina A. Mikocka-Walus, Simon R. Knowles
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Anxiety and depression in inflammatory bowel disease – author's reply
Gertrude van den Brink, Luuk Stapersma, Eva M. Szigethy, Elisabeth M.W.J. Utens, Johanna C. Escher
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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/cut-offs 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%[5]-50%[6] for anxiety symptoms and 0%[7]-33%[8] for depressive symptoms. Only a few studies investigated prevalence of anxiety and depressive disorders, which ranged respectively from 3%[9]-7% [10] and 1%[11]-17%[10] .

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. 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., included studies till 2009, investigating psychosocial functioning and quality of life. They found an increased incidence of anxiety and depressive disorders, varying from 25% to 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, 2 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 cut-off for elevated symptoms reported by the authors. Disagreement regarding extracted data was resolved 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. 2007[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 included 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, USA).

RESULTS

Study selection

During the database search 2020 records were found, four additional studies were identified through other sources (i.e. reference lists of included records). A total of 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 eight 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.

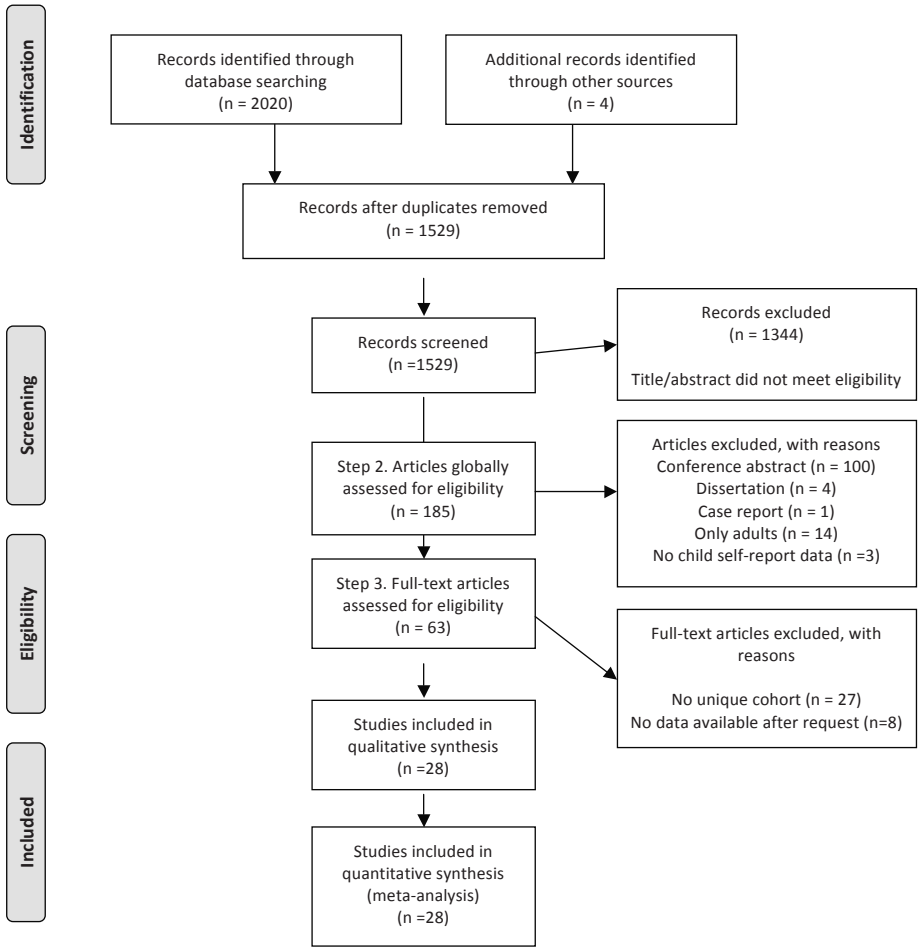


Figure 1. PRISMA Flow Diagram.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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, with 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, nine 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]. Twenty-five 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[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 (cut-off 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[7c]	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[11c]	2733	54	63	13.8 (<18)	-	16/27	Anxiety	ICD codes	-	-	4.8	-	-
							Depression	ICD codes	-	-	-	-	0.9
Arvanitis 2016[30c]	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[33c]	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[35c]	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[36c]	21	52	57	13.9 (6-20§)	33.3	13/27	Depression	Q	ChilD-S (Total score ≥11)	-	-	19.1	-

Table 1. continued

Iturralde 2017[37c]	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	-	-	-
Giannakopoulos 2016[40c]	85	41	67	13.2 (8-18)	50.6	11/27	Depression	Q	CDI (Total score ≥15)	-	-	14.0	-
Szigethy 2007[41c]	156	-	-	14.3 (11-17)	-	12/27	Depression	Q	CDI (Total score ≥9)	-	-	23.1	-
Szigethy 2014[42c]	765	-	-	- (9-17)	-	13/27	Depression	Q	CDI (Total score ≥10)	-	-	32.0	-
							Depression	I	K-SADS	-	-	-	10.5
Thompson 2012[43c]	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[48c]	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[50c]	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	-

Note: 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 c= data after request provided by (corresponding) author §all included patients were < 18 ¶data received of patients < 18.

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.

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, β = .004, p = .699) and gender (% male, β = .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 nine 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. 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, β = -.009, p = .125) and gender (% male, β = -.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

(β = .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

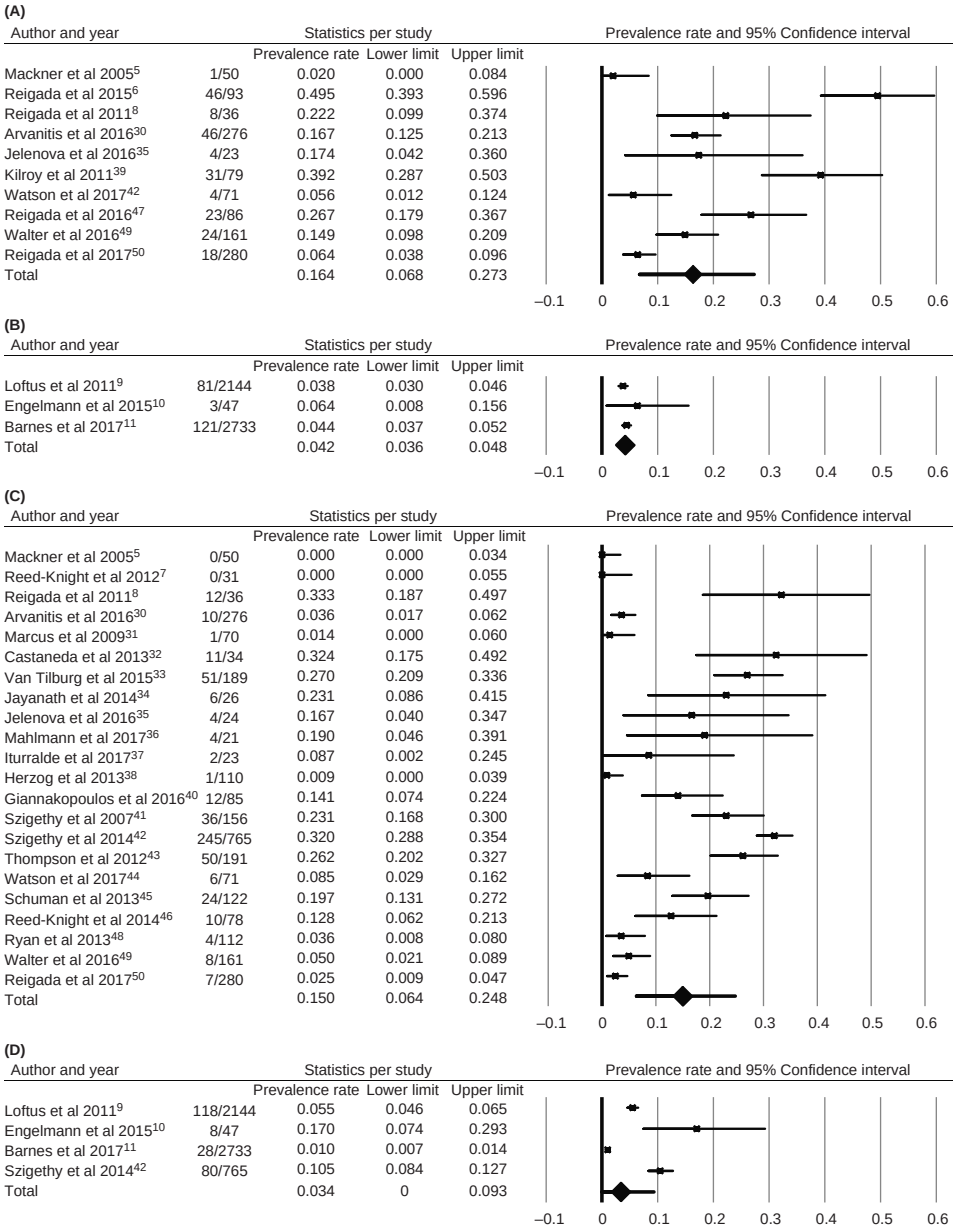


Figure 2. Forest Plots

(a) prevalence rate anxiety symptoms (b) prevalence rate anxiety disorders (c) prevalence rate depressive symptoms (d) prevalence rate depressive disorders.
Note: Sample sizes can differ from those mentioned in Table 1. due to missing data on the outcome measure.

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 cut-offs. 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 corticosteroids, 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. First, although all studies used validated instruments to assess anxiety or depressive symptoms, numerous different instruments were used, not all validated in paediatric IBD. Different cut-offs for the same instruments were used, and some used raw total scores, while others used (varying) T-scores. For example, for the CDI, cut-off scores ranged from 9[42] to 19[38] or 20[35] and for the SCARED, cut-off 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 cut-offs for each instrument. In addition, only four 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.

Second, 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%).

Third, 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.

Fourth, 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, two 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. First, knowing about this high heterogeneity is very important. Second, 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 et al[17] and include using the same validated screening measures and clinical diagnostic measures (psychiatric interview) with the same comparable cut-offs, 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 cut-offs, 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 cut-offs. More studies are necessary to determine the prevalence of anxiety/depressive disorders using a standardized psychiatric interview following DSM criteria. 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).

REFERENCES

1 Baumgart DC, Bernstein CN, Abbas Z, 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 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol* 2004;18(3):509-23.

3 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.

4 Greenley RN, Hommel KA, Nebel J, et al. A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. *J Pediatr Psychol* 2010;35(8):857-69.

5 Mackner LM, Crandall WV. Long-term psychosocial outcomes reported by children and adolescents with inflammatory bowel disease. *Am J Gastroenterol* 2005;100(6):1386-92.

6 Reigada LC, Hoogendoorn CJ, Walsh LC, et al. Anxiety symptoms and disease severity in children and adolescents with Crohn disease. *J Pediatr Gastroenterol Nutr* 2015;60(1):30-5.

7 Reed-Knight B, McCormick M, Lewis JD, Blount RL. Participation and attrition in a coping skills intervention for adolescent girls with inflammatory bowel disease. *J Clin Psychol Med Settings* 2012;19(2):188-96.

8 Reigada LC, Bruzzese JM, Benkov KJ, et al. Illness-specific anxiety: implications for functioning and utilization of medical services in adolescents with inflammatory bowel disease. *J Spec Pediatr Nurs* 2011;16(3):207-15.

9 Loftus EV, Jr., Guerin A, Yu AP, et al. Increased risks of developing anxiety and depression in young patients with Crohn's disease. *Am J Gastroenterol* 2011;106(9):1670-7.

10 Engelmann G, Erhard D, Petersen M, 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.

11 Barnes EL, Kochar B, Long MD, et al. The Burden of Hospital Readmissions among Pediatric Patients with Inflammatory Bowel Disease. *J Pediatr* 2017;191:184-189 e1.

12 ernstein CN. Psychological Stress and Depression: Risk Factors for IBD? *Dig Dis* 2016;34(1-2):58-63.

13 Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology* 2013;144(1):36-49.

14 Mikocka-Walus A, Pittet V, Rossel JB, von Kanel R, Swiss IBDCSG. Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2016;14(6):829-835 e1.

15 Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain-Gut Interactions in Patients With Inflammatory Bowel Disease. *Gastroenterology* 2018;154(6):1635-1646 e3.

16 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.

17 Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. *Inflamm Bowel Dis* 2016;22(3):752-62.

18 Brooks AJ, Rowse G, Ryder A, Peach EJ, Corfe BM, Lobo AJ. Systematic review: psychological morbidity in young people with inflammatory bowel disease - risk factors and impacts. *Aliment Pharmacol Ther* 2016;44(1):3-15.

19 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62(10):1006-12.

20 Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol* 2007;36(3):666-76.

21 National Institutes of Health. National Heart Lung And blood Institute. Quality Assessment for Observational Cohort and Cross-sectional studies.

22 Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Chapter 5: Systematic reviews of prevalence and incidence. In: Aromataris E, Munn Z (editors). *Joanna Briggs Institute Reviewer's Manual.* The Joanne Briggs Institute, 2017.

23 Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012;65(9):934-9.

24 Doi SA, Barendregt JJ, Khan S, Thalib L, Williams GM. Advances in the meta-analysis of heterogeneous clinical trials I: The inverse variance heterogeneity model. *Contemp Clin Trials* 2015;45(Pt A):130-8.

25 Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clin Microbiol Infect* 2014;20(2):123-9.

26 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-34.

27 Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001;54(10):1046-55.

28 Barendregt JJ, Doi SA. MetaXL User Guide Version 5.3. Sunrise Beach, Queensland, Australia: EpiGear International Pty Ltd; 2016.

29 Furuya-Kanamori L, Barendregt JJ, Doi SAR. A new improved graphical and quantitative method for detecting bias in meta-analysis. *Int J Evid Based Healthc* 2018;16(4):195-203.

30 Arvanitis M, DeWalt DA, Martin CF, et al. Patient-Reported Outcomes Measurement Information System in Children with Crohn's Disease. *J Pediatr* 2016;174:153-159 e2.

31 Marcus SB, Strople JA, Neighbors K, et al. Fatigue and health-related quality of life in pediatric inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2009;7(5):554-61.

32 Castaneda AE, Tuulio-Henriksson A, Aronen ET, Marttunen M, Kolho KL. Cognitive functioning and depressive symptoms in adolescents with inflammatory bowel disease. *World J Gastroenterol* 2013;19(10):1611-7.

33 van Tilburg MA, Claar RL, Romano JM, et al. Role of Coping With Symptoms in Depression and Disability: Comparison Between Inflammatory Bowel Disease and Abdominal Pain. *J Pediatr Gastroenterol Nutr* 2015;61(4):431-6.

34 Jayanath S, Lee WS, Chinna K, Boey CC. Depressive symptoms in children with chronic gastrointestinal disorders. *Pediatr Int* 2014;56(4):583-7.

35 Jelenova D, Prasko J, Ociskova M, et al. Quality of life and parental styles assessed by adolescents suffering from inflammatory bowel diseases and their parents. *Neuropsychiatr Dis Treat* 2016;12:665-72.

36 Mahlmann L, Gerber M, Furlano RI, et al. Aerobic exercise training in children and adolescents with inflammatory bowel disease: Influence on psychological functioning, sleep and physical performance - An exploratory trial. *Ment Health Phys Act* 2017;13:30-39.

37 Iturralde E, Adams RN, Barley RC, et al. Implementation of Depression Screening and Global Health Assessment in Pediatric Subspecialty Clinics. *J Adolesc Health* 2017;61(5):591-598.

38 Herzog D, Landolt MA, Buehr P, et al. Low prevalence of behavioural and emotional problems among Swiss paediatric patients with inflammatory bowel disease. *Arch Dis Child* 2013;98(1):16-9.

39 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.

40 Giannakopoulos G, Chouliaras G, Margoni D, et al. Stressful life events and psychosocial correlates of pediatric inflammatory bowel disease activity. *World J Psychiatry* 2016;6(3):322-8.

41 Szigethy E, Kenney E, Carpenter J, 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.

42 Szigethy EM, Youk AO, Benhayon D, et al. Depression subtypes in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2014;58(5):574-81.

43 Thompson RD, Craig AE, Mrakotsky C, Bousvaros A, DeMaso DR, Szigethy E. Using the Children's Depression Inventory in youth with inflammatory bowel disease: support for a physical illness-related factor. *Compr Psychiatry* 2012;53(8):1194-9.

44 Watson KL, Jr., Kim SC, Boyle BM, Saps M. Prevalence and Impact of Functional Abdominal Pain Disorders in Children With Inflammatory Bowel Diseases (IBD-FAPD). *J Pediatr Gastroenterol Nutr* 2017;65(2):212-217.

45 Schuman SL, Graef DM, Janicke DM, Gray WN, Hommel KA. An exploration of family problem-solving and affective involvement as moderators between disease severity and depressive symptoms in adolescents with inflammatory bowel disease. *J Clin Psychol Med Settings* 2013;20(4):488-96.

46 Reed-Knight B, Lobato D, Hagin S, et al. Depressive symptoms in youth with inflammatory bowel disease compared with a community sample. *Inflamm Bowel Dis* 2014;20(4):614-21.

47 Reigada LC, Satpute A, Hoogendoorn CJ, et al. Patient-reported Anxiety: A Possible Predictor of Pediatric Inflammatory Bowel Disease Health Care Use. *Inflamm Bowel Dis* 2016;22(9):2127-33.

48 Ryan JL, Mellon MW, Junger KW, 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.

49 Walter JG, Kahn SA, Noe JD, Schurman JV, Miller SA, Greenley RN. Feeling Fine: Anxiety and Depressive Symptoms in Youth with Established IBD. *Inflamm Bowel Dis* 2016;22(2):402-8.

50 Reigada LC, Moore MT, Martin CF, Kappelman MD. Psychometric Evaluation of the IBD-Specific Anxiety Scale: A Novel Measure of Disease-Related Anxiety for Adolescents With IBD. *J Pediatr Psychol* 2018;43(4):413-422.

51 Netherlands Youth Institute: Facts and figures anxiety and depressive problems. In: https://www.nji.nl/nl/Depressie-Probleemschets-Cijfers-Cijfers-over-angst--en-stemmingsproblemen. Accessed January 2018.

52 Lewinsohn PM, Shankman SA, Gau JM, Klein DN. The prevalence and co-morbidity of subthreshold psychiatric conditions. *Psychol Med* 2004;34(4):613-22.

53 Buchberger B, Huppertz H, Krabbe L, Lux B, Mattivi JT, Siafarikas A. Symptoms of depression and anxiety in youth with type 1 diabetes: A systematic review and meta-analysis. *Psychoneuroendocrinology* 2016;70:70-84.

54 Lu Y, Mak KK, van Bever HP, Ng TP, Mak A, Ho RC. Prevalence of anxiety and depressive symptoms in adolescents with asthma: a meta-analysis and meta-regression. *Pediatr Allergy Immunol* 2012;23(8):707-15.

55 Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review. *J Psychosom Res* 2016;87:70-80.

56 Angst J, Merikangas KR, Preisig M. Subthreshold syndromes of depression and anxiety in the community. *J Clin Psychiatry* 1997;58 Suppl 8:6-10.

57 Karsten J, Hartman CA, Smit JH, et al. Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. *Brit J Psychiat* 2011;198(3):206-212.

58 Costello EJ, Copeland W, Angold A. Trends in psychopathology across the adolescent years: what changes when children become adolescents, and when adolescents become adults? *J Child Psychol Psychiatry* 2011;52(10):1015-25.

59 Newman DL, Moffitt TE, Caspi A, Magdol L, Silva PA, Stanton WR. Psychiatric disorder in a birth cohort of young adults: prevalence, comorbidity, clinical significance, and new case incidence from ages 11 to 21. *J Consult Clin Psychol* 1996;64(3):552-62.

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"

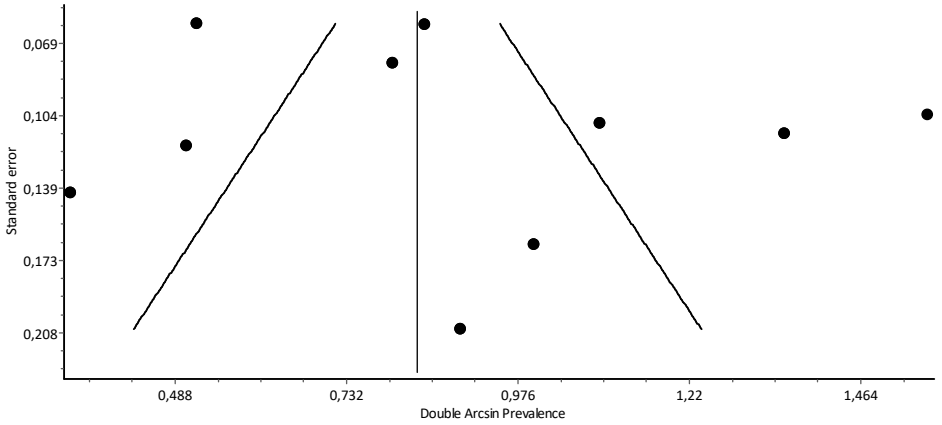
Appendix 2. Quality/risk of bias checklist

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

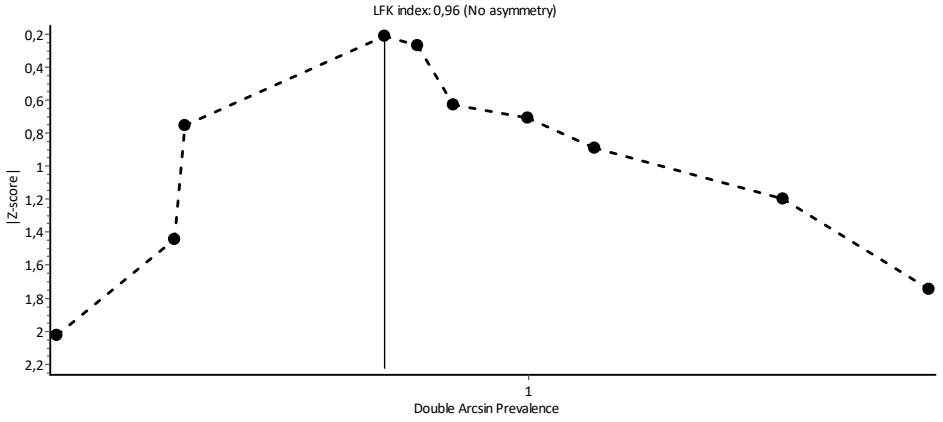
Maximum score: 27

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

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

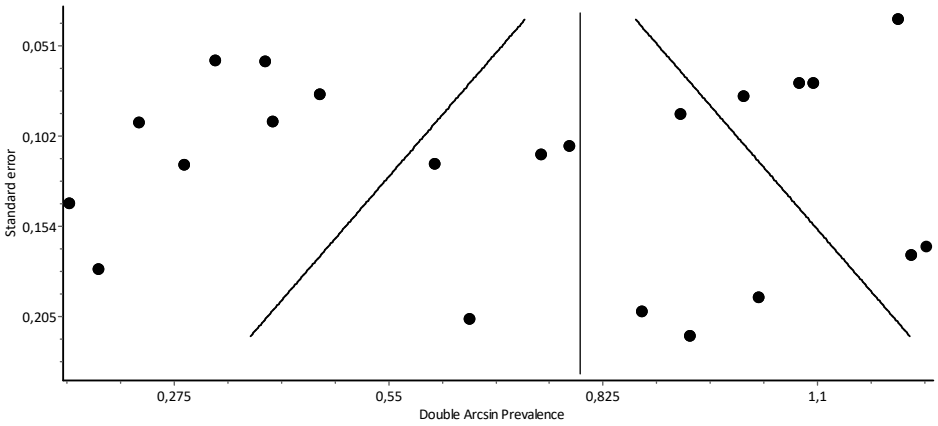


a) Funnel plot anxiety symptoms

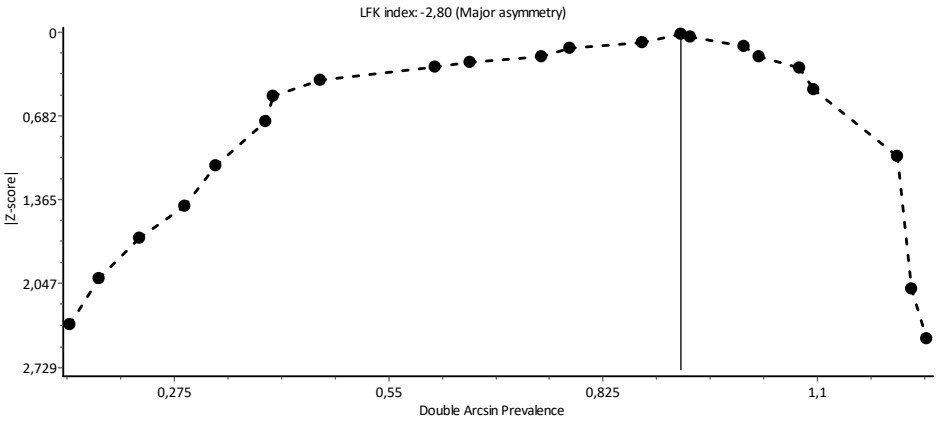


b) Doi plot anxiety symptoms

Abbreviation: LFK index: Luis Furuya-Kanamori index



c) Funnel plot depressive symptoms



d) Doi plot anxiety symptoms

Abbreviation: LFK index: Luis Furuya-Kanamori index

EDITORIAL:
ANXIETY AND DEPRESSION IN INFLAMMATORY BOWEL DISEASE

Antonina A. Mikocka-Walus, Simon R. Knowles

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, they[7] 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 diagnoseable psychological disorder.

As the rates of anxiety and depression are lower in children than in adults,[1,7,8] paediatric 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 paediatric 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.

REFERENCES

1 Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies revis- ited: a systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. *Inflamm Bowel Dis*. 2016;22: 752-762.

2 Mikocka-Walus A, Pittet V, Rossel JB, von Kanel R. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2016;14:829-835.e1.

3 Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain- Gut Interactions in patients with inflammatory bowel disease. *Gastroenterology*. 2018;154:1635-1646.e3.

4 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol*. 2004;18:509-523.

5 Adamiak T, Walkiewicz-Jedrzejczak D, Fish D, et al. Incidence, clinical characteristics, and natural history of pediatric IBD in Wisconsin: a population-based epidemiological study. *Inflamm Bowel Dis.* 2013;19: 1218-1223.

6 Coughlan A, Wylde R, Lafferty L, et al. A rising incidence and poorer male outcomes characterise early onset paediatric inflammatory bowel disease. *Aliment Pharmacol Ther.* 2017;45: 1534-1541.

7 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. *Aliment Pharmacol Ther*. 2018;48:496-506.

8 Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with inflammatory bowel disease: a systematic review. *J Psychosom Res.* 2016;87:70-80.

9 Timmer A, Preiss JC, Motschall E, Rucker G, Jantschek G, Moser G. Psychological interventions for treatment of inflammatory bowel dis- ease. *Cochrane Database Syst Rev*. 2011;2:Cd006913.

EDITORIAL:
ANXIETY AND DEPRESSION IN INFLAMMATORY BOWEL DISEASE – AUTHOR'S REPLY

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

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 (paediatric) 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 paediatric 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 cut-offs. 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.

REFERENCES

1 Mikocka-Walus A, Knowles SR. Editorial: anxiety and depression in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;48(6):686-687.

2 Stapersma L, van den Brink G, Szigethy EM, Escher JC, Utens E. Systematic review with meta-analysis: anxiety and depression in children and adolescents with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;48(5):496-506.

3 Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology*. 2013;144(1):36-49.

4 Abautret-Daly A, Dempsey E, Parra-Blanco A, Medina C, Harkin A. Gut-brain actions underlying comorbid anxiety and depression associated with inflammatory bowel disease. *Acta Neuropsychiatr*. 2018;30(5):275-296.

5 Mikocka-Walus A, Pittet V, Rossel JB, von Kanel R, Swiss IBDCSG. Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2016;14(6):829-835 e821.

6 Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain-Gut Interactions in Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2018;154(6):1635-1646 e1633.

7 Jakobsen C, Bartek J, Jr., Wewer V, et al. Differences in phenotype and disease course in adult and paediatric inflammatory bowel disease--a population-based study. *Aliment Pharmacol Ther*. 2011;34(10):1217-1224.

8 Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology*. 2008;135(4):1114-1122.

9 Ranoyen I, Lydersen S, Larose TL, et al. Developmental course of anxiety and depression from adolescence to young adulthood in a prospective Norwegian clinical cohort. *Eur Child Adolesc Psychiatry*. 2018;27(11):1413-1423.

10 Roza SJ, Hofstra MB, van der Ende J, Verhulst FC. Stable prediction of mood and anxiety disorders based on behavioral and emotional problems in childhood: a 14-year follow-up during childhood, adolescence, and young adulthood. *Am J Psychiatry*. 2003;160(12):2116-2121.

11 Gibb SJ, Fergusson DM, Horwood LJ. Burden of psychiatric disorder in young adulthood and life outcomes at age 30. *Br J Psychiatry*. 2010;197(2):122-127.

12 Trautmann S, Rehm J, Wittchen HU. The economic costs of mental disorders: Do our societies react appropriately to the burden of mental disorders? *EMBO Rep*. 2016;17(9):1245-1249.

13 van den Brink G, Stapersma L, Vlug LE, et al. Clinical disease activity is associated with anxiety and depressive symptoms in adolescents and young adults with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;48(3):358-369.

14 Szigethy E, Bujoreanu SI, Youk AO, 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):726-735.

15 Stapersma L, van den Brink G, van der Ende J, et al. Effectiveness of Disease-Specific Cognitive Behavioral Therapy on Anxiety, Depression, and Quality of Life in Youth With Inflammatory Bowel Disease: A Randomized Controlled Trial. *J Pediatr Psychol*. 2018;43(9):967-980.

CHAPTER 3

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)

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

BMJ Open Gastroenterol. 2016 2;3(1):e000071

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 multicentre randomised controlled trial (RCT) aims to test the effectiveness of an IBD-specific Cognitive Behavioural 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.

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 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. tumour 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. (2012) and Salim et al. (2012) 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 (2007) 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. (2014) 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. (2013) 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 randomised 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 RCTs 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 multi-center RCT, 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 randomised 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.

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.

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 for an overview of the procedure. 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 cut-off 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 cut-off on the total scale of the SCARED (26 for boys, 30 for girls) or 2) a score equal to or above the cut-off (8) on one of the subscales.[69]

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 randomisation if they meet criteria for a clinical depressive or anxiety disorder on the ADIS-C/P and score equal to or above the clinical cut-off 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 randomise them. For patients with subclinical depression and/or anxiety, the medical researcher performs the randomisation 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.

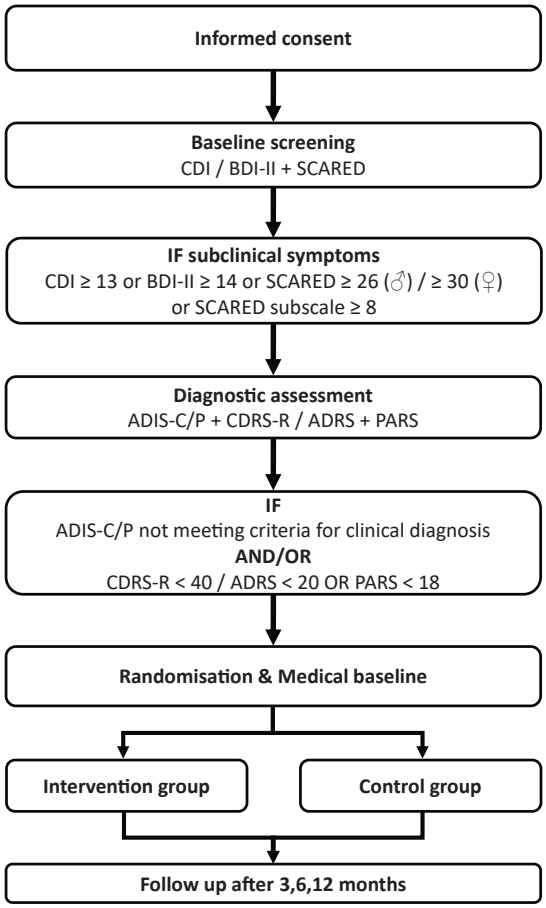


Figure 1. Flow chart study design

Abbreviations: ADIS-C/P, Anxiety Disorders Interview Schedule—Child and Parent Version; ADRS, Adolescent Depression Rating Scale; BDI-II, Beck Depression Inventory—Second Edition; CDI, Child Depression Inventory; CDRS-R, Child Depression Rating Scale—Revised; PARS, Pediatric Anxiety Rating Scale; SCARED, Screen for Child Anxiety Related Emotional Disorders.

Randomisation and blinding

Patients are allocated to PASCET-PI or CAU group by means of computer-based, block randomisation, 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 randomisation. 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
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: Pr = parent report, Pt = patient (self-report), M = medical file/(pediatric) gastroenterologist, Ps = psychologist, 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.

Intervention

The PASCET-PI focuses on behavioural 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 (Health Care) 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 analysed as either confounder, mediator, or moderator.

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 analysed using Z-scores of CDI and BDI-II, and CDRS-R and ADRS.

Table 2. Outline of the PASCET-PI[61]

Session number	Content of session
Session 1 *Live*	Introduction of ACT & THINK model and PASCET-PI, build alliance, psycho-education about IBD and depression or anxiety, illness narrative
Session 2 *Live*	Mood monitoring, explaining link between feelings, thoughts and behaviors, discussing feeling good and feeling bad, problem-solving
Session 3 *By telephone*	Link between behavior and feelings: Activities to feel better
Session 4 *Live*	Be Calm and Confident: relaxation exercises
Session 5 *Live*	Be Calm and Confident: positive self vs negative self, training social skills
Session 6 *By telephone*	Talents: developing talents and skills makes you feel better
Session 7 *Live*	Social problem solving, discussing the ACT skills and introduction of the THINK skills with discussing negative thoughts (Think positive)
Session 8 *By telephone*	Help from a friend, Identify the 'Silver Lining', and No replaying bad thoughts
Session 9 *By telephone*	Keep trying – Don't give up, making several plans to use the ACT & THINK skills
Session 10 *Live*	Quiz on ACT & THINK model, discussing use of ACT & THINK skills in the future, updating illness narrative
Booster 1 *By telephone*	Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills
Booster 2 *By telephone*	Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills
Booster 3 *By telephone*	Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills
Family 1 *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 *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 *Live*	Parental view on progress, family communication, parental depression or anxiety

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), hospitalise 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 -80C. 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 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 randomisation. 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 randomised 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 randomised 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 randomisation will be stratified for academic versus community hospitals. Randomised 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, 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):639-644.

2 Greenley RN, Hommel KA, Nebel J, et al. A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. *J ped psychology*. 2010;35(8):857-869.

3 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin gastroenterol*. 2004;18(3):509-523.

4 Rabizadeh S, Dubinsky M. Update in pediatric inflammatory bowel disease. *Rheum dis clin North Am*. 2013;39(4):789-799.

5 Engelmann G, Erhard D, Petersen M, 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):300-307.

6 Lynch T, Spence D. A qualitative study of youth living with Crohn disease. *Gastroenterol Nurs*. 2008;31(3):224-230; quiz 231-222.

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):275-279.

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):480-488.

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):1755-1764.

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):449-458.

11 Szigethy E, Craig AE, Iobst EA, 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. *Pediatr Clin North Am.* 2011;58(4):903-920, x-xi.

13 Burke P, Meyer V, Kocoshis S, et al. Depression and anxiety in pediatric inflammatory bowel disease and cystic fibrosis. *J Am Acad Child Adolesc Psychiatry*. 1989;28(6):948-951.

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):275-283.

15 Clark JG, Srinath AI, Youk AO, et al. Predictors of depression in youth with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2014;58(5):569-573.

16 Reigada LC, Bruzzese JM, Benkov KJ, et al. Illness-specific anxiety: implications for functioning and utilization of medical services in adolescents with inflammatory bowel disease. *J Spec Pediatr Nurs.* 2011;16(3):207-215.

17 Szigethy E, Kenney E, Carpenter J, et al. Cognitive-behavioral therapy for adolescents with inflammatory bowel disease and subsyndromal depression. *J Am Acad Child Adolesc Psychiatry*. 2007;46(10):1290-1298.

18 Szigethy E, Levy-Warren A, Whitton S, 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, et al. Anxiety symptoms and disease severity in children and adolescents with crohn disease. *J Pediatr Gastroenterol Nutr*. 2015;60(1):30-35.

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):225-234.

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):764-772.

23 Thompson RD, Craig A, Crawford EA, et al. Longitudinal results of cognitive behavioral treatment for youths with inflammatory bowel disease and depressive symptoms. *J Clin Psychol Med Settings*. 2012;19(3):329-337.

24 Loftus EV, Jr., Guerin A, Yu AP, et al. Increased risks of developing anxiety and depression in young patients with Crohn's disease. *Am J Gastroenterol*. 2011;106(9):1670-1677.

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):2301-2309.

27 Bennebroek Evertsz F, Thijssens NA, Stokkers PC, et al. Do Inflammatory Bowel Disease patients with anxiety and depressive symptoms receive the care they need? *J Crohns Colitis*. 2012;6(1):68-76.

28 Panara AJ, Yarur AJ, Rieders B, 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):802-810.

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):1105-1118.

30 Mittermaier C, Dejaco C, Waldhoer T, et al. Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. *Psychosom Medicine*. 2004;66(1):79-84.

31 Nahon S, Lahmek P, Durance C, et al. Risk factors of anxiety and depression in inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18(11):2086-2091.

32 Keethy D, Mrakotsky C, Szigethy E. Pediatric inflammatory bowel disease and depression: treatment implications. *Curr Opin Pediatr*. 2014;26(5):561-567.

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):389-396.

34 Engstrom I. Inflammatory bowel disease in children and adolescents: mental health and family functioning. *J Pediatr Gastroenterol Nutr*. Review. 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):237-244.

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):548-552.

38 Szigethy EM, Youk AO, Benhayon D, et al. Depression Subtypes in Pediatric Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr*. 2014 May;58(5):574-81.

39 Reed-Knight B, Lobato D, Hagin S, et al. Depressive symptoms in youth with inflammatory bowel disease compared with a community sample. *Inflamm Bowel Dis*. 2014;20(4):614-621.

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, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut*. 2008;57(10):1386-1392.

42 Bitton A, Sewitch MJ, Peppercorn MA, et al. Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. *Am J Gastroenterol*. 2003;98(10):2203-2208.

43 Levenstein S, Prantera C, Varvo V, et al. Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. *Am J Gastroenterol*. 2000;95(5):1213-1220.

44 Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut*. 2005;54(10):1481-1491.

45 Srinath AI, Goyal A, Zimmerman LA, et al. Predictors of abdominal pain in depressed pediatric inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2014;20(8):1329-1340.

46 Ryan JL, Mellon MW, Junger KW, 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):2666-2672.

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. *J Ped Psychology*. 2012;37(3):282-291.

48 O'Donovan A. Inflammation and depression: unraveling the complex interplay in inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2014;58(5):541-542.

49 Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in immunology*. Review. 2006;27(1):24-31.

50 Mawdsley JE, Rampton DS. The role of psychological stress in inflammatory bowel disease. *Neuroimmunomodulation*. Review. 2006;13(5-6):327-336.

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. *Psychol bull*. 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.* 2011;36(12):2375-2394.

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):171-186.

56 Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457.

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*. Review. 2012;27(1):6-14.

59 Salim S, Chugh G, Asghar M. Inflammation in anxiety. *Adv protein chem struct biol*. 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):447-455.

61 Szigethy E, Weisz JR, Findling RL. Cognitive-Behavior Therapy for Children and Adolescents. Arlington: American Psychiatric Publishing, 2012:331-378

62 Thompson RD, Delaney P, Flores I, Szigethy E. Cognitive-behavioral therapy for children with comorbid physical illness. *Child adoles psychiatr clin of N Am*. 2011;20(2):329-348.

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):1469-1477.

64 Szigethy E, Bujoreanu SI, Youk AO, 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):726-735.

65 Reigada LC, Benkov KJ, Bruzzese JM, et al. Integrating illness concerns into cognitive behavioral therapy for children and adolescents with inflammatory bowel disease and co-occurring anxiety. *J Spec Pediatr Nursing*. 2013;18(2):133-143.

66 Timbremont B, Brat C, Roelofs J. Handleiding Children's Depression Inventory (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):418-425.

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):1061-1069.

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):631-637.

84 Garnefski NK, 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):870-878.

88 Epstein NB, Baldwin LM, Bishop DS. The McMaster family assessment device. *J Mar Fam Ther 9, (2), 171-180.*

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):703-707.

90 Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr*. 1991;12(4):439-447.

91 Turner D, Griffiths AM, Walters TD, 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, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology*. 2007;133(2):423-432.

93 Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132(3):863-873; quiz 1165-1166.

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. *Eur Heart J*. 1998;19(5):801-807.

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):1403-1413.

96 Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol bull*. 2006;132(1):132-149.

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):251-262.

CHAPTER 4

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

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SUMMARY

Background

Youths 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 aimed 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 23.5% 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 paediatric 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 paediatric 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 paediatric 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 utilisation[21] 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 paediatric 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 paediatric 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 hypothesise 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 Organisation, 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 paediatric 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 randomised controlled trial investigating the effectiveness of cognitive behavioural therapy in youth with IBD and subclinical anxiety and/or depression (NCT02265588). For the randomised 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 φ >0.40 for anxiety symptoms, and to φ >0.30 for depressive symptoms. With 70 patients included in the randomised 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 randomised 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 behavioural 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 randomised 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 paediatric 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 emphasised 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 randomised 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[37] (10-20 years) and the Crohn's Disease Activity Index[38] (21-25 years) was used. For UC, the Paediatric Ulcerative Colitis Activity Index[39] (10-20 years) and the partial Mayo score[40, 41] (21-25 years).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, haematocrit, leukocyte count, thrombocyte count and faecal 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 cut-offs for elevated symptoms of anxiety were total SCARED score ≥ 26 for boys, ≥ 30 for 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.[48] 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 Paediatric 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 cut-off 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.

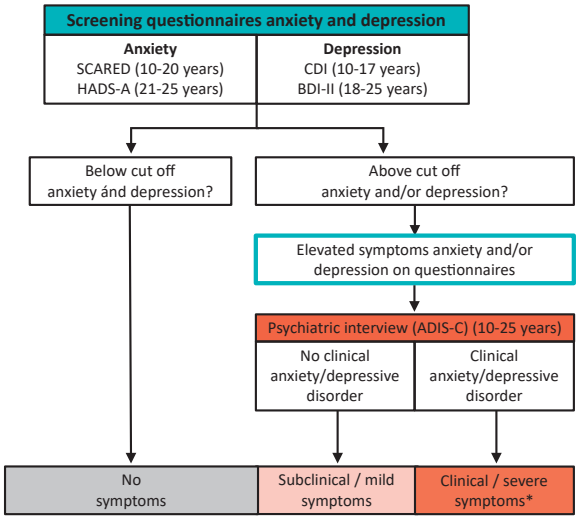

Figure 1. Flowchart screening anxiety/depression

Note: Cut-off scores for each questionnaire are specified in the text * indicative of a disorder
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

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 20-25), 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 standardised and used in the model as z-scores.

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 a multinomial logistic regression was conducted. Subgroup analysis was performed for patients 10-17 and 18-25 years. In the regression analysis, the α-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, USA) 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.

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)
Relapses preceding year	1 relapse	103 (27.5)
	≥2 relapses	22 (5.9)
Bowel resection in history		28 (7.5)
Extra intestinal Manifestations ‖		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%)

Prevalence of anxiety and depression

372 patients completed the depression questionnaires (CDI and BDI), 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%) ($\chi^2(3)=.98$, $p=0.808$). 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, generalised 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 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 randomised 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 randomised 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). Faecal 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.

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.

Notes: †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	available samples	89	52	23	
Rate (mm/h)	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

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).

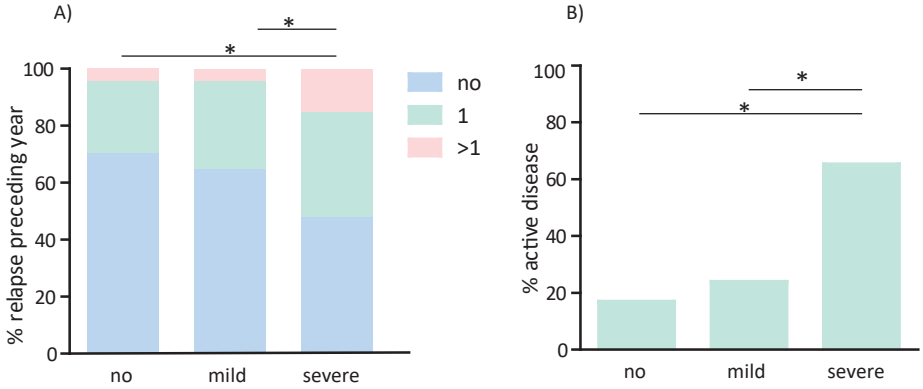

Figure 2.

(A) Patients with severe anxiety/depressive symptoms had more relapse preceding year compared to patients with mild or no anxiety/depressive symptoms.
(B) A higher percentage of active disease was found patients with severe anxiety/depressive symptoms compared to patients with mild or no anxiety/depressive symptoms *p<0.05

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 (χ^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 (data not shown). Lastly, when comparing no to severe anxiety/depressive symptoms, analysis showed that active disease (OR 7.8 [95%CI 3.3-18.0], $p<0.0001$) was associated with severe anxiety/depressive symptoms.

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		0.58-2.36	0.663	2.14	0.85-5.41	0.108
	IBD-U	0.74	0.24-2.25	0.597		0.28-2.60	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
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

Notes: [I] 2 missing, total 372; [II] 1 missing, total 373; [III] 2 missing, total 372

Abbreviations: OR: odds ratio, CI: confidence interval, CD: Crohn's disease, UC: ulcerative colitis, IBD-U: indeterminate colitis, 5-ASA: 5-aminosalicylic acid

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 paediatric 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, generalised 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 cut off 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. 2016[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 emphasises that attention should be given to emotional health in times of active disease. Support for this recommendation is found in studies that have shown an association between anxiety/depression and relapse.[8] 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. 2014[64] and several studies in adults with IBD[66] , but in contrast to other paediatric 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: paediatric as well as young adult IBD patients from regional as well as tertiary medical centers, which makes the results generalisable. 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 cut off scores is highly accepted, it does limit options for analyses. Furthermore, the BDI 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 paediatric 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 , faecal 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.

REFERENCES

1 Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis*. 2011;17(1):423-439.

2 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol*. 2004;18(3):509-523.

3 Bousvaros A, Sylvester F, Kugathasan S, et al. Challenges in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2006;12(9):885-913.

4 Northam EA. Psychosocial impact of chronic illness in children. *J Paediatr Child Health*. 1997;33(5):369-372.

5 Szigethy E, Levy-Warren A, Whitton S, 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.

6 Reed-Knight B, Lee JL, Greenley RN, Lewis JD, Blount RL. Disease Activity Does Not Explain It All: How Internalizing Symptoms and Caregiver Depressive Symptoms Relate to Health-related Quality of Life Among Youth with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2016;22(4):963-967.

7 Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology*. 2013;144(1):36-49.

8 Mikocka-Walus A, Pittet V, Rossel JB, von Kanel R, Swiss IBDCSG. Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2016;14(6):829-835 e821.

9 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):275-279.

10 Reigada LC, Bruzzese JM, Benkov KJ, et al. Illness-specific anxiety: implications for functioning and utilization of medical services in adolescents with inflammatory bowel disease. *J Spec Pediatr Nurs*. 2011;16(3):207-215.

11 Reigada LC, Hoogendoorn CJ, Walsh LC, et al. Anxiety symptoms and disease severity in children and adolescents with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2015;60(1):30-35.

12 Srinath AI, Goyal A, Zimmerman LA, et al. Predictors of abdominal pain in depressed pediatric inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2014;20(8):1329-1340.

13 Walter JG, Kahn SA, Noe JD, Schurman JV, Miller SA, Greenley RN. Feeling Fine: Anxiety and Depressive Symptoms in Youth with Established IBD. *Inflamm Bowel Dis*. 2016;22(2):402-408.

14 Hood KK, Huestis S, Maher A, Butler D, Volkening L, Laffel LM. Depressive symptoms in children and adolescents with type 1 diabetes: association with diabetes-specific characteristics. *Diabetes Care*. 2006;29(6):1389-1391.

15 Duff AJ, Abbott J, Cowperthwaite C, et al. Depression and anxiety in adolescents and adults with cystic fibrosis in the UK: a cross-sectional study. *J Cyst Fibros*. 2014;13(6):745-753.

16 Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review. *J Psychosom Res*. 2016;87:70-80.

17 Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch. Gen. Psych.* 2009;66(7):764-772.

18 Garber J, Weersing VR. Comorbidity of Anxiety and Depression in Youth: Implications for Treatment and Prevention. *Clin Psychol (New York)*. 2010;17(4):293-306.

19 Nass SJ, Beaupin LK, Demark-Wahnefried W, et al. Identifying and addressing the needs of adolescents and young adults with cancer: summary of an Institute of Medicine workshop. *Oncologist*. 2015;20(2):186-195.

20 Szigethy E, Bujoreanu SI, Youk AO, 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):726-735.

21 Brooks AJ, Rowse G, Ryder A, Peach EJ, Corfe BM, Lobo AJ. Systematic review: psychological morbidity in young people with inflammatory bowel disease - risk factors and impacts. *Aliment Pharmacol Ther*. 2016;44(1):3-15.

22 Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. *Inflamm Bowel Dis*. 2016;22(3):752-762.

23 Byrne G, Rosenfeld G, Leung Y, et al. Prevalence of Anxiety and Depression in Patients with Inflammatory Bowel Disease. *Can J Gastroenterol Hepatol*. 2017;2017:6496727.

24 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):2301-2309.

25 Walker JR, Ediger JP, Graff LA, et al. The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *Am J Gastroenterol*. 2008;103(8):1989-1997.

26 Ananthakrishnan AN, Gainer VS, Cai T, et al. Similar risk of depression and anxiety following surgery or hospitalization for Crohn's disease and ulcerative colitis. *Am J Gastroenterol*. 2013;108(4):594-601.

27 Marcus SB, Strople JA, Neighbors K, et al. Fatigue and health-related quality of life in pediatric inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2009;7(5):554-561.

28 Watson KL, Jr., Kim SC, Boyle BM, Saps M. Prevalence and Impact of Functional Abdominal Pain Disorders in Children With Inflammatory Bowel Diseases (IBD-FAPD). *J Pediatr Gastroenterol Nutr*. 2017;65(2):212-217.

29 Clark JG, Srinath AI, Youk AO, et al. Predictors of depression in youth with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2014;58(5):569-573.

30 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):251-262.

31 Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull*. 2006;132(1):132-149.

32 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. *Eur Heart J*. 1998;19(5):801-807.

33 Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr*. 2014;58(6):795-806.

34 Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis*. 2017;11(1):3-25.

35 Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis*. 2017;11(6):649-670.

36 Statistics Netherlands. In: Standaard Beroepen Classificatie 2010. The Hague: Statistics Netherlands 2010.

37 Kappelman MD, Crandall WV, Colletti RB, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. *Inflamm Bowel Dis*. 2011;17(1):112-117.

38 Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*. 1976;70(3):439-444.

39 Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology*. 2007;133(2):423-432.

40 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317(26):1625-1629.

41 D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology*. 2007;132(2):763-786.

42 Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis*. 2011;17(6):1314-1321.

43 Muris P, Mayer B, Bartelds E, Tierney S, Bogie N. The revised version of the Screen for Child Anxiety Related Emotional Disorders (SCARED-R): treatment sensitivity in an early intervention trial for childhood anxiety disorders. *Br J Clin Psychol.* 2001;40(Pt 3):323-336.

44 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):418-425.

45 De Croon EM, Nieuwenhuijsen K. Drie vragenlijsten voor diagnostiek van depressie en angststoornissen. *TBV Tijdschrift voor bedrijfs- en verzekeringsgeneeskunde*. 2005;13(4):114-119.

46 Muris P, Bodden D, Hale W, Birmaher B, Mayer B. Vragenlijst over angst en bang-zijn bij kinderen en adolescenten. Handleiding bij de gereviseerde Nederlandse versie van de Screen for Child Anxiety Related Emotional Disorders. Amsterdam: Boom test uitgevers; 2011.

47 Timbremont B, Braet C. Handleiding Children's Depression Inventory (herziene versie). Amsterdam: Pearson Assessment and Information B.V.; 2008.

48 Van der Does AJ. BDI-II-NL. Handleiding. De Nederlandse versie van de Beck Depression Inventory-2nd edition. Lisse: Harcourt Test Publishers; 2002.

49 Siebelink E, Treffers. Nederlandse bewerking van het Anxiety Disorder Interview Schedule for DSM-IV Child Version van Silverman & Albano. Lisse, Amsterdam: Swets & Zeitlinger, 2001

50 Silverman, Albano. Anxiety Disorders Interview Schedule for DSM-IV Child Version, Child Interview Schedule. San Antonio: The Psychological Corporation, 1996.

51 The Pediatric Anxiety Rating Scale (PARS): development and psychometric properties. *J Am Acad Child Adolesc Psychiatry*. 2002;41(9):1061-1069.

52 Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50-55.

53 Poznanski EO, Mokros H. Children's Depression Rating Scale Revised (CDRS-R). Los Angeles Western Psychological Services; 1996.

54 Revah-Levy A, Birmaher B, Gasquet I, Falissard B. The Adolescent Depression Rating Scale (ADRS): a validation study. *BMC psychiatry*. 2007;7:2.

55 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.

56 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.

57 de Boer AG, Wijker W, Bartelsman JF, de Haes HC. Inflammatory Bowel Disease Questionnaire: cross-cultural adaptation and further validation. *Eur J Gastroenterol Hepatol*. 1995;7(11):1043-1050.

58 Gray WN, Denson LA, Baldassano RN, Hommel KA. Disease activity, behavioral dysfunction, and health-related quality of life in adolescents with inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17(7):1581-1586.

59 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.

60 Otley A, Smith C, Nicholas D, et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2002;35(4):557-563.

61 van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw.* 2011;45(3):67.

62 Hochberg Y. A Sharper Bonferroni Procedure for Multiple Tests of Significance. *Biometrika*. 1988;75(4):800-802.

63 Netherlands Youth Institute: Facts and figures anxiety and depressive problems. In: https://www.nji.nl/nl/Depressie-Probleemschets-Cijfers-Cijfers-over-angst--en-stemmingsproblemen. Accessed May 2018.

64 Reed-Knight B, Lobato D, Hagin S, et al. Depressive symptoms in youth with inflammatory bowel disease compared with a community sample. *Inflamm Bowel Dis*. 2014;20(4):614-621.

65 Twenge JM, Nolen-Hoeksema S. Age, gender, race, socioeconomic status, and birth cohort differences on the children's depression inventory: a meta-analysis. *J Abnorm Psychol.* 2002;111(4):578-588.

66 Selinger CP, Lal S, Eaden J, et al. Better disease specific patient knowledge is associated with greater anxiety in inflammatory bowel disease. *J Crohns Colitis*. 2013;7(6):e214-218.

67 Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. *Front Neuroendocrinol*. 2014;35(3):320-330.

68 Szigethy E, Craig AE, Iobst EA, et al. Profile of depression in adolescents with inflammatory bowel disease: implications for treatment. *Inflamm Bowel Dis*. 2009;15(1):69-74.

69 Greenley RN, Hommel KA, Nebel J, et al. A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. *J Ped Psych*. 2010;35(8):857-869.

CHAPTER 5

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

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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 (β = -.412; β = -.438, $p < .001$) and more depression (β = -.454; β = -.279 , $p < .001$) were related to lower HRQOL. In the UC/IBD-U group, more anxiety was related to lower HRQOL (β = -.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 25% of patients, IBD starts in late childhood or adolescence .[1, 2] The designation IBD unclassified (IBDU) is used for patients in which it 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.[3] 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 (psychological, social, cognitive, academic). IBD can affect for example becoming more independent from parents, developing long-term friendships, starting secondary education, forming an own identity, but also experimenting with alcohol and drugs, finding a (side) job and having romantic relationships.[4] 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.[5, 6] Furthermore, high prevalence rates varying from 20-50% for anxiety and depression are found in these patients.[7-10] 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% .[11]

Other psychological factors are also important to consider in patients with IBD, such as illness perceptions and coping. Illness perceptions refer to the cognitive and emotional representations a patients forms about his or her disease.[12] 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).[12, 13] Coping refers to the strategies an individual uses in dealing with harm, threat or challenges[14], i.e. their disease for patients with IBD. A complete description of coping is outside the scope of this study. In short, several types of coping are described earlier, for example emotion-focused-coping (strategies to deal with the emotional responses to threat) versus problem-focused coping (strategies to deal with the threat itself), and adaptive coping (coping strategies that are associated with favorable outcomes) versus maladaptive coping (coping strategies associated with undesirable outcomes) or cognitive versus behavioral coping.[15]

The Common Sense Model (CSM) is a model to describe the relationships between disease characteristics, illness perceptions, coping, and anxiety, depression and HRQOL.[12] 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 is 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.[16, 17] Previous studies have also demonstrated a relationship between clinical disease activity and HRQOL, with a mediating role for anxiety and depressive symptoms .[16, 18-20] Furthermore, more negative illness perceptions are associated with lower HRQOL in adults with IBD[21] and also with more psychological problems in youth with IBD.[22] Coping was associated with anxiety and depression[19] or adjustment[23] in adults, and found as predictor of depression in youth with IBD as well.[24]

Unfortunately, very little is known on how all these factors combined affect health outcomes, more specifically HRQOL in young IBD patients. In adults, illness perceptions and coping have been reported to separately impact the relationship between clinical disease activity on HRQOL.[19, 20] Recently, Van Tilburg et al.[25] 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[17, 26, 27], and with anxiety and/or depression as well.[22, 28] Moreover, because the authors used a combined psychological construct their findings provide no insight on which psychological factors in particular psychological interventions 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 prospective 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. More specific insight on how psychological factors are associated with HRQOL can offer guidance on which factors psychological interventions should focus. 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.[32]). 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.[33 34, 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 eight 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[36], 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.[37] Scores range from 0 to 90 points.[38] The PUCAI comprises six items on abdominal pain, rectal bleeding, stool frequency and consistency, and activity level. Scores range from 0 to 85.

Psychological factors

Illness perceptions were assessed by the Brief Illness Perceptions Questionnaire (B-IPQ; [14, 39]). 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.[40] 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 to 5 points, 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.[41] 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.[42] The cutoffs for elevated anxiety were total score ≥ 26 for boys, ≥ 30 for girls, or subscale score ≥ 8.[43] 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.[44] 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.[45] 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.[46] The 35 items are scored (1-5; total score 35-175). Good psychometric properties have been found.[47] 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[48], and IBD-U has often a similar treatment approach as UC.[49] 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[50]). 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 (β = -.170, p = .001), more negative illness perceptions (β = -.412, p < .001), and more depressive symptoms (β = -.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/IBDU	Total
N		**147**	**115**	**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 (%)[c]		49.7	50.4	50.0
Elevated depression (%)[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)

Notes: [a] Not for all patients SES was available: CD N=130, UC/IBDU 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).
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.

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

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).

Table 3. Influence of demographic, disease, and psychological variables on HRQOL; results of multiple linear regression analysis – UC/IBDU 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

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 analysed 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.[22, 28] 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[31]), 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[23], but Sarid et al.[51] showed worse psychosocial outcomes in patients with UC.[27, 52] Thirdly, anxiety and depression are highly comorbid, have overlapping symptoms and anxiety is considered a precursor of depression.[53, 54] 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.[55] 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.[56, 57] 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.[58,59] More specifically, higher IBD-specific anxiety was associated with lower HRQOL in youth with both CD and UC.[58] 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.[27, 52] 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.[60] 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[61, 62], 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.[63] 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[19 21 64], and parental stress[64, 65] 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.[66-68] 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[69], as well as in

our own cohort.[31] Anxiety and depressive symptoms are known to affect HRQOL in youth with IBD.[21, 64] 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.[68], who also reported that older age was associated 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[30, 70] or the reversed association (lower HRQOL in younger patients[20]). 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).[30, 68] However, these studies included mainly CD patients (77% and 100% respectively).[30, 68] 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. 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 results.[6, 21, 64, 65] 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, 23]), 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.[71] 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 nonresponders.

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.[72] 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.[73, 74]

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.

REFERENCES

1 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol*. 2004;18(3):509-23.

2 Adamiak T, Walkiewicz-Jedrzejczak D, Fish D, et al. Incidence, clinical characteristics, and natural history of pediatric IBD in Wisconsin: a population-based epidemiological study. *Inflamm Bowel Dis*. 2013;19(6):1218-23.

3 Ghione S, Sarter H, Fumery M, et al. Dramatic Increase in Incidence of Ulcerative Colitis and Crohn's Disease (1988-2011): A Population-Based Study of French Adolescents. *Am J Gastroenterol*. 2018;113(2):265-72.

4 Rabizadeh S, Dubinsky M. Update in pediatric inflammatory bowel disease. *Rheum Dis Clin North Am.* 2013;39(4):789-99.

5 Arnett JJ. Adolescence and emerging adulthood: A cultural approach (International Edition). Fourth Edition ed. Prentice Hall, Upper Saddle River, NJ: Pearson; 2010.

6 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.

7 Knowles SR, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses—Part I. *Inflamm Bowel Dis.* 2018;24(4):742-51.

8 Clark JG, Srinath AI, Youk AO, et al. Predictors of depression in youth with Crohn disease. *J Pediatr Gastroenterol Nutr.* 2014;58(5):569-73.

9 Szigethy E, Bujoreanu SI, Youk AO, 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.

10 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.

11 Reigada LC, Hoogendoorn CJ, Walsh LC, et al. Anxiety symptoms and disease severity in children and adolescents with crohn disease. *J Pediatr Gastroenterol Nutr*. 2015;60(1):30-5.

12 Stapersma L, van den Brink G, Szigethy EM, Escher JC, Utens E. Systematic review with meta-analysis: anxiety and depression in children and adolescents with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2018;48(5):496-506.

13 Diefenbach M, Leventhal H. The common-sense model of illness representation: Theoretical and practical considerations. *J Soc Distress Homeless.* 1996;5(1):11-38.

14 Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res.* 2006;60(6):631-7.

15 Monat AE, Lazarus RS. (Eds.) Stress and coping: an anthology. 1991. New York: Columbia University Press.

16 Compas BE, Connor-Smith JK, Saltzman H, Thomsen AH, Wadsworth ME. Coping with stress during childhood and adolescence: problems, progress, and potential in theory and research. *Psychol Bull.* 2001;127(1):87-127.

17 Compas BE, Jaser SS, Bettis AH, et al. Coping, emotion regulation, and psychopathology in childhood and adolescence: A meta-analysis and narrative review. *Psychol Bull.* 2017;143(9):939-91.

18 Garnefski N, Kraaij V. Specificity of relations between adolescents' cognitive emotion regulation strategies and symptoms of depression and anxiety. *Cogn Emot*. 2018;32(7):1401-8.

19 Gray WN, Denson LA, Baldassano RN, Hommel KA. Disease activity, behavioral dysfunction, and health-related quality of life in adolescents with inflammatory bowel disease. *Inflamm Bowel Dis.* 2011;17(7):1581-6.

20 Chouliaras G, Margoni D, Dimakou K, Fessatou S, Panayiotou I, Roma-Giannikou E. Disease impact on the quality of life of children with inflammatory bowel disease. *World J Gastroenterol*. 2017;23(6):1067-75.

21 Engelmann G, Erhard D, Petersen M, 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.

22 Rochelle TL, Fidler H. The importance of illness perceptions, quality of life and psychological status in patients with ulcerative colitis and Crohn's disease. *J Health Psychol*. 2013;18(7):972-83.

23 Brooks AJ, Rowse G, Ryder A, Peach EJ, Corfe BM, Lobo AJ. Systematic review: psychological morbidity in young people with inflammatory bowel disease - risk factors and impacts. *Aliment Pharmacol Ther.* 2016;44(1):3-15.

24 McCombie AM, Mulder RT, Gearry RB. How IBD patients cope with IBD: A systematic review. *J Crohns Colitis.* 2013;7(2):89-106.

25 van Erp SJH, Brakenhoff LKMP, Vollmann M, et al. Illness Perceptions and Outcomes in Patients with Inflammatory Bowel Disease: Is Coping a Mediator? *Int. J. Behav. Med.* 2017;24(2):205-14.

26 van Tilburg MA, Claar RL, Romano JM, et al. Role of Coping With Symptoms in Depression and Disability: Comparison Between Inflammatory Bowel Disease and Abdominal Pain. *J Pediatr Gastroenterol Nutr.* 2015;61(4):431-6.

27 van der Have M, Minderhoud IM, Kaptein AA, et al. Substantial impact of illness perceptions on quality of life in patients with Crohn's disease. *J Crohns Colitis*. 2013;7(8):e292-301.

28 van Tilburg MA, Claar RL, Romano JM, et al. Psychological Factors May Play an Important Role in Pediatric Crohn's Disease Symptoms and Disability. *J Pediatr.* 2017;184:94-100 e1.

29 Katz L, Tripp DA, Ropeleski M, et al. Mechanisms of Quality of Life and Social Support in Inflammatory Bowel Disease. *J Clin Psychol Med.* 2016;23(1):88-98.

30 Hill R, Lewindon P, Muir R, et al. Quality of life in children with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2010;51(1):35-40.

31 van den Brink G, Stapersma L, Vlug LE, et al. Clinical disease activity is associated with anxiety and depressive symptoms in adolescents and young adults with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2018;48(3):358-69.

32 van den Brink G, Stapersma L, El Marroun H, et al. 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 Gastroenterol.* 2016;3(1):e000071.

33 Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr.* 2014;58(6):795-806.

34 Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis.* 2017;11(6):649-70.

35 Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis.* 2017;11(1):3-25.

36 Statistics Netherlands. Standaard Beroepen Classificatie 2010. The Hague: Statistics Netherlands; 2010.

37 Kappelman MD, Crandall WV, Colletti RB, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. *Inflamm Bowel Dis.* 2011;17(1):112-7.

38 Turner D, Griffiths AM, Walters TD, 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.

39 de Raaij EJ, Schröder C, Maissan FJ, Pool JJ, Wittink H. Cross-cultural adaptation and measurement properties of the Brief Illness Perception Questionnaire-Dutch Language Version. *Manual Therapy.* 2012;17(4):330-5.

40 Szigethy EM, Youk AO, Benhayon D, et al. Depression subtypes in pediatric inflammatory bowel disease*. J Pediatr Gastroenterol Nutr*. 2014;58(5):574-81.

41 Garnefski N, Legerstee J, Kraaij V, Van Den Kommer T, Teerds JAN. Cognitive coping strategies and symptoms of depression and anxiety: A comparison between adolescents and adults. *J Adolescence*. 2002;25(6):603-11.

42 Muris P, Bodden D, Hale W, Birmaher B, Mayer B. SCARED-NL. Handleiding bij de gereviseerde Nederlandse versie van de Screen for Child Anxiety Related Emotional Disorders. Amsterdam: Boom test uitgevers; 2011.

43 Bodden DHM, Bögels SM, Muris P. The diagnostic utility of the Screen for Child Anxiety Related Emotional Disorders-71 (SCARED-71). *Behaviour Research and Therapy*. 2009;47(5):418-25.

44. Timbremont B, Braet C, Roelofs J. Handleiding Children's Depression Inventory (herziene versie). Amsterdam: Pearson Assessment and Information B.V.; 2008.

45 Van der Does AJW. BDI-II-NL Handleiding. De Nederlandse versie van de Beck Depression Inventory-2nd edition. Lisse: Harcourt Test Publishers; 2002.

46 Otley A, Smith C, Nicholas D, et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease*. J Pediatr Gastroenterol Nutr.* 2002;35(4):557-63.

47 Loonen HJ, Grootenhuis MA, Last BF, Haan RJd, Bouquet J, Derkx BHF. Measuring Quality of Life in Children with Inflammatory Bowel Disease: The Impact-II (NL). *Qual Life Res.* 2002;11(1):47-56.

48 Birimberg-Schwartz L, Zucker DM, Akriv A, et al. Development and Validation of Diagnostic Criteria for IBD Subtypes Including IBD-unclassified in Children: a Multicentre Study From the Pediatric IBD Porto Group of ESPGHAN. *J Crohns Colitis.* 2017;11(9):1078-84.

49 Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care- an Evidence-Based Guideline from ECCO and ESPGHAN. *J Pediatr Gastroenterol Nutr*. 2018.

50 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011;30(4):377-99.

51 Sarid O, Slonim-Nevo V, Schwartz D, et al. Differing Relationship of Psycho-Social Variables with Active Ulcerative Colitis or Crohn's Disease. *Int J Behav Med.* 2018;25(3):341-50.

52 Dorrian A, Dempster M, Adair P. Adjustment to inflammatory bowel disease: The relative influence of illness perceptions and coping. *Inflamm Bowel Dis*. 2009;15(1):47-55.

53 Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. *Depression Anxiety*. 2001;14(2):67-78.

54 Garber J, Weersing VR. Comorbidity of Anxiety and Depression in Youth: Implications for Treatment and Prevention. *Clinical Psychology: Science and Practice*. 2010;17(4):293-306.

55 Cummings CM, Caporino NE, Kendall PC. Comorbidity of Anxiety and Depression in Children and Adolescents: 20 Years After. *Psych Bull.* 2014;140(3):816-45.

56 Iglesias-Rey M, Barreiro-de Acosta M, Caamano-Isorna F, et al. Psychological factors are associated with changes in the health-related quality of life in inflammatory bowel disease. *Inflamm Bowel Dis.* 2014;20(1):92-102.

57 Luo XP, Mao R, Chen BL, et al. Over-reaching beyond disease activity: the influence of anxiety and medical economic burden on health-related quality of life in patients with inflammatory bowel disease. *Patient Prefer Adherence*. 2017;11:23-31.

58 Reigada LC, Moore MT, Martin CF, Kappelman MD. Psychometric Evaluation of the IBD-Specific Anxiety Scale: A Novel Measure of Disease-Related Anxiety for Adolescents With IBD. *J Pediatr Psychol.* 2018;43(4):413-422.

59 Reigada LC, Bruzzese JM, Benkov KJ, et al. Illness-specific anxiety: implications for functioning and utilization of medical services in adolescents with inflammatory bowel disease. *J Spec Pediatr Nurs.* 2011;16(3):207-15.

60 Dempster M, Howell D, McCorry NK. Illness perceptions and coping in physical health conditions: A meta-analysis. *J Psychosom Res*. 2015;79(6):506-13.

61 Knowles SR, Wilson JL, Connell WR, Kamm MA. Preliminary examination of the relations between disease activity, illness perceptions, coping strategies, and psychological morbidity in Crohn's disease guided by the common sense model of illness. *Inflamm Bowel Dis*. 2011;17(12):2551-7.

62 Zhang M, Hong L, Zhang T, et al. Illness perceptions and stress: mediators between disease severity and psychological well-being and quality of life among patients with Crohn's disease. *Patient Prefer Adherence*. 2016;10:2387-96.

63 Knowles SR, Keefer L, Wilding H, Hewitt C, Graff LA, Mikocka-Walus A. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses—Part II. *Inflamm Bowel Dis.* 2018;24(5):966-76.

64 Reed-Knight B, Lee JL, Greenley RN, Lewis JD, Blount RL. Disease Activity Does Not Explain It All: How Internalizing Symptoms and Caregiver Depressive Symptoms Relate to Health-related Quality of Life Among Youth with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2016;22(4):963-7.

65 Gray WN, Boyle SL, Graef DM, et al. Health-related quality of life in youth with Crohn disease: role of disease activity and parenting stress. *J Pediatr Gastroenterol Nutr*. 2015;60(6):749-53.

66 Kunz JH, Hommel KA, Greenley RN. Health-related quality of life of youth with inflammatory bowel disease: A comparison with published data using the PedsQL 4.0 generic core scales. *Inflamm Bowel Dis*. 2010;16(6):939-46.

67 De Boer M, Grootenhuis M, Derkx B, Last B. Health-related quality of life and psychosocial functioning of adolescents with inflammatory bowel disease. *Inflamm Bow Diseases*. 2005;11(4):400-6.

68 Otley AR, Griffiths AM, Hale S, et al. Health-related quality of life in the first year after a diagnosis of pediatric inflammatory bowel disease. *Inflamm Bowel Dis.* 2006;12(8):684-91.

69 Altemus M, Sarvaiya N, Epperson CN. Sex differences in anxiety and depression clinical perspectives. *Front in neuroendocrinol*. 2014;35(3):320-30.

70 Gallo J, Grant A, Otley AR, et al. Do parents and children agree? Quality-of-life assessment of children with inflammatory bowel disease and their parents. *J Pediatr Gastroenterol Nutr*. 2014;58(4):481-5.

71 Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain-Gut Interactions in Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2018;154(6):1635-46 e3.

72 Christensen SS, Frostholm L, Ornbol E, Schroder A. Changes in illness perceptions mediated the effect of cognitive behavioural therapy in severe functional somatic syndromes. *J Psychosom Res*. 2015;78(4):363-70.

73 Weisz JR, Kuppens S, Ng MY, et al. What five decades of research tells us about the effects of youth psychological therapy: A multilevel meta-analysis and implications for science and practice. *Am Psychol.* 2017;72(2):79-117.

74 Compton SN, March JS, Brent D, Albano AM, Weersing VR, Curry J. Cognitive-Behavioral Psychotherapy for Anxiety and Depressive Disorders in Children and Adolescents: An Evidence-Based Medicine Review. *J Am Acad Child Adolesc Psychiatry*. 2004;43(8):930-59.

CHAPTER 6

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

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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.

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 multicenter 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 as follows: Compared with 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? 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 multicenter 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 of age 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 as 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 next paragraph). 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 α).

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 φ >0.40 for anxiety symptoms, and to φ >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.

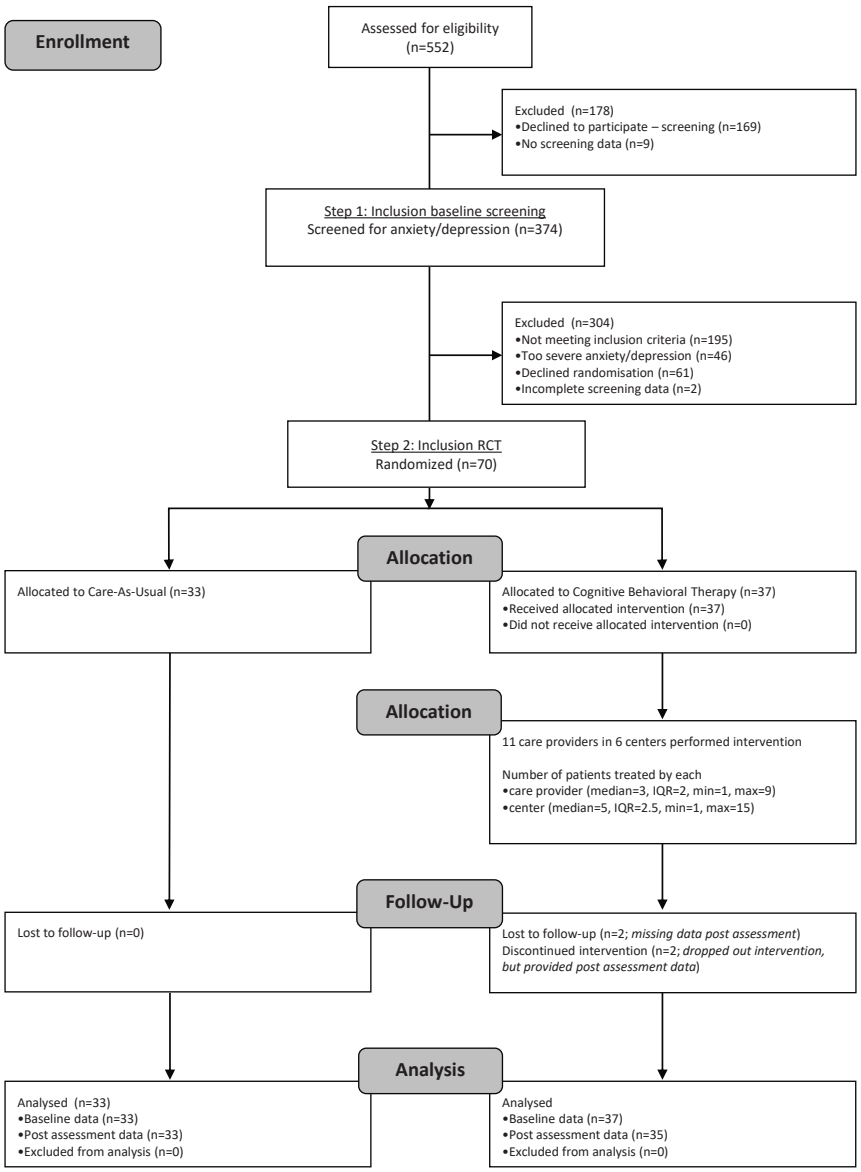

Figure 1. CONSORT study flow chart

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, mean (SD), years	1.65 (0.72)	1.55 (0.67)	.536[b]
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; IBDU = Inflammatory Bowel Disease Unclassified; SES; Socioeconomic Status
Notes: all demographic and disease characteristics were not significantly different between groups. [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)

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 (χ^2 (2) = 1.656, p = .465, φ = .159) and depression (χ^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.

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).

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
Notes: χ^2 =1.656, df = 2, p = .465, ϕ = .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

Notes: χ^2 =1.648, df = 2, p = .523, ϕ = .161 (95%BI 0.00-0.37). Numbers in parentheses indicate row percentages

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)	à	22.9 (2.6)	< .001		
CAU	40.5 (2.8)	à	25.0 (2.9)			
CBT vs. CAU					.526	-0.15 (-1.02-0.71)
HADS-A (0-14)						
CBT	9.9 (0.7)	à	7.1 (0.7)	< .001		
CAU	9.1 (0.8)	à	7.3 (0.8)			
CBT vs. CAU					.343	-0.06 (-1.49-1.37)
CDI (0-54)						
CBT	8.5 (1.1)	à	7.2 (1.1)	.130		
CAU	10.8 (1.2)	à	7.7 (1.2)			
CBT vs. CAU					.212	-0.11 (-1.11-1.02)
BDI-II (0-63)						
CBT	11.3 (1.1)	à	5.9 (1.1)	< .001		
CAU	14.2 (1.2)	à	8.2 (1.2)			
CBT vs. CAU					.719	-0.47 (-1.51-0.58)
IMPACT-III (35-175)						
CBT	137.1 (2.8)	à	148.1 (2.8)	< .001		
CAU	137.4 (2.9)	à	144.9 (3.0)			
CBT vs. CAU					.315	0.23 (-1.28-0.49)
IBDQ (32-224)						
CBT	164.6 (5.8)	à	179.6 (5.8)	< .001		
CAU	161.6 (6.4)	à	171.2 (6.7)			
CBT vs. CAU					.597	0.44 (-2.02-0.77)

Notes: 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.

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.

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 a 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] As 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, as 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.

REFERENCES

1 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol*. 2004;18(3):509-23.

2 Sauer CG, Kugathasan S. Pediatric inflammatory bowel disease: highlighting pediatric differences in IBD. *Gastroenterol Clin North Am*. 2009;38(4):611-28.

3 Mackner LM, Crandall WV, Szigethy EM. Psychosocial functioning in pediatric inflammatory bowel disease. *Inflamm Bowel Dis.* 2006;12(3):239-44.

4 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. *J Pediatr Psychol*. 2010;35(8):857-69.

5 Bonaz BL, Bernstein CN. Brain-Gut Interactions in Inflammatory Bowel Disease. *Gastroenterology*. 2013;144(1):36-49.

6 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.

7 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.

8 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.

9 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.

10 Herzog D, Landolt MA, Buehr P, Heyland K, Rogler D, Koller R, et al. Low prevalence of behavioural and emotional problems among Swiss paediatric patients with inflammatory bowel disease. *Arch Dis Child*. 2013;98(1):16-9.

11 Compton SN, March JS, Brent D, Albano AM, Weersing VR, Curry J. Cognitive-Behavioral Psychotherapy for Anxiety and Depressive Disorders in Children and Adolescents: An Evidence-Based Medicine Review. *J Am Acad Child Adolesc Psychiatry.* 2004;43(8):930-59.

12 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.

13 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. *J Spec Pediatr Nurs.* 2013;18(2):133-43.

14 Levy RL, van Tilburg MA, Langer SL, Romano JM, Walker LS, Mancl LA, et al. Effects of a Cognitive Behavioral Therapy Intervention Trial to Improve Disease Outcomes in Children with Inflammatory Bowel Disease. *Inflamm Bowel Dis.* 2016;22(9):2134-48.

15 Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. *Depression Anxiety.* 2001;14(2):67-78.

16 Garber J, Weersing VR. Comorbidity of Anxiety and Depression in Youth: Implications for Treatment and Prevention. *Clin Psychol Sci Pr.* 2010;17(4):293-306.

17 Mikocka-Walus A, Andrews JM, Bampton P. Cognitive Behavioral Therapy for IBD. *Inflamm Bowel Dis*. 2016;22(2):E5-6.

18 Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med*. 2017;167(1):40-7.

19 Bodden DHM, Bögels SM, Muris P. The diagnostic utility of the Screen for Child Anxiety Related Emotional Disorders-71 (SCARED-71). *Behaviour Research and Therapy.* 2009;47(5):418-25.

20 de Croon EM, Nieuwenhuijsen K, Hugenholtz NIR, Van Dijk FJH. Drie vragenlijsten voor diagnostiek van depressie en angststoornissen. *TBV–Tijdschrift voor Bedrijfs-en Verzekeringsgeneeskunde*. 2005;13(4):114-9.

21 Timbremont B, Braet C, Roelofs J. Handleiding Children's Depression Inventory (herziene versie). Amsterdam: Pearson Assessment and Information B.V.; 2008.

22 Van der Does AJW. BDI-II-NL Handleiding. De Nederlandse versie van de Beck Depression Inventory-2nd edition. Lisse: Harcourt Test Publishers; 2002.

23 Siebelink BM, Treffers PDA. Anxiety Disorders Interview Schedule for DSM-IV-Child version, ADIS-C Handleiding. Amsterdam: Harcourt Test Publishers; 2001.

24 Ginsburg G, Keeton C, Drazdowski T, Riddle M. The Utility of Clinicians Ratings of Anxiety Using the Pediatric Anxiety Rating Scale (PARS). *Child Youth Care Forum*. 2011;40(2):93-105.

25 Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50-5.

26 Matza LS, Morlock R, Sexton C, Malley K, Feltner D. Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder. *Int J Methods Psychiatr Res.* 2010;19(4):223-32.

27 Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary Studies of the Reliability and Validity of the Children's Depression Rating Scale. *J Am Acad Child Adolesc Psychiatry*. 1984;23(2):191-7.

28 Revah-Levy A, Birmaher B, Gasquet I, Falissard B. The Adolescent Depression Rating Scale (ADRS): a validation study. *BMC Psychiatry*. 2007;7:2.

29 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56-62.

30 Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord*. 2013;150(2):384-8.

31 van den Brink G, Stapersma L, El Marroun H, Henrichs J, Szigethy EM, Utens EM, et al. 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 Gastroenterol.* 2016;3(1):e000071.

32 Kuo B, Bhasin M, Jacquart J, Scult MA, Slipp L, Riklin EI, et al. Genomic and clinical effects associated with a relaxation response mind-body intervention in patients with irritable bowel syndrome and inflammatory bowel disease. *PLoS ONE*. 2015;10(4):e0123861.

33 Utens EMWJ, van Rijen EHM, Erdman RAM, Verhulst FC. Rotterdam's Kwaliteit van Leven Interview. Erasmus MC Rotterdam, Department of Child and Adolescent Psychiatry and Psychology; 2000.

34 Statistics Netherlands. Standaard Beroepen Classificatie 2010. The Hague: Statistics Netherlands; 2010.

35 Statistics Netherlands. Standaarddefinitie allochtonen. The Hague: Statistics Netherlands; 2000.

36 Muris P, Bodden D, Hale W, Birmaher B, Mayer B. SCARED-NL. Handleiding bij de gereviseerde Nederlandse versie van de Screen for Child Anxiety Related Emotional Disorders. Amsterdam: Boom test uitgevers; 2011.

37 Otley A, Smith C, Nicholas D, Munk M, Avolio J, Sherman PM, et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2002;35(4):557-63.

38 de Boer AG, Wijker W, Bartelsman JF, de Haes HC. Inflammatory Bowel Disease Questionnaire: cross-cultural adaptation and further validation. *Eur J Gastroenterol Hepatol.* 1995;7(11):1043-50.

39 Kappelman MD, Crandall WV, Colletti RB, Goudie A, Leibowitz IH, Duffy L, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. *Inflamm Bowel Dis.* 2011;17(1):112-7.

40 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.

41 Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*. 1976;70(3):439-44.

42 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.* 1987;317(26):1625-9.

43 Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. 1991;59(1):12.

44 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.

45 Weisz JR, McCarty CA, Valeri SM. Effects of Psychotherapy for Depression in Children and Adolescents: A Meta-Analysis. *Psychol bull*. 2006;132(1):132-49.

46 Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.

47 McCombie AM, Mulder RT, Gearry RB. Psychotherapy for inflammatory bowel disease: a review and update. *J Crohns Colitis*. 2013;7(12):935-49.

48 McCambridge J. From question-behaviour effects in trials to the social psychology of research participation. *Psychol Health*. 2015;30(1):72-84.

49 Arrindell WA. Changes in waiting-list patients over time: data on some commonly-used measures. Beware! *Behav Res Ther.* 2001;39(10):1227-47.

50 Bennebroek Evertsz F, Sprangers MAG, Sitnikova K, Stokkers PCF, Ponsioen CY, Bartelsman J, et al. Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: A multicenter randomized controlled trial. *J Consult Clin Psychol*. 2017;85(9):918-25.

51 Szigethy E, Youk AO, Gonzalez-Heydrich J, Bujoreanu SI, Weisz J, Fairclough D, et al. Effect of 2 Psychotherapies on Depression and Disease Activity in Pediatric Crohn's Disease. *Inflamm Bowel Dis*. 2015;21(6):1321-8.

52 Weisz JR, Kuppens S, Ng MY, Eckshtain D, Ugueto AM, Vaughn-Coaxum R, et al. What five decades of research tells us about the effects of youth psychological therapy: A multilevel meta-analysis and implications for science and practice. *Am Psychol.* 2017;72(2):79-117.

53 Gracie DJ, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *The Lancet Gastroenterol Hepatol.* 2017;2(3):189-99.

54 Bennett K, Manassis K, Duda S, Bagnell A, Bernstein GA, Garland EJ, et al. Preventing child and adolescent anxiety disorders: overview of systematic reviews. *Depression Anxiety.* 2015;32(12):909-18.

55 Alexakis C, Kumar S, Saxena S, Pollok R. Systematic review with meta-analysis: the impact of a depressive state on disease course in adult inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46(3):225-235.

56 van Tilburg MA, Claar RL, Romano JM, Langer SL, Drossman DA, Whitehead WE, et al. Psychological Factors May Play an Important Role in Pediatric Crohn's Disease Symptoms and Disability. *J Pediatr.* 2017;184:94-100 e1.

57 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.

58 Beesdo K, Knappe S, Pine DS. Anxiety and Anxiety Disorders in Children and Adolescents: Developmental Issues and Implications for DSM-V. *Psychiatr clin North Am.* 2009;32(3):483-524.

59 Copeland WE, Shanahan L, Costello E, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch Gen Psychiatry*. 2009;66(7):764-72.

60 Spinhoven PH, Ormel J, Sloekers PPA, Kempen GIJM, Speckens AEM, Hemert AMV. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med*. 1997;27(2):363-70.

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

Session number	Content of session
Session 1 *Live (60 min)*	Introduction of ACT & THINK model and PASCET-PI, building work alliance, psycho-education about IBD and depression or anxiety, illness narrative
Session 2 *Live (60 min)*	Mood monitoring, explaining link between feelings, thoughts and behaviors, discussing feeling good and feeling bad, problem-solving
Session 3 *By telephone (30 min)*	Link between behavior and feelings: Activities to feel better
Session 4 *Live (60 min)*	Be Calm and Confident: relaxation exercises
Session 5 *Live (60 min)*	Be Calm and Confident: positive self versus negative self, training social skills
Session 6 *By telephone (30 min)*	Talents: developing talents and skills makes you feel better
Session 7 *Live (60 min)*	Social problem solving, discussing the ACT skills and introduction of the THINK skills with discussing negative thoughts (Think positive)
Session 8 *By telephone (30 min)*	Help from a friend, Identify the 'Silver Lining', and No replaying bad thoughts
Session 9 *By telephone (30 min)*	Keep trying – Don't give up, making several plans to use the ACT & THINK skills
Session 10 *Live (60 min)*	Quiz on ACT & THINK model, discussing use of ACT & THINK skills in the future, updating illness narrative
Booster 1 *By telephone (30 min)*	Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills
Booster 2 *By telephone (30 min)*	Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills
Booster 3 *By telephone (30 min)*	Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills
Family 1 *Live (60 min)*	Parental view on IBD, family situation, psycho-education about IBD and depression or anxiety, introduction of ACT & THINK model and PASCET-PI
Family 2 *Live (60 min)*	Parental view on progress, the ACT & THINK skills that are most effective for the patient, expressing emotions within family, family communication, family stress game
Family 3 *Live (60 min)*	Parental view on progress, family communication, parental depression or anxiety

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

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 = 4.38 | 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.

CHAPTER 7

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

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Submitted

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.

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, 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

Step 1: Inclusion baseline screening

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

Sample size and power

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

RESULTS

Demographic data

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

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

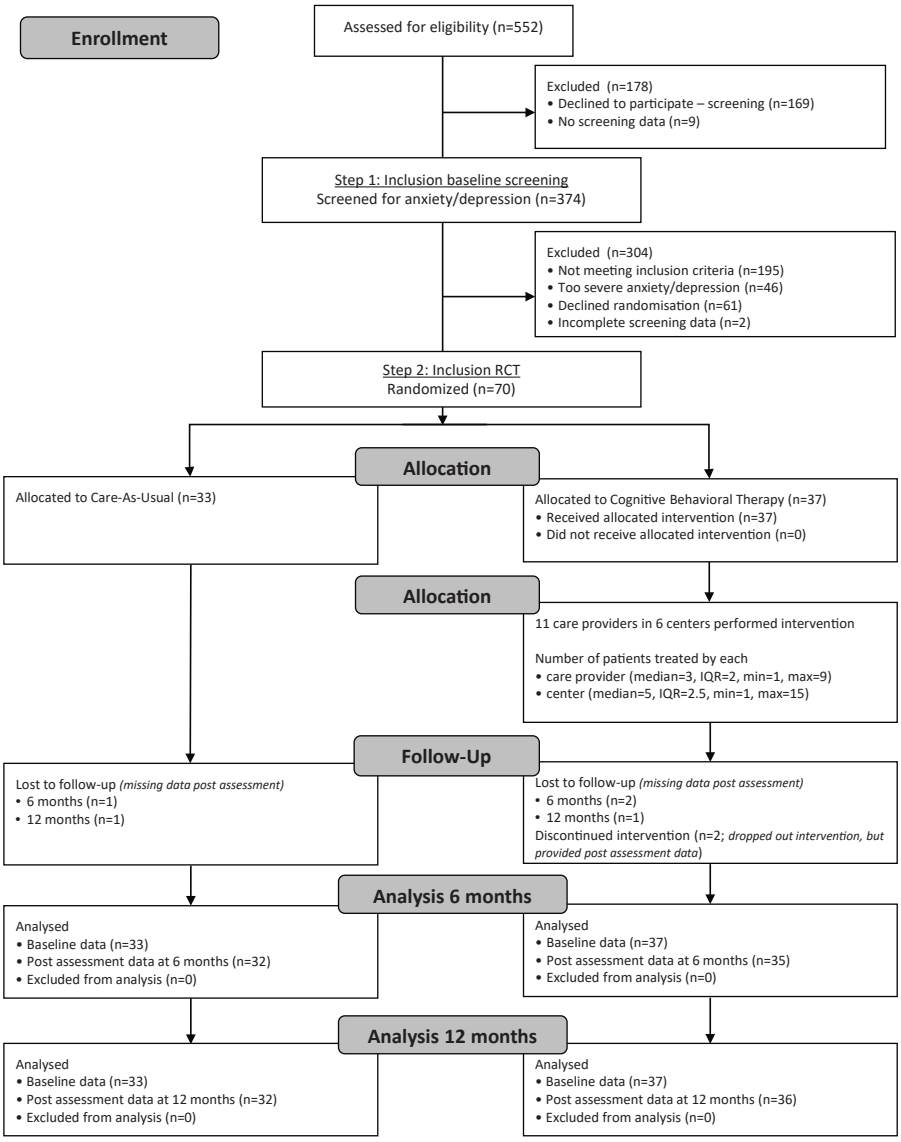


Figure 1. CONSORT study flow chart

Abbreviations: RCT= randomized controlled trial, IQR= inter quartile range

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

In the chi-square tests, some cells in the cross-tabulation were smaller than 5. Only few patients (0-4) were in the 'Reliable increase of score / deterioration' category (i.e. deteriorated in anxiety or depression). Therefore, we combined this category with the 'No reliable change' category, to test if the PASCET-PI and CAU groups differed with respect to the proportions of patients who had improved on anxiety or depression. In these main analyses, RCI values for anxiety (χ^2 (1) = .226, p = .801) and depression (χ^2 (1) = 2.680, p = .141) after 6 months did not differ between the groups, and neither did the RCI values for anxiety (χ^2 (1) = .337, p = .626) after 12 months. This indicates that in both groups a similar proportion of patients improved. For depression after 12 months, the RCI values differed significantly between the groups, indicating that a higher proportion of patients in the CAU group improved than in the PASCET-PI group (χ^2 (1) = 5.460, p = .026), see Table 1. In the PASCET-PI group, two patients developed clinical anxiety and/or depression during follow-up, versus one patient in the CAU group, which was not significantly different (χ^2 (1) = .240, p = .543).

Table 1. Crosstabulation of 6 and 12 month RCI of symptoms of anxiety and depression versus 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
Note. Pearson Chi-square = .226, p = .801, ϕ = -.058 (95%BI .000-.293). Numbers in parentheses indicate row percentages			
	RCI categories depression (CDI or BDI-II)		
CAU	11 (34.4%)	21 (65.6%)	32
CBT	19 (54.3%)	16 (45.7%)	35
Note. Pearson Chi-square = 2.680, p = .141, ϕ = .200 (95%BI .000-.439). Numbers in parentheses indicate row percentages			
12 months			
	Reliable increase of score / deterioration or no reliable change	Reliable decrease of score / improvement	Total
	RCI categories anxiety (SCARED or HADS-A)		
CAU	12 (37.5%)	20 (62.5%)	32
CBT	16 (44.4%)	20 (55.6%)	36
Note. Pearson Chi-square = .337, p = .626, ϕ = .070 (95%BI .000-.306). Numbers in parentheses indicate row percentages			
	RCI categories depression (CDI or BDI-II)		
CAU	8 (25.0%)	24 (75%)	32
CBT	19 (52.8%)	17 (47.2%)	36
Note. Pearson Chi-square = 5.460, p = .026, ϕ = .283 (95%BI .036- .521). Numbers in parentheses indicate row percentages			

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

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

No 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. First, 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.

Second, 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 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 or improved 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.

REFERENCES

1 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol*. 2004;18(3):509-523.

2 Rosen MJ, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. *JAMA Pediatr*. 2015;169(11):1053-1060.

3 Adamiak T, Walkiewicz-Jedrzejczak D, Fish D, et al. Incidence, clinical characteristics, and natural history of pediatric IBD in Wisconsin: a population-based epidemiological study. *Inflamm Bowel Dis*. 2013;19(6):1218-1223.

4 Sauer CG, Kugathasan S. Pediatric inflammatory bowel disease: highlighting pediatric differences in IBD. *Gastroenterol Clin North Am*. 2009;38(4):611-628.

5 Brooks AJ, Rowse G, Ryder A, Peach EJ, Corfe BM, Lobo AJ. Systematic review: psychological morbidity in young people with inflammatory bowel disease - risk factors and impacts. *Aliment Pharmacol Ther*. 2016;44(1):3-15.

6 Greenley RN, Hommel KA, Nebel J, et al. A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. *J Pediatr Psychol*. 2010;35(8):857-869.

7 Loftus Jr EV, Guerin A, Yu AP, et al. Increased risks of developing anxiety and depression in young patients with crohn's disease. *Am J Gastroenterol.* 2011;106(9):1670-1677.

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):480-488.

9 van der Zaag-Loonen HJ, Grootenhuis MA, Last BF, Derkx HHF. Coping strategies and quality of life of adolescents with inflammatory bowel disease. *Qual Life Res*. 2004;13(5):1011-1019.

10 McCombie AM, Mulder RT, Gearry RB. How IBD patients cope with IBD: A systematic review. *J Crohns Colitis*. 2013;7(2):89-106

11 Knowles SR, Wilson JL, Connell WR, Kamm MA. Preliminary examination of the relations between disease activity, illness perceptions, coping strategies, and psychological morbidity in Crohn's disease guided by the common sense model of illness. *Inflamm Bowel Dis*. 2011;17(12):2551-2557.

12 Rochelle TL, Fidler H. The importance of illness perceptions, quality of life and psychological status in patients with ulcerative colitis and Crohn's disease. *J Health Psychol*. 2013;18(7):972-983.

13 Manhart A-K, Hellmann S, Hamelmann E, Schlarb AA. The association of sleep with inflammatory bowel disease in children and adolescents. *Somnologie*. 2016;20(3):212-218.

14 Pirinen T, Kolho K-L, Ashorn M, Aronen ET. Sleep and Emotional and Behavioral Symptoms in Adolescents with Inflammatory Bowel Disease. *Sleep Disorders*. 2014;2014:5.

15 Mikocka-Walus A, Pittet V, Rossel JB, von Kanel R, Swiss IBDCSG. Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2016;14(6):829-835 e821.

16 Sweeney L, Moss-Morris R, Czuber-Dochan W, Meade L, Chumbley G, Norton C. Systematic review: psychosocial factors associated with pain in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;47(6):715-729.

17 van Tilburg MA, Claar RL, Romano JM, et al. Psychological Factors May Play an Important Role in Pediatric Crohn's Disease Symptoms and Disability. *J Pediatr*. 2017;184:94-100.

18 Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain-Gut Interactions in Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2018;154(6):1635-1646.

19 Bonaz BL, Bernstein CN. Brain-Gut Interactions in Inflammatory Bowel Disease. *Gastroenterology*. 2013;144(1):36-49.

20 Levy RL, van Tilburg MA, Langer SL, et al. Effects of a Cognitive Behavioral Therapy Intervention Trial to Improve Disease Outcomes in Children with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2016;22(9):2134-2148.

21 Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-Behavioural Therapy for Inflammatory Bowel Disease: 24-Month Data from a Randomised Controlled Trial. *Int J Behav Med*. 2017 Feb;24(1):127-13.

22 Szigethy E, Bujoreanu SI, Youk AO, 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):726-735.

23 Thompson RD, Craig A, Crawford EA, et al. Longitudinal results of cognitive behavioral treatment for youths with inflammatory bowel disease and depressive symptoms. *J Clin Psychol Med Settings*. 2012;19(3):329-337.

24 Arnett JJ. Adolescence and emerging adulthood: A cultural approach (International Edition). Fourth Edition ed. Prentice Hall, Upper Saddle River, NJ: Pearson; 2010.

25 Szigethy E, McLafferty L, Goyal A. Inflammatory bowel disease. *Pediatr Clin North Am*. 2011;58(4):903-920.

26 Stapersma L, van den Brink G, van der Ende J, et al. Effectiveness of Disease-Specific Cognitive Behavioral Therapy on Anxiety, Depression, and Quality of Life in Youth With Inflammatory Bowel Disease: A Randomized Controlled Trial. *J Pediatr Psychol*. 2018;43(9):967-980.

27 Kendall PC, Cummings CM, Villabo MA, et al. Mediators of change in the Child/Adolescent Anxiety Multimodal Treatment Study. *J Consult Clin Psychol*. 2016;84(1):1-14.

28 Christensen SS, Frostholm L, Ornbol E, Schroder A. Changes in illness perceptions mediated the effect of cognitive behavioural therapy in severe functional somatic syndromes. *J Psychosom Res*. 2015;78(4):363-370.

29 van den Brink G, Stapersma L, El Marroun H, et al. 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 Gastroenterol*. 2016;3(1):e000071.

30 Szigethy E, Kenney E, Carpenter J, et al. Cognitive-behavioral therapy for adolescents with inflammatory bowel disease and subsyndromal depression. *J Am Acad Child Adolesc Psychiatry*. 2007;46(10):1290-1298.

31 Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med*. 2017;167(1):40-47.

32 Bodden DHM, Bögels SM, Muris P. The diagnostic utility of the Screen for Child Anxiety Related Emotional Disorders-71 (SCARED-71). *Behav Res Ther*. 2009;47(5):418-425.

33 De Croon EM, Nieuwenhuijsen K, Hugenholtz NIR, Van Dijk FJH. Drie vragenlijsten voor diagnostiek van depressie en angststoornissen. *TBV–Tijdschrift voor Bedrijfs-en Verzekeringsgeneeskunde*. 2005;13(4):114-119.

34 Timbremont B, Braet C, Roelofs J. Handleiding Children's Depression Inventory (herziene versie). Amsterdam: Pearson Assessment and Information B.V.; 2008.

35 Van der Does AJW. BDI-II-NL Handleiding. De Nederlandse versie van de Beck Depression Inventory-2nd edition. Lisse: Harcourt Test Publishers; 2002.

36 Siebelink BM, Treffers PDA. Anxiety Disorders Interview Schedule for DSM-IV-Child version, ADIS-C Handleiding. Amsterdam: Harcourt Test Publishers; 2001.

37 Ginsburg G, Keeton C, Drazdowski T, Riddle M. The Utility of Clinicians Ratings of Anxiety Using the Pediatric Anxiety Rating Scale (PARS). *Child Youth Care Forum*. 2011;40(2):93-105.

38 Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50-55.

39 Matza LS, Morlock R, Sexton C, Malley K, Feltner D. Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder. *Int J Methods Psychiatr Res*. 2010;19(4):223-232.

40 Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary Studies of the Reliability and Validity of the Children's Depression Rating Scale. *J Am Acad Child Adolesc Psychiatry*. 1984;23(2):191-197.

41 Revah-Levy A, Birmaher B, Gasquet I, Falissard B. The Adolescent Depression Rating Scale (ADRS): a validation study. *BMC Psychiatry*. 2007;7:2-2.

42 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56-62.

43 Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord*. 2013;150(2):384-388.

44 Utens EMWJ, van Rijen EHM, Erdman RAM, Verhulst FC. Rotterdam's Kwaliteit van Leven Interview. Erasmus MC Rotterdam, Department of Child and Adolescent Psychiatry and Psychology, 2000.

45 Statistics Netherlands. Standaard Beroepen Classificatie 2010. The Hague: Statistics Netherlands, 2010.

46 Statistics Netherlands. Standaarddefinitie allochtonen. The Hague: Statistics Netherlands, 2000

47 Muris P, Bodden D, Hale W, Birmaher B, Mayer B. *SCARED-NL.* Handleiding bij de gereviseerde Nederlandse versie van de Screen for Child Anxiety Related Emotional Disorders. Amsterdam: Boom test uitgevers; 2011.

48 Otley A, Smith C, Nicholas D, et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2002;35(4):557-563.

49 de Boer AG, Wijker W, Bartelsman JF, de Haes HC. Inflammatory Bowel Disease Questionnaire: cross-cultural adaptation and further validation. *Eur J Gastroenterol Hepatol*. 1995;7(11):1043-1050.

50 Garnefski N, Legerstee J, Kraaij V, Van Den Kommer T, Teerds JAN. Cognitive coping strategies and symptoms of depression and anxiety: A comparison between adolescents and adults. *J Adolesc.* 2002;25(6):603-611.

51 Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res*. 2006;60(6):631-637.

52 de Raaij EJ, Schröder C, Maissan FJ, Pool JJ, Wittink H. Cross-cultural adaptation and measurement properties of the Brief Illness Perception Questionnaire-Dutch Language Version. *Man Ther*. 2012;17(4):330-335.

53 Achenbach TM, Rescorla LA. Manual for the ASEBA School-age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2001.

54 Achenbach TM, Rescorla LA. Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2003.

55 Kappelman MD, Crandall WV, Colletti RB, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. *Inflamm Bowel Dis*. 2011;17(1):112-117.

56 Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology*. 2007;133(2):423-432.

57 Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*. 1976;70(3):439-444.

58 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317(26):1625-1629.

59 Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psych*. 1991;59(1):12.

60 Luke SG. Evaluating significance in linear mixed-effects models in R. *Behav Res Meth*. 2017;49(4):1494-1502.

61 Serrano D. Error of Estimation and Sample Size in the Linear Mixed Model. Department of Psychology, Vol. MA. Chapel Hill: University of North Carolina, 2008:212

62 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):251-262.

63 Weisz JR, McCarty CA, Valeri SM. Effects of Psychotherapy for Depression in Children and Adolescents: A Meta-Analysis. *Psych bull*. 2006;132(1):132-149.

64 Szigethy E, Youk AO, Gonzalez-Heydrich J, et al. Effect of 2 Psychotherapies on Depression and Disease Activity in Pediatric Crohn's Disease. *Inflamm Bowel Dis*. 2015;21(6):1321-1328.

65 Hill R, Lewindon P, Muir R, et al. Quality of life in children with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2010;51(1):35-40.

66 Mackner LM, Crandall WV. Long-term psychosocial outcomes reported by children and adolescents with inflammatory bowel disease. *Am J Gastroenterol*. 2005;100(6):1386-1392.

67 Schröder A, Rehfeld E, Ornbøl E, Sharpe M, Licht RW, Fink P. Cognitive-behavioural group treatment for a range of functional somatic syndromes: Randomised trial. *Br J Psychiatry*. 2012;200(6):499-507.

68 Busscher B, Spinhoven P. Cognitive Coping as a Mechanism of Change in Cognitive-Behavioral Therapy for Fear of Flying: A Longitudinal Study With 3-Year Follow-Up. *J Clin Psychol*. 2017;73(9):1064-1075.

69 Bennebroek Evertsz F, Sprangers MAG, Sitnikova K, et al. Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: A multicenter randomized controlled trial. *J Consult Clin Psychol*. 2017;85(9):918-925.

70 Grootenhuis MA, Maurice-Stam H, Derkx BH, Last BF. Evaluation of a psychoeducational intervention for adolescents with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2009;21(4):340-345.

71 Scholten L, Willemen AM, Last BF, et al. Efficacy of psychosocial group intervention for children with chronic illness and their parents. *Pediatrics*. 2013;131(4):e1196-1203.

72 Forgeron P, King S, Reszel J, Fournier K. Psychosocial interventions to improve social functioning of children and adolescents with chronic physical conditions: A systematic review. *Children's Health Care*. 2017:1-30.

73 Hommel KA, Hente EA, Odell S, et al. Evaluation of a group-based behavioral intervention to promote adherence in adolescents with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2012;24(1):64-69.

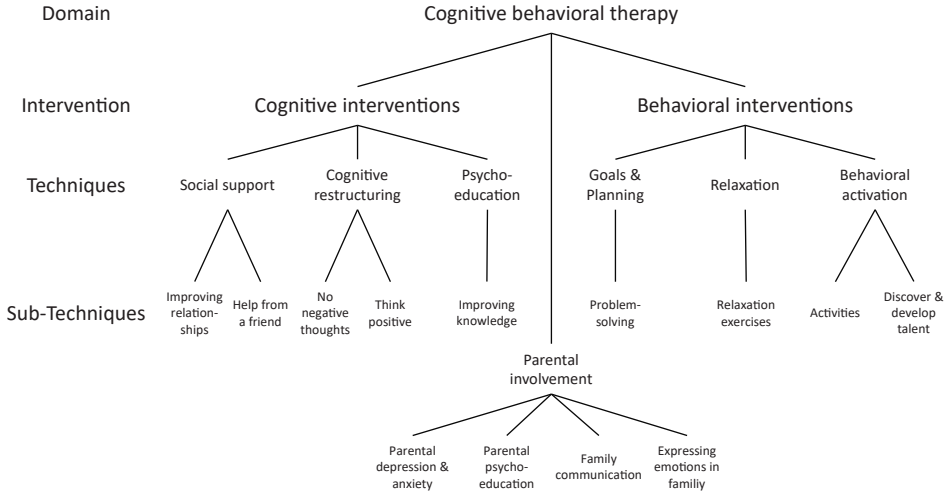
74 Spinhoven PH, Ormel J, Sloekers PPA, Kempen GIJM, Speckens AEM, Hemert AMV. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med*. 1997;27(2):363-370.

APPENDIX 1A. Outline of the PASCET-PI [29, 30]

Session number	Content of session
Session 1 *Live (60 min)*	Introduction of ACT & THINK model and PASCET-PI, building work alliance, psycho-education about IBD and depression or anxiety, illness narrative
Session 2 *Live (60 min)*	Mood monitoring, explaining link between feelings, thoughts and behaviors, discussing feeling good and feeling bad, problem-solving
Session 3 *By telephone (30 min)*	Link between behavior and feelings: Activities to feel better
Session 4 *Live (60 min)*	Be Calm and Confident: relaxation exercises
Session 5 *Live (60 min)*	Be Calm and Confident: positive self versus negative self, training social skills
Session 6 *By telephone (30 min)*	Talents: developing talents and skills makes you feel better
Session 7 *Live (60 min)*	Social problem solving, discussing the ACT skills and introduction of the THINK skills with discussing negative thoughts (Think positive)
Session 8 *By telephone (30 min)*	Help from a friend, Identify the 'Silver Lining', and No replaying bad thoughts
Session 9 *By telephone (30 min)*	Keep trying – Don't give up, making several plans to use the ACT & THINK skills
Session 10 *Live (60 min)*	Quiz on ACT & THINK model, discussing use of ACT & THINK skills in the future, updating illness narrative
Booster 1 *By telephone (30 min)*	Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills
Booster 2 *By telephone (30 min)*	Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills
Booster 3 *By telephone (30 min)*	Several plans to use the ACT & THINK skills, updating illness narrative, personalizing ACT & THINK skills
Family 1 *Live (60 min)*	Parental view on IBD, family situation, psycho-education about IBD and depression or anxiety, introduction of ACT & THINK model and PASCET-PI
Family 2 *Live (60 min)*	Parental view on progress, the ACT & THINK skills that are most effective for the patient, expressing emotions within family, family communication, family stress game
Family 3 *Live (60 min)*	Parental view on progress, family communication, parental depression or anxiety

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

APPENDIX 1B. Tree Diagram



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)	

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; IBDU= 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)

CHAPTER 8

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

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ABSTRACT

Background

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

Methods

In this multicenter parallel group randomized controlled trial, IBD patients were randomized to disease-specific CBT in addition to standard medical care (CBT + Care us 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. (2014) 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 et al. (2016).[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 cut-off (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 cut-off (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. 2018.[13]

Step 2: Inclusion RCT

If patients scored above the cut-off 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; cut-off ≥18) and the Hamilton Anxiety rating scale[50, 51] (HAM-A; 21-25 years; cut-off ≥15) were used for anxiety symptoms. Depression was rated using the Child Depression Rating Scale Revised[52] (CDRS-R; 10-12 years; cut-off ≥40), the Adolescent Depression Rating Scale Revised[53] (ADRS-R; 13-20 years; cut-off ≥20) and the Hamilton Depression Rating Scale[54, 55] (HAM-D; 21-25 years; cut-off ≥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 cut-off 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 1 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 one 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.

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, non penetrating	18 (100%)	18 (100%)	
	Stricturing, 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
Relapse preceding year		15 (40.5%)	10 (30.3%)	0.39
Bowel resection in history		3 (8.1%)	2 (6.1%)	1.00

EIM [||]		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%).

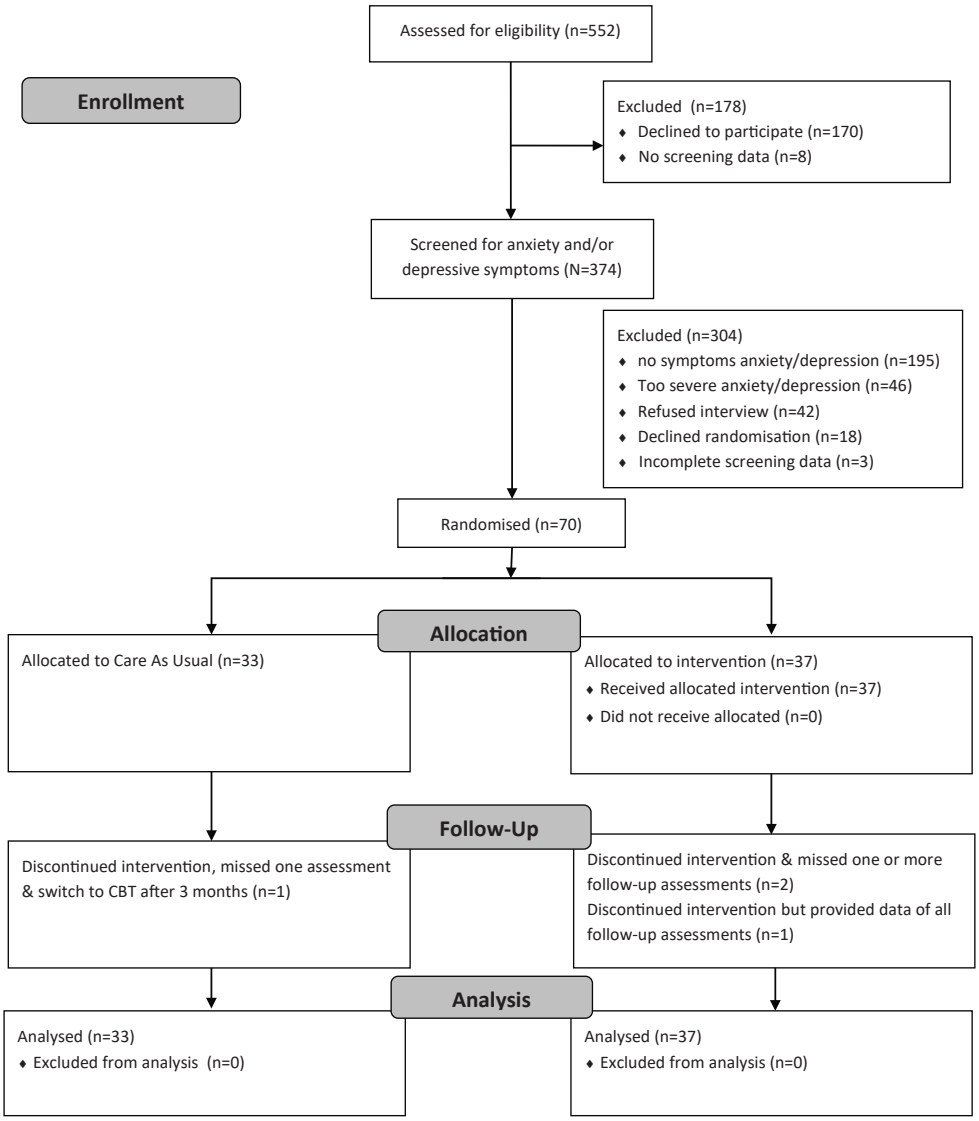


Figure 1. Consort study flowchart

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).

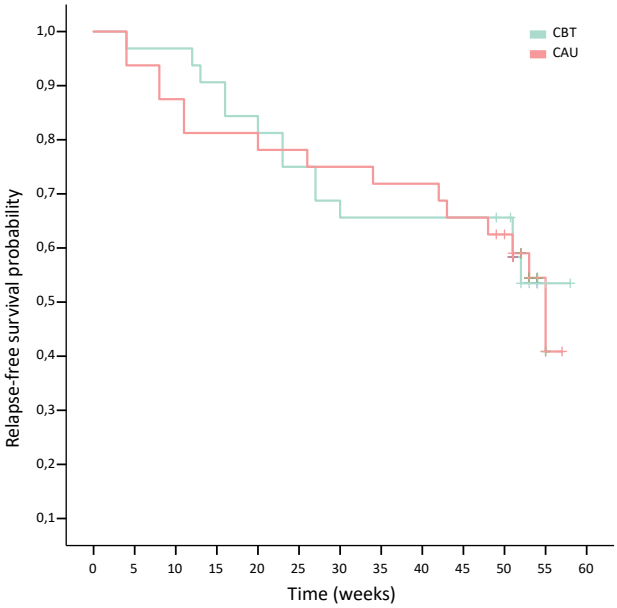


Figure 2. Survival curve time to first flare

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

Notes: "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)

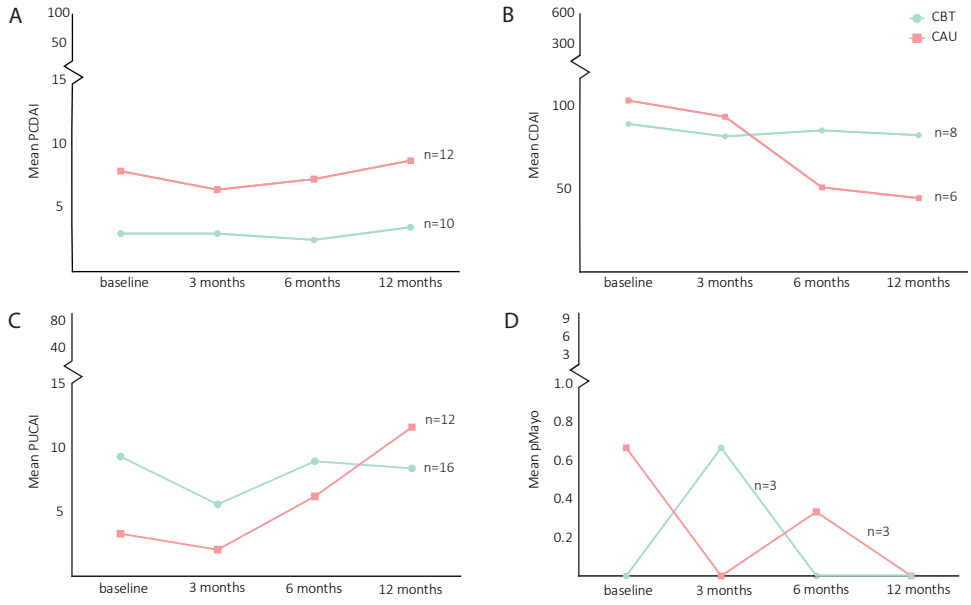


Figure 3. Raw means of clinical disease activity scores over time

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+ Care as Usual, CAU: Care as Usual

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).

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., submitted). 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 subanalysis was limited by the liberal definition of relapse, without considering objective items such as treatment intensification. Secondly, Szigethy et al. (2014) studied the effect of 2 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 Mickocka-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, favouring 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. (2014) 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. (2014) 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. (2016), reporting a significant reduction in IBD-related healthcare use following CBT.[70] We attempted to analyse 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. 2018, submitted) 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 generalisability. 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 generalisability 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 (Stapersma et al. 2018 submitted).[63] 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.

CONCLUSION

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.

REFERENCES

1 Rosen MJ, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. *JAMA Pediatr*. 2015;169(11):1053-1060.

2 Daniel JM. Young adults' perceptions of living with chronic inflammatory bowel disease. *Gastroenterol Nurs*. 2002;25(3):83-94.

3 Kemp K, Griffiths J, Lovell K. Understanding the health and social care needs of people living with IBD: a meta-synthesis of the evidence. *World J Gastroenterol*. 2012;18(43):6240-6249.

4 Greenley RN, Hommel KA, Nebel J, et al. A Meta-analytic Review of the Psychosocial Adjustment of Youth with Inflammatory Bowel Disease. *J Ped Psychol*. 2010;35(8):857-69

5 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):449-458.

6 Hummel TZ, Tak E, Maurice-Stam H, Benninga MA, Kindermann A, Grootenhuis MA. Psychosocial developmental trajectory of adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2013;57(2):219-224.

7 Regueiro M, Greer JB, Szigethy E. Etiology and Treatment of Pain and Psychosocial Issues in Patients With Inflammatory Bowel Diseases. *Gastroenterology*. 2017;152(2):430-439 e434.

8 Brooks AJ, Rowse G, Ryder A, Peach EJ, Corfe BM, Lobo AJ. Systematic review: psychological morbidity in young people with inflammatory bowel disease - risk factors and impacts. *Aliment Pharmacol Ther*. 2016;44(1):3-15.

9 Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review. *J Psychosom Res.* 2016;87:70-80.

10 Stapersma L, van den Brink G, Szigethy EM, Escher JC, Utens E. Systematic review with meta-analysis: anxiety and depression in children and adolescents with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018 Sep;48(5):496-506

11 Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology*. 2013;144(1):36-49.

12 Mikocka-Walus A, Pittet V, Rossel JB, von Kanel R, Swiss IBDCSG. Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2016;14(6):829-835 e821.

13 van den Brink G, Stapersma L, Vlug LE, et al. Clinical disease activity is associated with anxiety and depressive symptoms in adolescents and young adults with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;48(3):358-369.

14 Reigada LC, Satpute A, Hoogendoorn CJ, et al. Patient-reported Anxiety: A Possible Predictor of Pediatric Inflammatory Bowel Disease Health Care Use. *Inflamm Bowel Dis*. 2016;22(9):2127-2133.

15 Alexakis C, Kumar S, Saxena S, Pollok R. Systematic review with meta-analysis: the impact of a depressive state on disease course in adult inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46(3):225-235.

16 Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain-Gut Interactions in Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2018;154(6):1635-1646 e1633.

17 Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Holtmann GJ, Andrews JM. Does psychological status influence clinical outcomes in patients with inflammatory bowel disease (IBD) and other chronic gastroenterological diseases: an observational cohort prospective study. *Biopsychosoc Med*. 2008;2:11.

18 Bitton A, Dobkin PL, Edwardes MD, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut*. 2008;57(10):1386-1392.

19 Singh H, Nugent Z, Brownell M, Targownik LE, Roos LL, Bernstein CN. Academic Performance among Children with Inflammatory Bowel Disease: A Population-Based Study. *J Pediatr*. 2015;166(5):1128-1133.

20 De Boer AG, Bennebroek Evertsz F, Stokkers PC, et al. Employment status, difficulties at work and quality of life in inflammatory bowel disease patients. *Eur J Gastroenterol Hepatol*. 2016;28(10):1130-1136.

21 Burisch J, Jess T, Martinato M, Lakatos PL, EpiCom E. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis*. 2013;7(4):322-337.

22 Compton SN, March JS, Brent D, Albano AMt, Weersing R, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. *J Am Acad Child Adolesc Psychiatry*. 2004;43(8):930-959.

23 Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cogn Ther Res*. 2012;36(5):427-440.

24 Reigada LC, Benkov KJ, Bruzzese JM, et al. Integrating illness concerns into cognitive behavioral therapy for children and adolescents with inflammatory bowel disease and co-occurring anxiety. *J Spec Pediatr Nurs*. 2013;18(2):133-143.

25 Szigethy E, Bujoreanu SI, Youk AO, 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):726-735.

26 Knowles SR, Monshat K, Castle DJ. The efficacy and methodological challenges of psychotherapy for adults with inflammatory bowel disease: a review. *Inflamm Bowel Dis*. 2013;19(12):2704-2715.

27 Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med*. 2017;167(1):40-47.

28 Garber J, Weersing VR. Comorbidity of Anxiety and Depression in Youth: Implications for Treatment and Prevention. *Clin Psychol (New York)*. 2010;17(4):293-306.

29 van den Brink G, Stapersma L, El Marroun H, et al. 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 Gastroenterol*. 2016;3(1):e000071.

30 Statistics Netherlands. Standaard beroepen classificatie 2010. The Hague: Statistics Netherlands; 2010.

31 Utens EMWJ, van Rijen, EH, Erdman RAM ea. Rotterdam's Kwaliteit van Leven Interview. Erasmus MC Rotterdam, Netherlands, Department of Child and Adolescent Psychiatry and Psychology. 2000.

32 Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis*. 2011;17(6):1314-1321.

33 Muris P, Bodden D, Hale W, Birmaher B, Mayer B. SCARED-NL. Vragenlijst over angst en bang-zijn bij kinderen en adolescenten. Handleiding bij de gereviseerde Nederlandse versie van de Screen for Child Anxiety Related Emotional Disorders. Amsterdam: Boom test uitgevers; 2007.

34 de Croon EM, Nieuwenhuijsen K, Hugenholtz NIR, van Dijk FJH. Drie vragenlijsten voor diagnostiek van depressie en angststoornissen. *TBV – Tijdschrift voor Bedrijfs- en Verzekeringsgeneeskunde*. 2005;13(4):114-119.

35 Timbremont B, Braet C, Roelofs J. Children's Depression Inventory. Handleiding (herziene uitgave). Amsterdam, NL: Pearson, 2008

36 Van der Does AJW. BDI-II-NL Handleiding. De Nederlandse versie van de Beck Depression Inventory-2nd edition. Lisse: Harcourt Test Publishers; 2002.

37 Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology*. 2007;133(2):423-432.

38 D'Haens G, Sandborn WJ, Feagan BG, et al. A Review of Activity Indices and Efficacy End Points for Clinical Trials of Medical Therapy in Adults With Ulcerative Colitis. *Gastroenterology*. 2007;132(2):763-786.

39 Turner D, Griffiths AM, Walters TD, 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.

40 Sandborn WJ, Feagan BG, Hanauer SB, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology*. 2002;122(2):512-530.

41 Bessissow T, Lemmens B, Ferrante M, et al. Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. *Am J Gastroenterol*. 2012;107(11):1684-1692.

42 Minami N, Yoshino T, Matsuura M, et al. Tacrolimus or infliximab for severe ulcerative colitis: short-term and long-term data from a retrospective observational study. *BMJ Open Gastroenterol*. 2015;2(1):e000021.

43 Heida A, Park KT, van Rheenen PF. Clinical Utility of Fecal Calprotectin Monitoring in Asymptomatic Patients with Inflammatory Bowel Disease: A Systematic Review and Practical Guide. *Inflamm Bowel Dis*. 2017;23(6):894-902.

44 Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132(3):863-873; 1165-1166.

45 Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis*. 2017;11(1):3-25.

46 Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr*. 2014;58(6):795-806.

47 Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis*. 2017;11(6):649-670.

48 Siebelink, Treffers. Nederlandse bewerking van het Anxiety Disorder Interview Schedule for DSM-IV Child Version van Silverman & Albana. Lisse / Amsterdam: Swets & Zeitlinger; 2001.

49 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 Forum*. 2011;40(2):93-105.

50 Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50-55.

51 Matza LS, Morlock R, Sexton C, Malley K, Feltner D. Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder. *Int J Methods Psychiatr Res*. 2010;19(4):223-232.

52 Poznanski EO, Mokros H. Children's Depression Rating Scale Revised (CDRS-R). Los Angeles: Western Psychological Services; 1996.

53 Revah-Levy A, Birmaher B, Gasquet I, Falissard B. The Adolescent Depression Rating Scale (ADRS): a validation study. *BMC Psychiatry*. 2007;7(1):2.

54 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.

55 Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord*. 2013;150(2):384-388.

56 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):703-707.

57 Szigethy EVA, 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):1469-1477.

58 Heida A, Dijkstra A, Groen H, Muller Kobold A, Verkade H, van Rheenen P. Comparing the efficacy of a web-assisted calprotectin-based treatment algorithm (IBD-live) with usual practices in teenagers with inflammatory bowel disease: study protocol for a randomized controlled trial. *Trials*. 2015;16:271.

59 Martinelli M, Giugliano FP, Russo M, et al. The Changing Face of Pediatric Ulcerative Colitis: A Population-based Cohort Study. *J Pediatr Gastroenterol Nutr*. 2018;66(6):903-908.

60 Vester-Andersen MK, Vind I, Prosberg MV, et al. Hospitalisation, surgical and medical recurrence rates in inflammatory bowel disease 2003-2011-a Danish population-based cohort study. *J Crohns Colitis*. 2014;8(12):1675-1683.

61 Boye B, Lundin KE, Jantschek G, et al. INSPIRE study: does stress management improve the course of inflammatory bowel disease and disease-specific quality of life in distressed patients with ulcerative colitis or Crohn's disease? A randomized controlled trial. *Inflamm Bowel Dis*. 2011;17(9):1863-1873.

62 Keefer L, Taft TH, Kiebles JL, Martinovich Z, Barrett TA, Palsson OS. Gut-directed hypnotherapy significantly augments clinical remission in quiescent ulcerative colitis. *Aliment Pharmacol Ther*. 2013;38(7):761-771.

63 Stapersma L, van den Brink G, van der Ende J, et al. Effectiveness of Disease-Specific Cognitive Behavioral Therapy on Anxiety, Depression, and Quality of Life in Youth With Inflammatory Bowel Disease: A Randomized Controlled Trial. *J Pediatr Psychol*. 2018;43(9):967-980.

64 Levy RL, van Tilburg MA, Langer SL, et al. Effects of a Cognitive Behavioral Therapy Intervention Trial to Improve Disease Outcomes in Children with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2016;22(9):2134-2148.

65 McCombie A, Gearry R, Andrews J, Mulder R, Mikocka-Walus A. Does Computerized Cognitive Behavioral Therapy Help People with Inflammatory Bowel Disease? A Randomized Controlled Trial. *Inflamm Bowel Dis*. 2016;22(1):171-181.

66 Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-behavioural therapy has no effect on disease activity but improves quality of life in subgroups of patients with inflammatory bowel disease: a pilot randomised controlled trial. *BMC Gastroenterol*. 2015;15:54.

67 Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-Behavioural Therapy for Inflammatory Bowel Disease: 24-Month Data from a Randomised Controlled Trial. *Int J Behav Med*. 2017;24(1):127-135.

68 Schoultz M, Atherton I, Watson A. Mindfulness-based cognitive therapy for inflammatory bowel disease patients: findings from an exploratory pilot randomised controlled trial. *Trials*. 2015;16:379.

69 Gracie DJ, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2(3):189-199.

70 Keerthy D, Youk A, Srinath AI, et al. Effect of Psychotherapy on Health Care Utilization in Children With Inflammatory Bowel Disease and Depression. *J Pediatr Gastroenterol Nutr*. 2016;63(6):658-664.

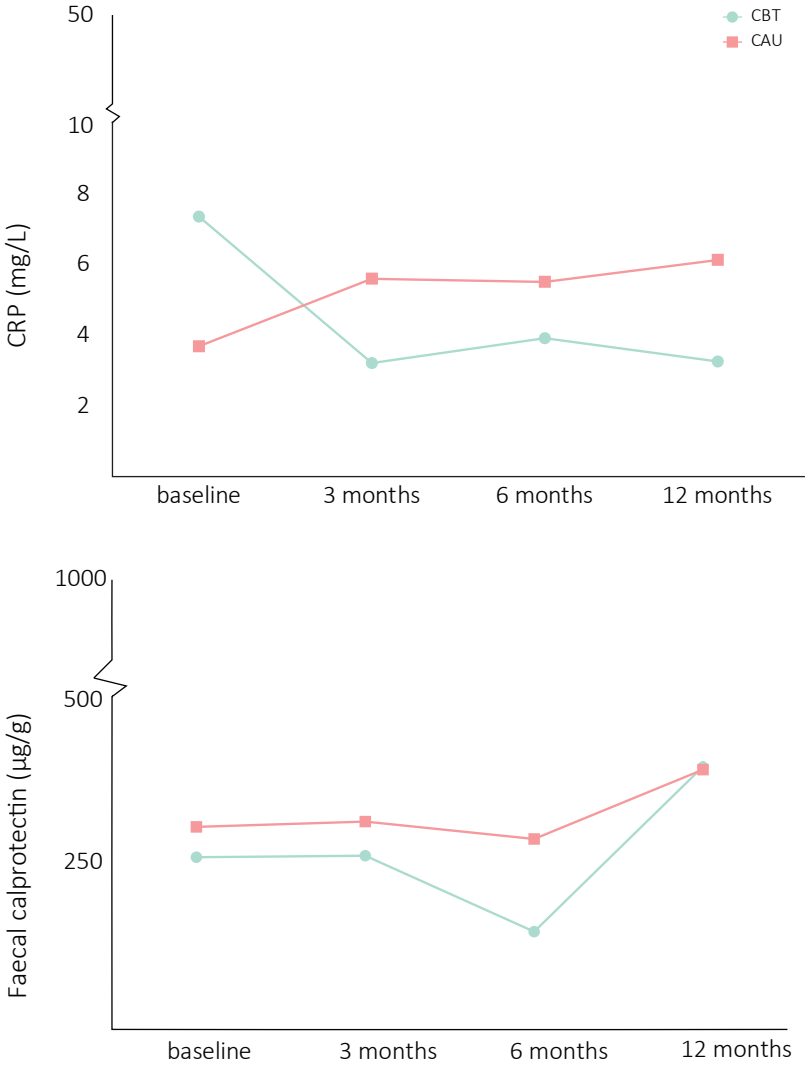
71 Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JAJ, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: A meta-analysis of randomized placebo-controlled trials. *Depress Anxiety*. 2018;35(6):502-514.

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

CHAPTER 9

Plasma protein profiles associated with anxiety and/or depressive symptoms in young IBD patients and the effect of cognitive behavioural therapy

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Submitted

ABSTRACT

Background

Anxiety and depression are common in Inflammatory Bowel Disease (IBD). Within the brain-gut axis a bidirectional relationship is hypothesized: psychological stress can lead to (intestinal) inflammation, and vice versa. Psychological treatment may improve clinical symptoms, but also intestinal and systemic inflammation in IBD. To explore this, we investigated whether specific inflammatory protein signatures associated with anxiety/depressive symptoms and assessed whether psychotherapy altered these profiles.

Methods

In this ancillary study of a randomized controlled trial (RCT), young IBD patients were screened for anxiety/depression forming a cohort of patients with no, mild or severe anxiety and/or depression. Patients with mild symptoms were randomized to either Cognitive Behavioral Therapy (CBT) + Care as Usual (CAU) or CAU only. Plasma protein profiling of 92 inflammatory proteins was performed.

Results

Forty-five IBD patients, predominantly in clinical remission of intestinal disease, were included, among which 30 were randomized to CBT or CAU. Protein profiling revealed four distinctive inflammatory protein signatures associating with symptoms of anxiety and/or depression and response to CBT. Within these, leukemia inhibitory factor receptor (LIF-R) and the chemokine C-C motif ligand 4 (CCL4) were increased in patients with psychological symptoms and decreased after CBT.

Conclusions

Unbiased plasma protein analyses yields distinct immune signatures associating with anxiety and/or depressive symptoms in young IBD patients, which can be altered by CBT. This innovative approach potentially identifies new pathways associated with anxiety/depression in young IBD patients, and shows that CBT affects both LIF-R and CCL4.

INTRODUCTION

Inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis [UC]) is a chronic inflammatory disorder of the intestine. In approximately 10-25% of patients, IBD develops during childhood or adolescence[1-3] and is often accompanied by embarrassing and invalidating intestinal and systemic symptoms, with often an unpredictable disease course.[4]

Anxiety and depression are common in IBD: 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[5, 6], which is estimated to be two to three times higher than in healthy controls.[7, 8]

In the pathophysiology of both IBD and mood disorders, activation of the innate and adaptive immune system is implicated, as shown by the upregulation of innate (Tumor Necrosis Factor alpha [TNF-α], Interleukin [IL]-1, IL-1β, IL-6, IL-12, IL-23), and adaptive (interferon gamma [IFN-γ], IL-17, IL-22) cytokines.[9-18] In addition, for anxiety and depression, similar pathways of immune activation have been reported.[19]

Clear evidence for bidirectional interactions between the central nervous system and the gut has emerged from animal studies, and is commonly referred to as the 'brain-gut axis'.[20-22] As such, intestinal inflammatory immune responses as occur in IBD may be biologically related to psychological problems. The brain-gut axis describes interactions between the central, autonomic, and enteric nervous system, the hypothalamic-pituitary-adrenal (HPA) axis and gut microbiome. Through feedback loops, (para)sympathetic signals reach peripheral organs including cells of the immune system. Any kind of (psychological) stress activates the sympathetic system and the HPA-axis, with the release of neurotransmitters, hormones and pro-inflammatory cytokines. Many of these factors have pro-inflammatory properties, but HPA-axis activation also serves to limit the effect of inflammation by means of the release of cortisol.[23] In IBD patients, all these processes may lead to increased colonic motility, increased water and ion secretion and increased bacterial transfer into the mucosa, all contributing to increased intestinal symptoms.[20, 22] In turn, pro-inflammatory cytokines in the bloodstream or enteric tissue can directly (through the blood brain barrier) and indirectly (e.g. through signaling from peripheral nerve terminals to the central nervous system) communicate with cerebral (immune) cells. This results in a local inflammatory response dysregulating neurotransmitter metabolism (e.g. dopamine, serotonin), dysregulated HPA axis functioning (e.g. glucocorticoid resistance) and altered neural activity in brain regions involved in mood and behavior.[9, 24-29]

Evidence for the implication of the brain-gut axis in IBD was thoroughly summarized by Gracie et al.[30] Indeed in IBD patients, anxiety and/or depression can increase intestinal inflammation and may contribute to disease relapse. Conversely, intestinal inflammation can negatively influence mood.[20, 30] Several clinical studies support this by showing an association between clinical disease activity and anxiety[5, 31, 32] and depression.[5, 31, 33] Some longitudinal studies also provide support[30, 34-37], while others do not.[38, 39] However, all these

studies solely focused on clinical parameters but did not investigate the underlying biological processes. To our knowledge, only one study in adult IBD patients previously reported on this association at a molecular level, but only investigated a limited selection of cytokines.[40]

The existence of these brain-gut interactions brings to light a potential novel and attractive therapeutic approach to ameliorate intestinal symptoms in IBD patients suffering from anxiety and/or depression through treatment of psychological symptoms. Several studies investigated whether psychiatric (e.g. anti-depressants) or psychological treatments improved disease course.[41] In adult patients, two systematic reviews did not find a benefit of psychotherapy on disease activity or disease course. However, the included patients did not have a diagnosis of anxiety or depression at baseline.[43, 44] In children, three randomized controlled trials[45-47] addressed the effect of psychotherapy on disease course, with one study showing a positive effect on clinical disease activity.[46] Importantly, however, the effect of psychotherapy on inflammatory activity or cytokine levels has not been studied.

Therefore, our overall aim was to explore plasma profiles of inflammatory proteins in young IBD patients with anxiety and/or depressive symptoms using a large unbiased cytokine panel. In our previous study we screened young IBD patients for anxiety and depression ("cohort study"), and included patients with mild anxiety and/or depressive symptoms in an RCT investigating the efficacy of cognitive behavioral therapy (versus care as usual).[48] In the current, ancillary and hypothesis-generating study, a subgroup of patients from the screening cohort as well as the RCT was included. As anxiety can precede depression and anxiety and depressive symptoms often occur together[49], we studied these symptoms simultaneously. Using the screening cohort, we investigated whether particular protein signatures were associated with anxiety and/or depressive symptoms (to reflect the patient group with 'a psychological burden'). Secondly, using data from the RCT, we investigated whether cognitive behavioral therapy induced changes in protein signatures.

METHODS

Design

This study is an ancillary study to the multicenter randomized controlled trial (RCT) HAPPY-IBD, designed according to the CONSORT guidelines for trials of non-pharmacologic treatments. Participants were recruited from two academic and four regional teaching hospitals in the South-West of The Netherlands from September 2014 until October 2016. Most important study characteristics will be summarized here, as detailed information can be found elsewhere.[31, 48] This study conformed to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Erasmus Medical Centre and of each participating center. The study was registered at ClinicalTrials.gov with study number NCT02265588.

Recruitment and procedure

Cohort study

We screened 10 to 25-year-old patients with confirmed IBD for anxiety and depressive symptoms using online self-report instruments with validated cut-off scores.[31] If patients scored above the cut-off of the anxiety and/or depression questionnaire (see below), a trained psychologist performed a diagnostic psychiatric interview (Anxiety Disorders Interview Schedule - Child and Parent Versions [ADIS-C/P][50]) by telephone to determine the severity of the symptoms using age appropriate severity rating scales (see van den Brink et al. 2018).[31] Following this procedure, three groups were formed; (1) patients without anxiety and/or depressive symptoms ("no symptoms"), (2) patients with mild or subclinical anxiety and/or depressive symptoms (elevated symptoms not meeting the criteria for a psychiatric disorder) and (3) patients with severe, clinical symptoms (meeting criteria for an anxiety/depressive disorder). Group 3 patients were directly referred for psychological help. For this study, we grouped the patients with elevated anxiety and/or depressive symptoms, to describe the patient group with 'a psychological burden'. Collection of blood samples for immunological analysis was performed only in the patients that were enrolled in the Erasmus Medical Center (EMC).

Randomized controlled trial

Patients from group 2 (mild anxiety and/or depressive symptoms) were randomized to either 3 months (10 sessions) of disease-specific CBT (CBT+CAU; "CBT") in addition to Care as Usual or to the control condition, Care as Usual (CAU). Randomization procedure and details about the intervention and control condition can be found elsewhere.[31] After randomization, blood samples for immunological analyses, medical and psychological data were collected at baseline and after 3 months.

Measurements

Demographic characteristics Age and gender were collected at baseline.

Clinical characteristics Disease type, age at diagnosis, disease duration, current therapy, previous steroid therapy or relapses were collected at baseline.

Anxiety and depressive symptoms For anxiety, the Screen for Child Anxiety Related Emotional Disorders (SCARED; 10-20 years)[51] and the Hospital Anxiety and Depression Scale – Anxiety Scale (HADS-A; 21-25 years)[52] was used. For depression the Child Depression Inventory (CDI; 10-17 years)[53] and the Beck Depression Inventory – Second edition[54] (BDI-II; 18-25 years) 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[55] (PUCAI; 10-20 years) and the partial Mayo score[56] (pMayo; 21-25 years) were used. In CD patients, the Pediatric

Crohn's Disease Activity Index (PCDAI; 10-20 years) and the Crohn's Disease Activity Index[57] (CDAI; 21-25) were used.

Inflammatory markers Serum C-reactive protein (CRP) and fecal calprotectin were obtained at baseline/screening and after three months during visits to the outpatient clinic as part of routine clinical care.

Plasma protein profile Blood samples were collected in vacutainers coated with EDTA and centrifuged at 216g for 10 minutes at room temperature. Plasma was stored at -80 ^{o}C until analysis. The commercally available panel, ProSeek Multiplex Inflammation I 96x96 (Olink Proteomics,Uppsala, Sweden) was used to measure plasma levels of 92 proteins related to inflammation using Proximity Extension Analysis (PEA): This technique uses two paired antibodies labeled with oligonucleotides as a probe for each protein. When a pair of probes recognizes and binds to a protein, the DNA oligonucleotides hybridize, allowing formation of a new PCR sequence. The resulting sequence is subsequently detected and quantified using standard real-time quantitative PCR (qPCR). Using the Olink Wizard for GenEx (Multid Analyses, Sweden), Ct values from the qPCR were translated into the relative quantification unit, Normalized Protein eXpression (NPX) on a log-2 scale. Each sample includes two technical controls, one extension control, and one detection control to determine the lower limit of detection and to allow for normalization. Antibody cross-reactivity is prevented as only matched DNA reporter pairs are amplified.[58, 59] Proteins with signals below the lower limit of detection (LOD) in more than 70% of the samples were excluded, this was also applied to each subanalysis.[60] The analyses were performed at the Clinical Biomarkers Facility, Science for Life Laboratory, Uppsala.

Preparation of data set Protein concentrations were assessed in 75 plasma samples from 45 individuals. Ninety-one target proteins were quantified successfully. The analysis of Brain-derived neurotrophic factor (BDNF) failed because of technical issues. Thymic stromal lymphopoietin (TSLP), IL-2, IL-22RA1, and IL-1α were below lower limit of detection in > 70% of the individuals irrespective of patient group or intervention, and were excluded from the analysis, leaving 87 proteins available for analysis.

Statistical Analysis

Descriptive statistics were computed for demographic and clinical characteristics for each group (no vs mild vs severe psychological symptoms). Chi^2/Fisher exact or Mann-Whitney-U tests were used where appropriate, to assess differences between groups.

In the cohort study, Principal Components Analysis (PCA) (for linear algorithms) and t-Distributed Stochastic Neighbor Embedding plots (t-SNE; for non-linear algorithms) were used to visualize data patterns.[61] In addition, linear regression, corrected for age and gender, was used to test associations between anxiety or depressive symptoms, calprotectin and proteins levels. Two regressions were performed for anxiety and for depressive symptoms due to the age restrictions of the questionnaires (depression: < 18 and ≥ 18 years (young

adults), anxiety: < 21 and ≥21 years (young adults)). Log transformation of calprotectin was used to assure normality.

Using Welch's T-test, proteins levels between patients with no and patients with (mild or severe) anxiety and/or depressive symptoms were compared. Furthermore, "fold change (FC)" was calculated to quantify the difference between groups. FC was calculated by a) taking the difference (the mean NPX of group A – the mean NPX of group B (log 2 scale), and b) 2^(absolute value of the difference in NPX). The fold-change always has the same direction as the difference.

For the RCT, change in anxiety and depressive symptoms from baseline to 3 months was calculated using a Reliable Change Index (RCI), which can have three possible values; reliably improved, no reliable change, and reliably deteriorated.[62] The RCI method is further explained in Stapersma et al. (2018).[63] A chi-square test was used to compare the RCI values between the CBT and CAU group. In addition, exploratory linear mixed models were used to compare change between the groups from baseline to directly after CBT for anxiety (SCARED or HADS-A), depression (CDI or BDI-II).[63] Time, group (CBT vs. CAU) and the interaction between time and group were included as fixed factors. Using an Identity covariance structure, random intercepts were estimated for each participant. Restricted maximum likelihood (REML) was applied as estimation method.

(Paired) T-tests were used to investigate changes in protein levels within and between the CBT and CAU group over time.

Except for the mixed model analysis, all p-values were adjusted for multiple comparisons using the Benjamin Hochberg approach (controlling the false discovery rate).[64] Adjusted p-values were considered significant when $p < 0.05$. Nominal or unadjusted p-values below 0.05 are also reported, because they are of interest considering the exploratory nature of our study.

Overall, with these analyses we aimed to identify clusters of proteins, denoted as signatures, associated with for example response to CBT.

Data analyses were performed using SPSS version 24.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA), GraphPad Prism version 5.00 (GraphPad Software, La Jolla California USA) and R. version 3.4.5 (R Foundation for Statistical computing, Vienna, Austria).

RESULTS

Study population

For the cohort study, plasma samples were available from 10 IBD patients without anxiety and/or depressive symptoms, 30 patients with mild anxiety and/or depressive symptoms and 5 patients with severe anxiety and/or depressive symptoms. From 27 out of 30 patients with mild anxiety and/or depressive symptoms, receiving either Cognitive Behavioral Therapy (CBT) + Care As Usual (CAU) or CAU only as part of the RCT, a plasma sample 3

months after baseline (after the last CBT session) was available. This subgroup of 30 patients (enrolled in the EMC, where blood samples were taken) did not differ from the other 40 patients enrolled in the RCT, with respect to baseline anxiety and depression scores, disease type or clinical disease activity (data not shown).

Table 1 summarizes the demographic, clinical and psychological characteristics. Most patients were in clinical remission or had mild disease activity. Comparing patients without anxiety and/or depressive symptoms to patients with symptoms (mild and severe combined), showed that patients without psychological symptoms were significantly older ($\chi^2(1) = 12.8$, $p<0.001$; median age 23.7 vs 16.5). Fecal calprotectin levels were non-significantly higher in the patients with no and severe anxiety and/or depression. For patients included in the RCT (mild anxiety and/or depressive symptoms), disease duration was significantly longer in the CBT group (3.0 vs 1.3 years ; $\chi^2(1) = 4.9$, $p=0.026$). Disease type, disease activity or medication used were not different between younger (<18) and older (>18) patients (data not shown).

Table 1. Study population characteristics

		NO ANXIETY/DEPRESSION N = 10	MILD ANXIETY/DEPRESSION N = 30		SEVERE ANXIETY/DEPRESSION N = 5
			CBT (n=15)	CAU(n=15)	
Cohort Study/Baseline RCT					
Gender, Male, (n)		2	4	8	2
Age (years)	*Median (IQR)*	23.7 (22.6.1-25.2)*	17.2 (15.5-22.8)*	14.1 (12.3-18.0)*	17.1 (15.6-24.9)*
% < 18 years		0	10	12	3
Disease duration (years)	*Median (IQR)*	5.0 (2.3-9.6)	3.0 (1.8-6.9)[#]	1.3 (0.6-6.6)[#]	3.0 (0.8-6.1)
Disease Type (n)	CD	8	7	6	3
	UC	2	5	7	2
	IBD-U	0	3	2	0
Baseline Clinical Disease activity[¥] (n)	Remission	9	14	11	2
	Mild	1	1	4	2
	Moderate	0	0	0	1
	Severe	0	0	0	0
Medication Use (n)	Aminosalicylates	3	8	7	1
	Immunomodulators	4	7	8	2
	Anti-TNF biologicals	5	2	5	2
	Corticosteroids[¶]	0	1	1	2
	Topical treatment[§]	0	2	0	1
	No medication	1	1	0	0
CRP (mg/L)		3.4 (0.8-5.4)	1.6 (0.3-2.6)	0.4 (0.3-1.5)	n=4| 0.7 (0.4-49.0)
Fecal calprotectin (µg/g)		n=6 | 415.5 (66.8-811.5)	n=13| 61.8 (24.9-168.9)	26.5 (19.5-230)	578.3 (138.5-1095.0)
Leukocyte count (10^9/L)		6.4 (4.7-8.5)	6.3 (5.1-9.4)	7.2 (5.7-8.6)	7.5 (6.0-9.5)
Anxiety score	SCARED < 21y (0 -138)	n=1 |1.0 (1.0-1.0)	n=11| 32.0 (27.0-44.0)	n=13 | 38 (32.5-51.0)	n=3| 38.0 (26.0 - NA)
Median (IQR)	HADS-A > 21 y (0-21)	n=9 | 5.0 (2.5-6.5)	n=4 |9.5 (8.3-13.8)	n=2| 8.5 (6.0- NA)	n=2| (12.0 (11.0- NA)
Depression score	CDI < 18 y (0-54)	n=0 | --	n=10|8.0 (5.5-11.5)	n=12| 10.0 (7.3-14.5)	n=3| 9.0 (2.0-NA)
Median (IQR)	BDI >18 y (0-63)	n=10| 3.0 (1.8-5.0)	n=5|12.0 (9.5-21.5)	n=3|18.0 (17.0- NA)	n=2|24.0 (22.0- NA)
RCT: follow up 3 months					
Clinical Disease	Remission	-	12	11	-
Activity 3 months[¥] (n)	Mild	-	1	4	-
	Moderate	-	1	0	-
	Severe	-	0	0	-
Fecal calprotectin (µg/g)		-	n=13| 160.2 (25.1-605.7)	55.0 (19.5-683.1)	-

Abbreviations: CBT: Cognitive behavioral therapy, CAU: care as usual. IQR: interquartile range, CD: Crohn's Disease, UC: ulcerative colitis, IBD-U: IBD-unclassified, CRP: C-reactive protein, NA: not available (due to low numbers)

Notes: [¥]Based on disease activity scores [¶]prednisone /budesonide [§] aminosalicylate/corticosteroid *patients without anxiety/depressive symptoms were older than patients with symptoms (p<0.001) [#]RCT: disease duration longer in CBT group (p 0.026).

Results of the cohort study

No clustering of patients with no, mild or severe anxiety and/or depression at baseline

To assess whether immune plasma protein profiles discriminated between patient groups, we performed unbiased analyses using Principal Component Analysis (PCA) and t-Distributed Stochastic Neighbor Embedding plots (TSNE). Analyses did not show clustering of patients with no, mild, or severe anxiety and/or depression, which means that overall, the immunological signature of the three groups did not significantly differ (Figure 1).

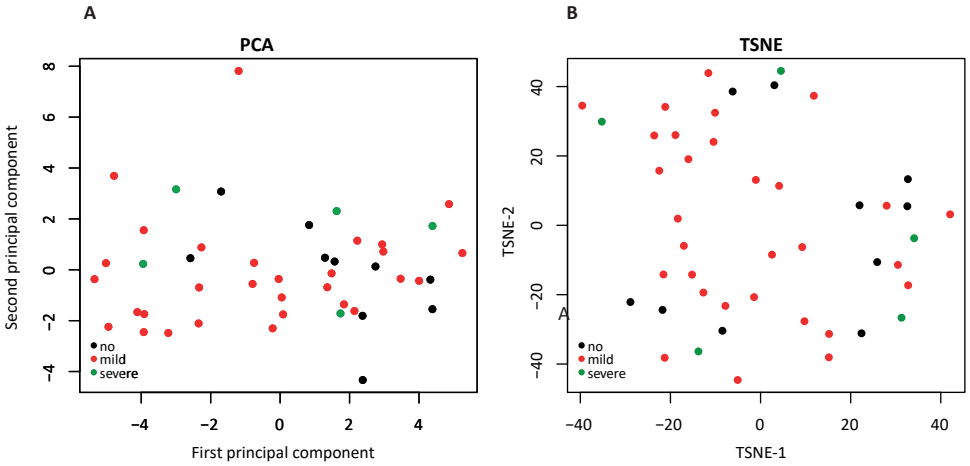


Figure 1. PCA and TSNE plots no, mild or severe anxiety and/or depression

Panel A: Principal component analyses (PCA) and in Panel B: t-Distributed Stochastic Neighbor Embedding (TSNE) plots of protein profiles of all 45 patients. Each dot represents a sample and each color represents a patient category, respectively patients with no, mild or severe anxiety and/or depressive symptoms.

IL-17A, IL-6 and MCP-4 were associated with fecal calprotectin levels

To investigate if proteins known to be associated with IBD-activity could also be found in our cohort, we studied which proteins were associated with fecal calprotectin levels, a proxy for mucosal inflammation. For 39/45 patients, fecal samples were available. As expected, fecal calprotectin levels were significantly associated with pro-inflammatory cytokines IL-17A (β 1.098 [95% Confidence interval (CI) 0.723-1.473], *p* 0.0004), IL-6 (β 1.030 [CI 0.543-1.519], *p* 0.0004) and also to chemokine Monocyte Chemoattractant Protein (MCP)-4 (β -0.609 [CI -0.988- -0.230], *p* 0.0580) after correction for multiple testing (Figure 2, Figure 3 panel E). Another 7 proteins were associated with fecal calprotectin with unadjusted p-values <0.05 (Figure 3 panel E, Supplementary Figure 1).

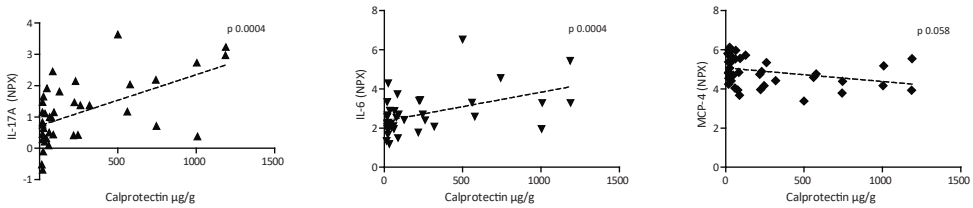


Figure 2. IL-17A and IL-6 positively and MCP-4 negatively associated with fecal calprotectin

Scatter plots of the association between fecal calprotectin and IL-17A, IL-6 and MCP-4. Adjusted R2 of the regression models including age and gender as predictors were respectively 54.8%, 34.2%, 16.9%. All p-values are corrected for multiple testing.

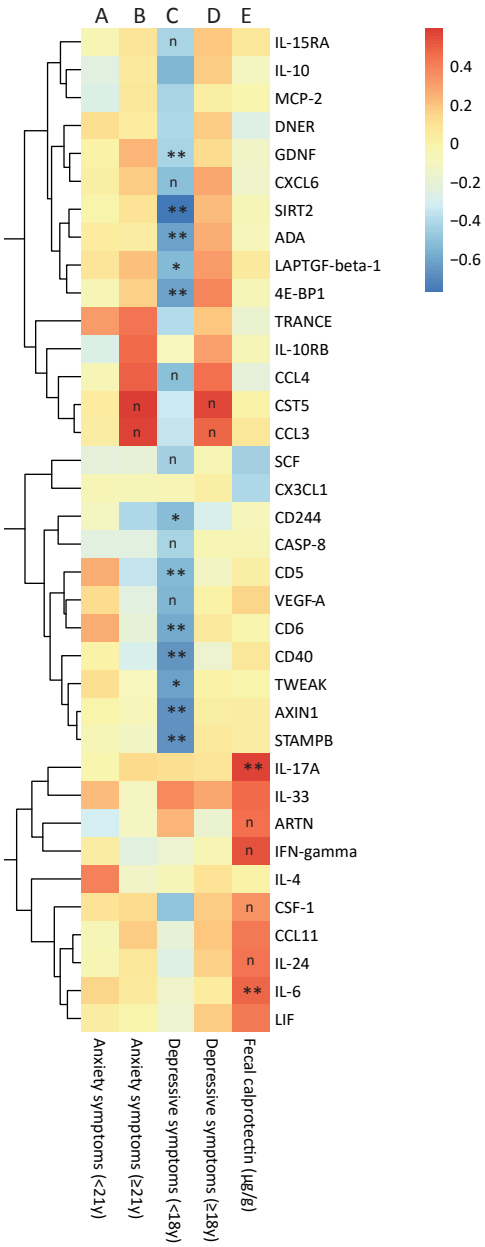


Figure 3. Correlation matrix for anxiety and depressive symptoms and fecal calprotectin

Correlation matrix (correlation coefficient -0.4 – 0.4) for anxiety symptoms (A<21 years B>21 years), depressive symptoms (C<18 years, D>18 years), fecal calprotectin (E) and inflammatory proteins. Shades of red indicate increasing positive correlation coefficient, shades of blue indicate increasing negative correlation coefficient. *represents adjusted p-value in regression analysis corrected for age and gender < 0.05, ** < 0.01, *** < 0.001. n indicates nominal unadjusted p-value < 0.05.

Four proteins significantly higher in patients with anxiety and/or depressive symptoms

To investigate whether proteins differentiated patients with and without psychological symptoms, data from patients with mild and severe anxiety and/or depressive symptoms were pooled. Comparing 35 patients with (mild or severe) symptoms to 10 patients without anxiety and/or depressive symptoms revealed four proteins that were significantly higher in the mild/severe group after correction for multiple testing (Figure 4, Supplementary Table 1). Leukemia inhibitory factor receptor (LIF-R) is a member of the IL-6 family and has many functions, one of them is activation of the HPA-axis. Tumor necrosis factor receptor superfamily member 9 (TNFRSF9; also denoted as 4-1BB) is involved in the activation of T cells, Urokinase-type plasminogen activator (uPA) is part of the plasminogen activation system and is involved in the recruitment of immune cells. CST5 controls proteolytic activity during inflammatory processes. Another 15 proteins had unadjusted p-values < 0.05 (Supplementary Table 1).

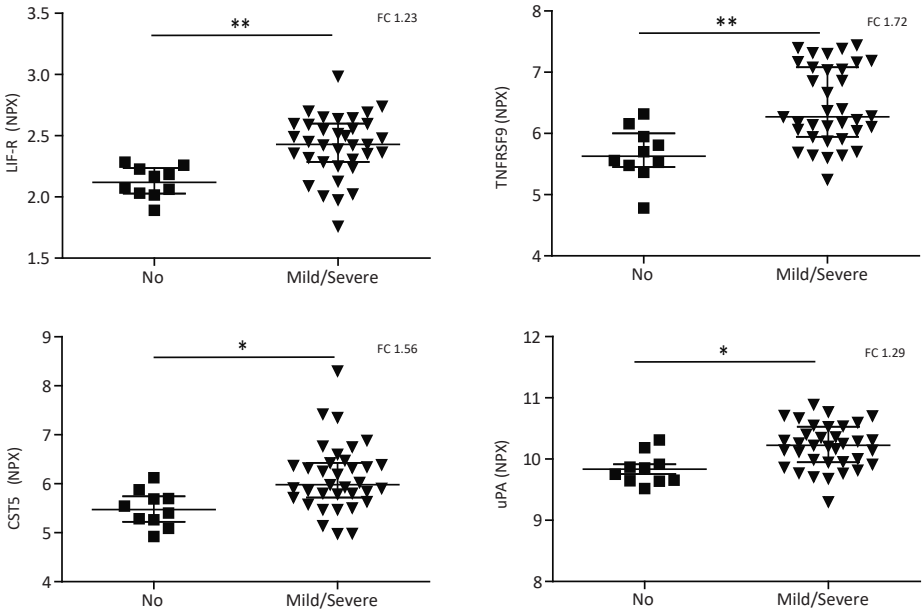


Figure 4. Four proteins significantly higher in patients with mild/severe anxiety and/or depressive symptoms compared to patients without symptoms of anxiety and/or depression.

Scatter plots showing NPX levels of LIF-R, TNFRSF9, CST5 and uPA in patient without symptoms of anxiety and/or depression compared to patients with mild or severe anxiety and/or depression. Fold change (FC) was calculated to quantify the difference between the two groups. * represents adjusted p-value < 0.05, and ** < 0.01

To investigate whether anxiety or depressive symptoms were associated to certain specific protein signatures, separate regression analyses were performed. After correction for multiple testing, significant associations were found for depressive symptoms only (CDI questionnaire (< 18 years, n=25)): for 12 proteins, higher depression scores were significantly associated with lower protein levels (Figure 2 panel C, Supplementary Table 2 and Supplementary Figure 2). In addition, CST5, which controls proteolytic activity during inflammatory processes and CCL3, a chemokine involved in the recruitment and activation of polymorphonuclear leukocytes were positively associated (unadjusted p-value< 0.05) to anxiety and to depressive symptoms in young adults (data not shown) Figure 3 panel B and D).

Results RCT

CBT did not alter fecal calprotectin levels

To investigate if CBT reduced IBD-activity, change in calprotectin levels was studied and compared between the CBT and CAU group. At baseline (*p* 0.961) or at 3 months (*p* 0.533), fecal calprotectin levels did not differ between the CAU (n=15) or CBT (n=15) group. In addition, the change (delta) in fecal calprotectin levels over time was not significantly different between both groups (*p* 0.576). Because of the four clinical disease activity scores that were used, groups became too small to investigate the effect of CBT on clinical disease activity.

Anxiety and depressive symptoms improved in both the CBT as well as the CAU group

Two methods were used to investigate how anxiety and depressive symptoms evolved over time. First, calculating the three categories of Reliable Change Index (reliably improved, no reliable change (stable symptoms), and reliably deteriorated) showed no difference between the two groups for both anxiety ($\chi 2$ (2) = 2.227, *p* 0.255) and depression ($\chi 2$ (2) = 1.150, *p* 0.567). Overall, patients in both groups either remained stable or improved in their symptoms of anxiety and depression (Supplementary Table 3).

Second, exploratory mixed model analyses did not show a difference between the CBT and CAU group over time for anxiety or depressive symptoms (interaction group * time not significant for SCARED, HADS-A, CDI or BDI-II), but showed that within both groups patients improved in their symptoms of anxiety (SCARED (t(21.395) = -6.062, p<0.001), HADS-A (t(2.913) = -5.037, *p* 0.016) and depression (CDI (t(19.260) = -3.351, *p* 0.003), BDI-II (t(4.938) = -3.776, *p* 0.013) (data not shown).

In summary, analyses showed that anxiety and depressive symptoms improved over time in both the CBT and the CAU group.

Several proteins changed over time within the CBT and CAU group and significantly differed between groups

To investigate change in protein levels over time, paired analyses were conducted within the CBT and the CAU group and between both groups.

There were no significant differences in protein levels between both groups at baseline or at 3 months (data not shown). For both the CBT and CAU group, change in protein levels over time (baseline to 3 months) was not significant after correction for multiple testing. However, several proteins had unadjusted p-values < 0.05.

Within the CBT group, 7/87 protein levels decreased over time (unadjusted p-value <0.05): LIF-R (mean difference -0.225, *p* 0.004, Figure 5), IL18-R1 (mean difference -0.161, *p* 0.006. Figure 5), Fractalkine (CX3CL1) (mean difference -0.232, *p* 0.011), CCL25 (mean difference -0.165, *p* 0.026), CXCL5 (mean difference -0.112, *p* 0.031), CCL28 (mean difference -0.267, *p* 0.039) and CCL3 (mean difference 0.323, *p* 0.048, Figure 5).

Within the CAU group 3/87 proteins increased over time (unadjusted p-value <0.05): IL-7 (mean difference 0.477, *p* 0.027*),* TRANCE (mean difference 0.407, p 0.036), and Matrix metalloproteinase-1 (MMP-1) (mean difference 0.295, p 0.048) and 1 protein decreased over time Monocyte chemotactic protein 1 (MCP-1 also denoted CCL2) (mean difference -0.325, p 0.048, Figure 5).

Analyses comparing the change (the delta) in protein levels from baseline to 3 months for the CBT compared to the CAU group revealed 9 proteins with an unadjusted p-value < 0.05: LIF-R (*t*(23.618)=2.984, *p* 0.007, fold change (FC) -1.2), Signaling lymphocytic activation molecule (SLAMF1) (*t*(24.859)=2.853, p 0.009, FC -1.4), IL-7 (*t*(22.570)=2.871, p 0.009, FC -1.6), IL-18R1 (*t*(18.352)=2.599, p 0.018, FC -1.3), CCL4 (*t*(23.626)=2.192, p 0.038, FC -1.3), CCL3 (*t*(21.789)=2.190, *p* 0.040, FC -1.3), ARTN (*t*(24.061)=2.143, *p* 0.042, FC -1.2), MCP-1 (*t*(23.589)=-2.080, *p* 0.049, FC +1.3) and LAPTGF-Beta-1 (*t*(22.843)=2.082, *p* 0.049, FC -1.3). All showed a decrease in the CBT group compared to the CAU group, except for MCP-1 (Figure 5)

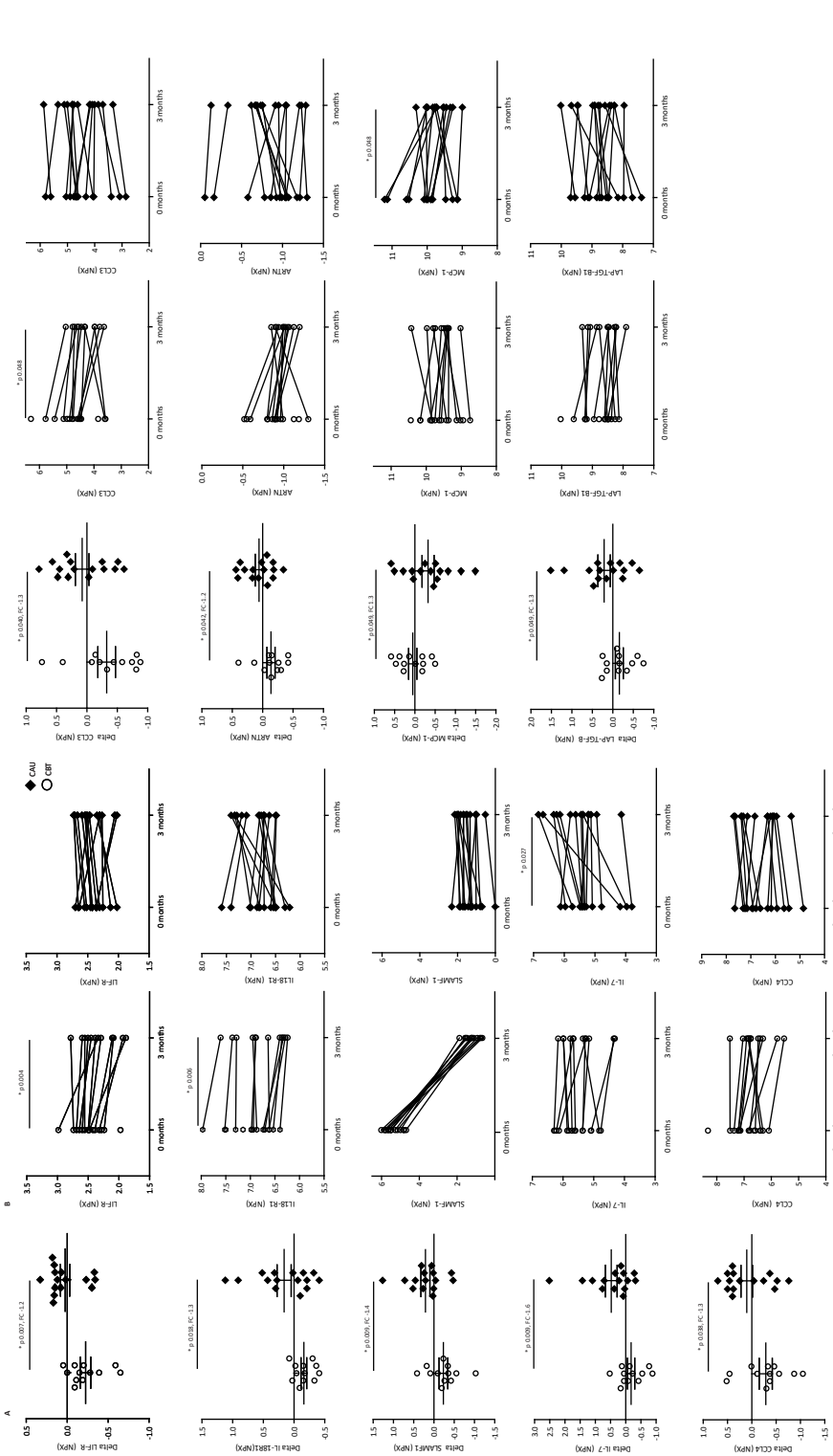


Figure 5. Difference in protein levels over time: CBT versus the CAU group

Panel A shows scatter plots with on the Y-axis the difference in protein levels over time (protein NPX level 3 months – 0 months; a negative value indicates a decrease) and on the X-axis the CBT (○) and the CAU (◆) group. Fold change (FC) was calculated to quantify the difference between the two groups. Panel B displays the course of protein levels over time (0 to 3 months), with on the Y axis protein NPX levels. * all p-values unadjusted p<0.05.

Figure 6 shows a summary of all proteins found to be associated to anxiety and/or depressive symptoms and which proteins were responsive to CBT.

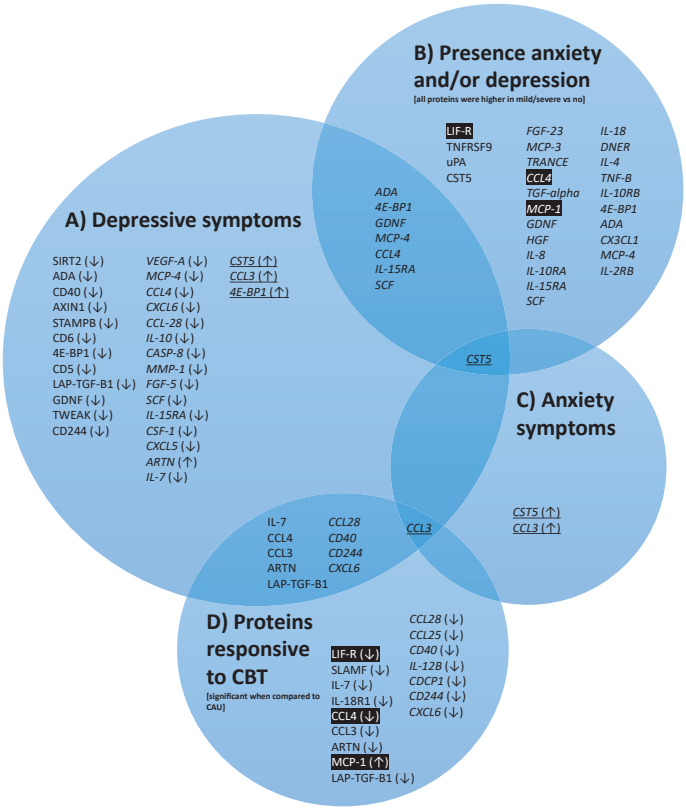


Figure 6. Summary of all proteins found to be associated to anxiety and/or depressive symptoms and response to CBT

Panel A) depressive symptoms, panel B) presence of anxiety and/or depressive symptoms (mild/severe symptoms compared to no symptoms of anxiety and/or depression) panel C) anxiety symptoms. Panel D: proteins significantly changed after cognitive behavioral therapy (CBT) compared to the Care as usual (CAU) group. Underlined proteins reflect the young adults (above 18 or 21); ↑ reflects higher anxiety/depressive symptoms associated to higher protein levels. ↓ reflects higher anxiety/depressive symptoms associated to lower protein levels; Italic reflects unadjusted p-value < 0.05; Black shaded black proteins: Associated to 'Response to CBT" and severity.

DISCUSSION

This study is the first to explore the relationship between psychological symptoms and inflammation in young IBD patients using unbiased inflammatory plasma protein analyses. The bidirectional association between psychological symptoms and clinical disease activity in IBD has been unequivocally established. With this study, we aimed to take the first step in unraveling the hypothesis that psychological therapy may reduce systemic inflammation, with ultimately a positive effect on intestinal inflammation in IBD. We show distinct protein profiles in IBD patients in clinical remission but suffering from symptoms of anxiety and/or depression. More importantly, we demonstrate that cognitive behavioral therapy associates with detectable changes in inflammation at a molecular level.

To our knowledge, only one study, in adult IBD, previously reported on the association between IBD and anxiety/depression and plasma proteins. Abautret-Daly et al. (2017) cross-sectionally investigated a limited selection of cytokines, and described an association between clinically active disease, anxiety /depressive symptoms, and increased intestinal expression of IL-1β, IL-6 and MMP-9 and increased circulating IL-6 and CRP.[40] In our cohort, these associations were not found, which could be due to the fact that most patients were in remission at baseline.

As a comparison, several studies have focused on cytokine levels in otherwise healthy adolescents and adults with anxiety and depression, but unfortunately investigated a limited number (up to 20[65]) of proteins. Mainly associations with IL-1β, IL-2, IL-6, IL-8, CRP, IFN- γ, and TNF-α have been reported.[10, 11, 13, 16, 18, 66-69] A recent meta-analysis investigating chemokines in adult depression reported higher levels of MCP-1 (CCL2), CCL3 , CCL11, CXCL4, CXCL7 and lower levels of CCL4.[70]

Our study is unique in using an unbiased approach with a large protein panel and found several novel proteins to be associated with anxiety and depressive symptoms in IBD patients. Amongst these, the associations of depressive symptoms with the chemokines CCL3 and CCL4 agree with previous reports.[70] CCL3 (also denoted Macrophage Inflammatory Protein (MIP)-1α) and CCL4 (MIP-1β) are mainly involved in chemotaxis, the migration of proinflammatory cells.[71] Studies investigating CCL3 and CCL4 in IBD show increased, but also decreased levels in IBD.[72-74]

In addition, our analyses show that four proteins (LIF-R, TNFRSF9, CST5 and uPA) are significantly upregulated in the group with (mild or severe) anxiety and/or depressive symptoms compared the group without psychological symptoms, of which LIF-R was most significantly different. Leukemia inhibitory factor (LIF) is a polyfunctional cytokine which belongs to the IL-6 family, with both inflammatory and anti-inflammatory properties. The LIF-R receptor is found in different organs (liver, bone, and central nervous system) and LIF is involved in reproduction, bone remodelling, and neuronal development. More importantly, LIF mediates HPA axis activity, it stimulates ACTH secretion in response to emotional and inflammatory stress and also induces steroidogenesis.[75-78] Little is known about the role of

LIF in IBD, two studies describe the presence of LIF in serum[75] and colonic liquid perfusion[70] in IBD patients. LIF has been of interest in the aetiology of depression, a study in LIF knockout mice suggests that LIF has a role in depressive-like behaviour.[79]

In this sub-analysis of our randomized trial, all 30 patients show improvement of anxiety and depressive symptoms. As for symptoms of mucosal inflammation, CBT did not influence calprotectin levels (this study), and analyses of all 70 patients in the RCT showed no influence of CBT on CRP-levels, fecal calprotectin, or clinical disease activity scores.[31] We showed that CBT significantly influenced plasma protein levels of LIF-R, SLAMF1, IL-7, IL-18R1, CCL4, CCL3, LAP-TGF-B1 and ARTN, compared to CAU. Unfortunately, due to small numbers in each age group (e.g. depression < and > 18 years), we were not able to correlate change in psychological symptoms over time in each treatment group to change in these protein levels.

In IBD, studies investigating the effect of psychotherapy on cytokine levels are scarce. To our knowledge, only one pilot study is available, describing that one session of gut-focused hypnotherapy in 17 patients with active ulcerative colitis resulted in a decrease of LPS stimulated serum IL-6 levels directly after the session, no change in IL-13 levels was seen.[80]

However, several studies have reported on the effect of psychological interventions on inflammation in adult patients with various diseases, summarized in two recently published systematic reviews. Lopresti et al. (2017) reviewed 18 publications on the effect of CBT on inflammation in adult patients with depression and/or a comorbid medical condition (e.g. breast cancer, cardiovascular disease, rheumatoid arthritis). Mostly observational studies were included (11-214 participants;CBT duration 4 -52 weeks) measuring 2 to 14 cytokines (mostly IL-1β, IL-2, IL-4, IL-6, IFN-γ, TNF-α). Overall, 60% of the studies showed a decrease in at least one inflammatory marker over time. Three studies examined the relationship between improvement of depression following CBT and change in inflammation, one found a positive correlation. Overall, robust conclusions cannot be drawn considering the low quality and high heterogeneity of the included studies.[81] O'Toole et al. (2018) included 19 studies (RCTs; n=1510; 6/19 CBT intervention), 18/19 studies measured 1-4 biomarkers, mainly IL-1β, IL-6, TNF-α and CRP. Meta-analyses showed that CRP only significantly decreased directly after the psychological intervention (mean reduction 1.6mg/dL), this was not maintained at follow-up. The greatest (but not significant) decrease was seen in studies that selected patients based on psychological distress (five studies, of which three selected on depression).[82]

All previous studies investigating the effect of psychological interventions on inflammation (in IBD) used small (biased) protein panels. Our unbiased analyses shows that several proteins decreased after CBT (all unadjusted p-value < 0.05) (Figure 5 and 6). LIF-R was the top protein, this was not surprising, considering LIF-R was also strongly associated to the presence of anxiety and/or depression. The association with LIF-R was only detectable when grouping all patients with psychological symptoms (anxiety and/or depression), and not in the smaller subgroup analyses in anxiety and depression separately. In addition, CCL4 levels also decreased after CBT and were higher in patients with anxiety and/or depression.

We are amongst the first using the broad Inflammation Panel of Olink Proteomics in IBD to characterize plasma protein profiles in IBD patients. We validated the use of this panel by confirming that proteins known to be associated to fecal calprotectin (as a proxy for mucosal inflammation in IBD), such as IL-17A, IL-6[83], were also found in our cohort. As the included patients were in clinical remission or had mildly active disease, we anticipate that the reported plasma protein signatures more likely reflect anxiety/depression in IBD, rather than IBD activity.

Strengths and limitations

This study is the first to explore the relationship between anxiety and depressive symptoms and inflammation in IBD at plasma protein levels. Secondly, investigating this relationship cross-sectionally, but also prospectively after an intervention in a multicenter RCT, strengthens our study. Thirdly, the inclusion of both pediatric and young adult patients increases generalizability, but forced us to use two questionnaires for both anxiety and depression, necessitating subgroup analyses with less power. Fourthly, including IBD patients mostly in remission increases the homogeneity of our cohort, and assists in unraveling the complex interplay between psychological symptoms and inflammation in IBD. Finally, a major strength is the use of a large unbiased protein panel, including both cytokines and chemokines, which is in contrast to most other studies using a limited protein panel, often selecting only the proteins found in previous research. In addition, using the relatively new method from Olink proteomics enabled us to adopt a new, innovative and unbiased approach in finding proteins associating with anxiety and depression and the response to CBT.

The study is limited by the small number of patients included in group with no and severe psychological symptoms. Secondly, drawing extra blood for immunological analysis was only possible in the Erasmus Medical Center, which could have introduced bias. However, we do not think this is likely, considering there was no difference in baseline anxiety and depression scores or clinical disease activity between patients included in the Erasmus Medical Center and the other centers. Thirdly, it would have been interesting to have included HPA-axis derivates (e.g. morning serum cortisol) in our analyses, but this was not part of the study design. At last, due to the exploratory nature of this study we were able to control only for age and gender, but not for other confounders.

Conclusion

To conclude, using an innovative and unbiased approach with a large protein panel, we found distinct plasma protein signatures associating with anxiety and/or depression in IBD patients mostly in remission. These immune signatures were altered in patients receiving CBT in addition to CAU, compared to patients receiving CAU only. Several proteins not previously investigated in anxiety and depression (in IBD) were now analyzed, providing a novel perspective on involved proteins. Leukemia inhibitory factor receptor (LIF-R) and chemokine CCL4 were upregulated in patients with psychological symptoms and decreased

after CBT, and are therefore candidate proteins reflecting response to psychotherapy. To better understand protein profiles in anxiety and depression in IBD, but also in anxiety/depression research in otherwise healthy patients, future studies should use large unbiased protein panels and larger patient samples. We have now identified protein signatures for anxiety and depression in IBD patients mostly in remission, larger studies sufficiently powered to perform subgroup analyses should help unravel whether these protein profiles are maintained in active disease. In addition, future studies should also investigate whether these protein signatures are different for Crohn's disease versus ulcerative colitis and for responders versus non-responders to psychotherapy.

REFERENCES

1 Adamiak T, Walkiewicz-Jedrzejczak D, Fish D, et al. Incidence, clinical characteristics, and natural history of pediatric IBD in Wisconsin: a population-based epidemiological study. *Inflamm Bowel Dis*. 2013;19(6):1218-1223.

2 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol*. 2004;18(3):509-523.

3 Ghione S, Sarter H, Fumery M, et al. Dramatic Increase in Incidence of Ulcerative Colitis and Crohn's Disease (1988-2011): A Population-Based Study of French Adolescents. *Am J Gastroenterol*. 2018;113(2):265-272.

4 Rosen MJ, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. *JAMA Pediatr*. 2015;169(11):1053-1060.

5 Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review. *J Psychosom Res*. 2016;87:70-80.

6 Stapersma L, van den Brink G, Szigethy EM, Escher JC, Utens E. Systematic review with meta-analysis: anxiety and depression in children and adolescents with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018.

7 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.

8 Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. *Inflamm Bowel Dis*. 2016;22(3):752-762.

9 Abautret-Daly A, Dempsey E, Parra-Blanco A, Medina C, Harkin A. Gut-brain actions underlying comorbid anxiety and depression associated with inflammatory bowel disease. *Acta Neuropsychiatr*. 2018;30(5):275-296.

10 Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457.

11 Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171-186.

12 Salim S, Chugh G, Asghar M. Inflammation in anxiety. *Adv Protein Chem Struct Biol*. 2012;88:1-25.

13 Hou R, Baldwin DS. A neuroimmunological perspective on anxiety disorders. *Hum Psychopharmacol*. 2012;27(1):6-14.

14 Neurath MF. Cytokines in inflammatory bowel disease. *Nat Rev Immunol*. 2014;14(5):329-342.

15 Peloquin JM, Goel G, Villablanca EJ, Xavier RJ. Mechanisms of Pediatric Inflammatory Bowel Disease. *Annu Rev Immunol*. 2016;34:31-64.

16 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):447-455.

17 Zou W, Feng R, Yang Y. Changes in the serum levels of inflammatory cytokines in antidepressant drug-naive patients with major depression. *PLoS One*. 2018;13(6):e0197267.

18 Lamers F, Milaneschi Y, Smit JH, Schoevers RA, Wittenberg G, Penninx B. Longitudinal Association Between Depression and Inflammatory Markers: Results From the Netherlands Study of Depression and Anxiety. *Biol Psychiatry*. 2019.

19 Camacho A. Is anxious-depression an inflammatory state? *Med Hypotheses*. 2013;81(4):577-581.

20 Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology*. 2013;144(1):36-49.

21 Bernstein CN. Psychological Stress and Depression: Risk Factors for IBD? *Dig Dis*. 2016;34(1-2):58-63.

22 Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut*. 2005;54(10):1481-1491.

23 Stasi C, Orlandelli E. Role of the brain-gut axis in the pathophysiology of Crohn's disease. *Dig Dis*. 2008;26(2):156-166.

24 Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. *Am J Psychiatry*. 2015;172(11):1075-1091.

25 Mackner LM, Clough-Paabo E, Pajer K, Lourie A, Crandall WV. Psychoneuroimmunologic factors in inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17(3):849-857.

26 Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46-56.

27 Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol Bull*. 2014;140(3):774-815.

28 Raison CL, Miller AH. Do cytokines really sing the blues? *Cerebrum*. 2013;2013:10.

29 Martin-Subero M, Anderson G, Kanchanatawan B, Berk M, Maes M. Comorbidity between depression and inflammatory bowel disease explained by immune-inflammatory, oxidative, and nitrosative stress; tryptophan catabolite; and gut-brain pathways. *CNS Spectr*. 2016;21(2):184-198.

30 Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain-Gut Interactions in Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2018;154(6):1635-1646 e1633.

31 van den Brink G, Stapersma L, Vlug LE, et al. Clinical disease activity is associated with anxiety and depressive symptoms in adolescents and young adults with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;48(3):358-369.

32 Reigada LC, Hoogendoorn CJ, Walsh LC, et al. Anxiety symptoms and disease severity in children and adolescents with crohn disease. *J Pediatr Gastroenterol Nutr*. 2015;60(1):30-35.

33 Clark JG, Srinath AI, Youk AO, et al. Predictors of depression in youth with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2014;58(5):569-573.

34 Alexakis C, Kumar S, Saxena S, Pollok R. Systematic review with meta-analysis: the impact of a depressive state on disease course in adult inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46(3):225-235.

35 Kochar B, Barnes EL, Long MD, et al. Depression Is Associated With More Aggressive Inflammatory Bowel Disease. *Am J Gastroenterol*. 2018;113(1):80-85.

36 Mikocka-Walus A, Pittet V, Rossel JB, von Kanel R, Swiss IBDCSG. Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2016;14(6):829-835 e821.

37 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.

38 Bitton A, Dobkin PL, Edwardes MD, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut*. 2008;57(10):1386-1392.

39 Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Holtmann GJ, Andrews JM. Does psychological status influence clinical outcomes in patients with inflammatory bowel disease (IBD) and other chronic gastroenterological diseases: an observational cohort prospective study. *Biopsychosoc Med*. 2008;2:11.

40 Abautret-Daly A, Dempsey E, Riestra S, et al. Association between psychological measures with inflammatory anddisease-related markers of inflammatory bowel disease. *Int J Psychiatry Clin Pract*. 2017;21(3):221-230.

41 Macer BJ, Prady SL, Mikocka-Walus A. Antidepressants in Inflammatory Bowel Disease: A Systematic Review. *Inflamm Bowel Dis*. 2017;23(4):534-550.

42 Wiedlocha M, Marcinowicz P, Krupa R, et al. Effect of antidepressant treatment on peripheral inflammation markers - A meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;80:217-226.

43 Gracie DJ, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2(3):189-199.

44 McCombie AM, Mulder RT, Gearry RB. Psychotherapy for inflammatory bowel disease: a review and update. *J Crohns Colitis*. 2013;7(12):935-949.

45 Levy RL, van Tilburg MA, Langer SL, et al. Effects of a Cognitive Behavioral Therapy Intervention Trial to Improve Disease Outcomes in Children with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2016;22(9):2134-2148.

46 Szigethy E, Bujoreanu SI, Youk AO, 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):726-735.

47 van den Brink G, Stapersma L, Bom AS, et al. 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. *Inflamm Bowel Dis*. 2019 May 3 [Epub ahead of print]

48 van den Brink G, Stapersma L, El Marroun H, et al. 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 Gastroenterol*. 2016;3(1):e000071.

49 Garber J, Weersing VR. Comorbidity of Anxiety and Depression in Youth: Implications for Treatment and Prevention. *Clin Psychol (New York)*. 2010;17(4):293-306.

50 Siebelink, Treffers. Nederlandse bewerking van het Anxiety Disorder Interview Schedule for DSM-IV Child Version van Silverman & Albana. Lisse / Amsterdam: Swets & Zeitlinger; 2001.

51 Muris P, Bodden D, Hale W, Birmaher B, Mayer B. SCARED-NL. Vragenlijst over angst en bang-zijn bij kinderen en adolescenten. Handleiding bij de gereviseerde Nederlandse versie van de Screen for Child Anxiety Related Emotional Disorders. Amsterdam: Boom test uitgevers; 2007.

52 de Croon EM, Nieuwenhuijsen K, Hugenholtz NIR, van Dijk FJH. Drie vragenlijsten voor diagnostiek van depressie en angststoornissen. *TBV – Tijdschrift voor Bedrijfs- en Verzekeringsgeneeskunde*. journal article. 2005;13(4):114-119.

53 Timbremont B, Braet C, Roelofs J. Handleiding Children's Depression Inventory (herziene versie). Amsterdam: Pearson Assessment and Information B.V.; 2008.

54 Van der Does AJW. BDI-II-NL Handleiding. De Nederlandse versie van de Beck Depression Inventory-2nd edition. Lisse: Harcourt Test Publishers; 2002.

55 Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology*. 2007;133(2):423-432.

56 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317(26):1625-1629.

57 Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's Disease Activity Index. *Gastroenterology*. 1976;70(3):439-444.

58 Assarsson E, Lundberg M, Holmquist G, et al. Homogenous 96-plex PEA immunoassay exhibiting high sensitivity, specificity, and excellent scalability. *PLoS One*. 2014;9(4):e95192.

59 Olink Proteomics. White papers: PEA: An enabling technology for high-multiplex protein biomarker discovery Vol. 2018: Olink proteomics, 2018

60 Andersson E, Bergemalm D, Kruse R, et al. Subphenotypes of inflammatory bowel disease are characterized by specific serum protein profiles. *PLoS One*. 2017;12(10):e0186142.

61 van der Maaten LJP, Accelerating t-SNE using Tree-Based Algorithms. *J Mach. Learn. Res.* 2014;15:3221-3245.

62 Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. 1991;59(1):12-19.

63 Stapersma L, van den Brink G, van der Ende J, et al. Effectiveness of Disease-Specific Cognitive Behavioral Therapy on Anxiety, Depression, and Quality of Life in Youth With Inflammatory Bowel Disease: A Randomized Controlled Trial. *J Pediatr Psychol*. 2018;43(9):967-980.

64 Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc.* 1995;B 57:289-300.

65 Vogelzangs N, de Jonge P, Smit JH, Bahn S, Penninx BW. Cytokine production capacity in depression and anxiety. *Transl Psychiatry*. 2016;6(5):e825.

66 O'Donovan A, Hughes BM, Slavich GM, et al. Clinical anxiety, cortisol and interleukin-6: evidence for specificity in emotion-biology relationships. *Brain Behav Immun*. 2010;24(7):1074-1077.

67 Liukkonen T, Rasanen P, Jokelainen J, et al. The association between anxiety and C-reactive protein (CRP) levels: results from the Northern Finland 1966 birth cohort study. *Eur Psychiatry*. 2011;26(6):363-369.

68 Al-Hakeim HK, Al-Rammahi DA, Al-Dujaili AH. IL-6, IL-18, sIL-2R, and TNFalpha proinflammatory markers in depression and schizophrenia patients who are free of overt inflammation. *J Affect Disord*. 2015;182:106-114.

69 Pallavi P, Sagar R, Mehta M, et al. Serum cytokines and anxiety in adolescent depression patients: Gender effect. *Psychiatry Res*. 2015;229(1-2):374-380.

70 Leighton SP, Nerurkar L, Krishnadas R, Johnman C, Graham GJ, Cavanagh J. Chemokines in depression in health and in inflammatory illness: a systematic review and meta-analysis. *Mol Psychiatry*. 2018;23(1):48-58.

71 Maurer M, von Stebut E. Macrophage inflammatory protein-1. *Int J Biochem Cell Biol*. 2004;36(10):1882-1886.

72 Pender SL, Chance V, Whiting CV, et al. Systemic administration of the chemokine macrophage inflammatory protein 1alpha exacerbates inflammatory bowel disease in a mouse model. *Gut*. 2005;54(8):1114-1120.

73 Banks C, Bateman A, Payne R, Johnson P, Sheron N. Chemokine expression in IBD. Mucosal chemokine expression is unselectively increased in both ulcerative colitis and Crohn's disease. *J Pathol*. 2003;199(1):28-35.

74 Kleiner G, Zanin V, Monasta L, et al. Pediatric patients with inflammatory bowel disease exhibit increased serum levels of proinflammatory cytokines and chemokines, but decreased circulating levels of macrophage inhibitory protein-1beta, interleukin-2 and interleukin-17. *Exp Ther Med*. 2015;9(6):2047-2052.

75 Bamberger AM, Schulte HM, Wullbrand A, Jung R, Beil FU, Bamberger CM. Expression of leukemia inhibitory factor (LIF) and LIF receptor (LIF-R) in the human adrenal cortex: implications for steroidogenesis. *Mol Cell Endocrinol*. 2000;162(1-2):145-149.

76 Nicola NA, Babon JJ. Leukemia inhibitory factor (LIF). *Cytokine Growth Factor Rev*. 2015;26(5):533-544.

77 Yue X, Wu L, Hu W. The regulation of leukemia inhibitory factor. *Cancer Cell Microenviron*. 2015;2(3).

78 Gadient RA, Patterson PH. Leukemia inhibitory factor, Interleukin 6, and other cytokines using the GP130 transducing receptor: roles in inflammation and injury. *Stem Cells*. 1999;17(3):127-137.

79 Pechnick RN, Chesnokova VM, Kariagina A, Price S, Bresee CJ, Poland RE. Reduced immobility in the forced swim test in mice with a targeted deletion of the leukemia inhibitory factor (LIF) gene. *Neuropsychopharmacology*. 2004;29(4):770-776.

80 Mawdsley JE, Jenkins DG, Macey MG, Langmead L, Rampton DS. The effect of hypnosis on systemic and rectal mucosal measures of inflammation in ulcerative colitis. *Am J Gastroenterol*. 2008;103(6):1460-1469.

81 Lopresti AL. Cognitive behaviour therapy and inflammation: A systematic review of its relationship and the potential implications for the treatment of depression. *Aust N Z J Psychiatry*. 2017;51(6):565-582.

82 O'Toole MS, Bovbjerg DH, Renna ME, Lekander M, Mennin DS, Zachariae R. Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans: A systematic review and meta-analysis. *Brain Behav Immun*. 2018;74:68-78.

83 Bourgonje AR, von Martels JZH, de Vos P, Faber KN, Dijkstra G. Increased fecal calprotectin levels in Crohn's disease correlate with elevated serum Th1- and Th17-associated cytokines. *PLoS One*. 2018;13(2):e0193202.

SUPPLEMENTARY TABLES

Supplementary Table 1. Proteins associated with mild/severe anxiety and/or depressive symptoms

Protein	Mean difference	Fold Change	Adjusted p-value	Function
LIF-R	0.2959	1.23	0.0014	activation HPA-axis
TNFRSF9	0.7809	1.72	0.0089	development T cells
CST5	0.6408	1.56	0.0158	proteolysis
uPA	0.3723	1.29	0.0288	proteolysis
FGF-23	0.7945	1.73	0.0539	regulator of inflammatory gene expression
MCP-3	0.5492	1.46	0.0742	chemotaxis inflammatory response
TRANCE	0.6485	1.57	0.1159	regulation of T cell immune response
CCL4	0.5138	1.43	0.1203	chemotaxis inflammatory response
TGF-alpha	0.3625	1.29	0.1203	growth factor / epithelial development
MCP-1	0.4163	1.33	0.1393	chemotaxis inflammatory response
GDNF	0.3198	1.25	0.1393	neuron survival and regeneration
HGF	0.3949	1.31	0.1398	growth. motility and morphogenic factor
IL-8	0.5173	1.43	0.1690	pro-inflammatory cytokine. innate response
IL-10RA	0.5918	1.51	0.1833	anti-inflammatory activity
IL-15RA	0.1522	1.11	0.2009	T-cell proliferation
SCF	0.2874	1.22	0.2030	production proinflammatory cytokines/ chemokines
IL-18	0.2991	1.23	0.2030	cell-mediated immunity/IFN-γ production
DNER	0.2775	1.21	0.2030	activator of the NOTCH1 pathway
IL-4	0.3452	1.27	0.2054	activates naïve Tcells/ B. T cell proliferation

Notes: Fold change reflects mild/severe compared to no anxiety and/or depressive symptoms

Supplementary Table 2. Proteins associated to depressive symptoms in patients < 18 years

Protein	Beta [CI]	Adjusted R^{2*}	Adjusted P-*value*
SIRT2	-0.083 [-0.109 --0.056]	67.4%	0.0002
ADA	-0.125 [-0.171- -0.080]	57.5%	0.0005
CD40	-0.054 [-0.077- -0.031]	49.6%	0.0026
AXIN1	-0.100 [-0.147- -0.053]	51.5%	0.0043
STAMPB	-0.083 [-0.123- -0.043]	49.1%	0.0043
CD6	-0.161 [-0.238- -0.084]	40.5%	0.0043
4E-BP1	-0.047 [-0.072- -0.022]	42.2%	0.0095
CD5	-0.109 [-0.168- -0.050]	36.1%	0.0098
LAP TGF-beta-1	-0.059 [-0.096- -0.023]	35.4%	0.0261
GDNF	-0.066 [-0.107- -0.025]	32.9%	0.0261
TWEAK	-0.031 [-0.052- -0.010]	32.4%	0.0435
CD244	-0.062 [-0.105- - 0.019]	25.6%	0.0478
VEGFA	-0.069 [-0.118- -0.020]	22.3%	0.0523#
MCP-4	-0.072 [-0.125- -0.020]	27.4%	0.0569#
CCL4	-0.067 [-0.117- -0.017]	17.0%	0.0638#
CXCL6	-0.079 [-0.138- -0.019]	24.1%	0.0638#
CCL28	-0.049 [-0.087 - -0.012]	32.9%	0.0638#
IL-10	-0.084 [-0.151- -0.016]	21.9%	0.0849#
CASP-8	-0.087 [-0.158- -0.016]	16.4%	0.0878#
MMP-1	-0.095 [-0.177- -0.013]	25.9%	0.1084#
FGF-5	-0.016 [-0.030- -0.001]	17.4%	0.1498#
SCF	-0.029 [-0.058- -0.001]	22.9%	0.1583#

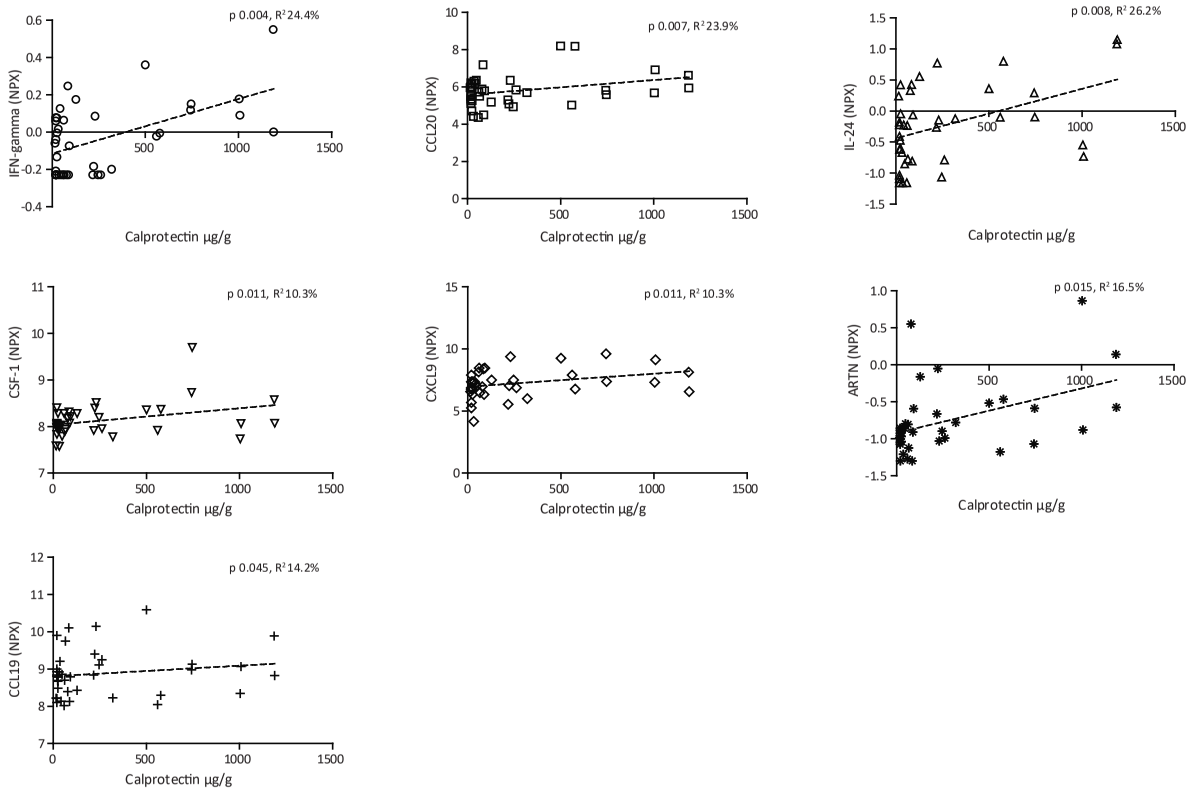
***Abbreviations**:* CI: confidence interval SIRT2: SIR2-like protein 2, ADA: Adenosine Deaminase, CD40: CD40L receptor, STAMPB: STAM-binding protein, CD5: T-cell surface glycoprotein CD5 CD6: T cell surface glycoprotein CD6 isoform, 4E-BP1: Eukaryotic translation initiation factor 4E-binding protein 1, LAP TGF-beta-1: Latency-associated peptide transforming growth factor beta-1, GDNF: Glial cell line-derived neurotrophic factor, TWEAK: Tumor necrosis factor (Ligand) superfamily, member 12, CD244: Natural killer cell receptor 2B4
Notes: all regression models corrected for age and gender # unadjusted p-value < 0.05; adjusted R^2 reflects the regression model including age and gender as predictors.

Supplementary Table 3. Reliable change index for anxiety and depressive symptoms

	No reliable change	Reliable deterioration (increase in score)	Reliable improvement (decrease in score)
	Anxiety symptoms (SCARED or HADS-A)		
CAU	10 (66.7%)	0 (0%)	5 (33.3%)
CBT	5 (38.5%)	0 (0%)	8 (61.5%)
χ^2 =2.227. df = 2. p = .255.			
	Depressives symptoms (CDI or BDI-II)		
CAU	8 (53.3%)	0 (0%)	7 (46.7%)
CBT	5 (38.5%)	1 (7.7%)	7 (53.8%)
χ^2 = 1.150. df = 2. *p* = .567.			

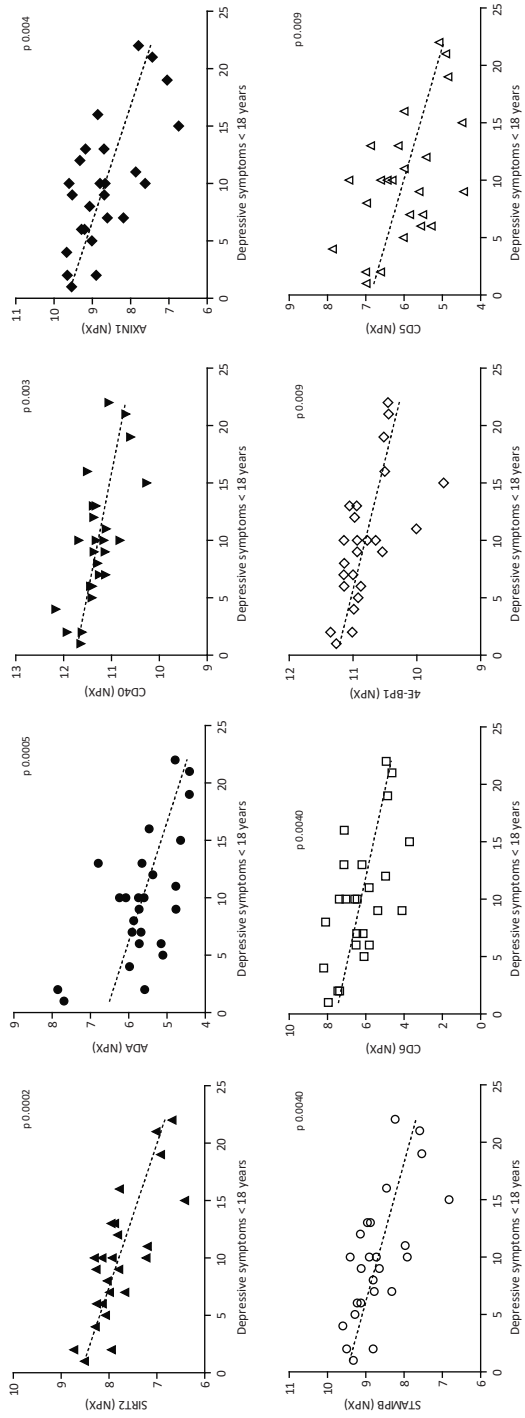
Notes: Numbers in parentheses indicate row percentages. For 2/15 patients allocated to CBT. the Reliable Change Index could not be calculated because 3-month data were incomplete.

SUPPLEMENTARY FIGURES



Supplementary Figure 1. Proteins associated to fecal calprotectin levels (unadjusted p value <0.05)

Scatter plots of the association between fecal calprotectin and 7 proteins. P-values are not corrected for multiple testing.



Supplementary Figure 2. Proteins significantly associated to depressive symptoms in patients < 18 years

Scatter plots of the association between depressive symptoms in patients under the age of 18 with 10 different proteins. P-values are corrected for multiple testing.

PART II
Transition

CHAPTER 10

Self-efficacy did not predict the outcome of the transition to adult care in adolescents with inflammatory bowel disease

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ABSTRACT

Aim

It can be difficult for adolescents with inflammatory bowel disease (IBD) to make the transition from paediatric to adult care. We studied the outcomes of this process and defined what constituted a successful transition.

Methods

In 2008, 50 adolescents who attended our IBD transition clinic completed IBD-yourself, a self-efficacy questionnaire that we had previously developed and validated. We approached the subjects in 2014, two to six years after they transferred to adult care, and 35 agreed to take part in the current study. The outcome of transition was assessed by our newly developed Transition Yourself Score. In addition, the relationship between self-efficacy and the outcome of the transition was measured.

Results

The mean age of the patients was 21.8 years and 69% suffered from Crohn's disease. The transition process was successful in 63% of cases, moderately successful in 31% and failed in 6%. A successful transition was associated with effective use of medication and clinical remission at the time of transfer, but could not be predicted by self-efficacy. The Transition Yourself Score will be validated in future studies.

Conclusion

Nearly two-thirds (63%) of the adolescents who attended the IBD transition clinic had a successful transition to adult care.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disorder of the intestine and manifests in adolescence in about 25% of cases.[1, 2] As IBD is a lifelong disease, all paediatric patients will need to undergo the transfer to adult care. It is advisable to have a transition period to prepare patients and parents for the transfer, which refers to the actual handover of the patient to adult healthcare.[3] A failed transition can adversely affect IBD related outcomes. It can increase non-adherence, non-attendance, hospitalisation rates and the need for surgery.[4, 5] During the transition process, patients, their parents and the paediatric and adult gastroenterologist have specific tasks. Patients should acquire disease knowledge, autonomy and self-management[6, 7], while parents need to stimulate their child's independence and physicians should be knowledgeable about adolescents' developmental and health issues and prepare them for transfer.[3] Transition programmes are designed to facilitate the transition process and increase knowledge and self-management.[3, 8] Self-efficacy, a person's belief in their capability to organise and execute the actions required to deal with prospective situations, is thought to be a prerequisite for self-management.[9, 10] It reflects self-care responsibility and has been shown to be a predictor of readiness to transfer.[11] We previously developed and validated IBD-yourself, a specific IBD knowledge and self-efficacy questionnaire.[12]

The optimal model for IBD transitional care is currently unknown, as is the definition of a successful transition, due to the scarcity of outcome research. We aimed to develop a tool, the Transition Yourself Score, to measure the success of transition. The Transition Yourself Score was applied to our IBD transition cohort to assess transition outcomes one year after transfer. In addition, we assessed the predictive value of self-efficacy for successful transition.

METHODS

Participants

In 2008, 50 patients from our IBD transition clinic participated in the validation study of the self-efficacy questionnaire, IBD-yourself.[12] Of these, 35 gave informed consent to participate in the current study in 2014. Data on patient characteristics, disease type, treatment and outpatient clinic visits after transfer were retrieved from their medical records. The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, The Netherlands.

IBD transition clinic

Adolescents aged 16 to 18 years old with IBD are seen at the outpatient clinic, which is located in the adult gastroenterology department. A multidisciplinary team, consisting of a paediatric gastroenterologist, a paediatric IBD nurse specialist, an adult gastroenterologist and a family therapist, discuss all patients before the start of the clinic. Patients visit the clinic at least four times a year, where they are seen by either the paediatric gastroenterologist or the paediatric IBD nurse specialist. Once a year the adolescent patients also meet the adult gastroenterologist, to get acquainted with the adult healthcare system. During clinic visits, both the nurse and doctors check for disease knowledge, self-efficacy and self-management skills. Around the age of 18, patients are transferred, either within our centre or to a hospital closer to home. The choice of the adult care team depends primarily on the complexity of the disease and secondarily on the patient's preference and where they live. As part of the routine care for all patients, irrespective of their disease severity, an appointment at the gastroenterology department is made within three to six months after transfer. At this time an extensive transfer letter, including the patient's medical history, is sent to the adult medical healthcare provider, with a copy to the patient.

Measurements

Transition Yourself Score

A score reflecting the outcome of the transition process was developed based on previous literature[13] and the outcome of a focus group meeting with IBD experts. The Transition Yourself Score was applied to participants one year after their transfer to adult care. The following items were rated: adherence to visits at the gastroenterology outpatient clinic, adherence to medication and qualitative evaluation of transition by the patient. A pre-test of the score with a representative group of 10 patients resulted in minor adjustments in the language.

We scored the adherence to the visits to the adult gastroenterologist by determining when the patients first appeared in the gastroenterology outpatient clinic. The percentage of missed scheduled outpatient visits within the first year was calculated by dividing the number of missed visits by the number of planned visits times 100. Rescheduled visits were not counted as non-attendance. Adherence to medication was determined by an adherence interview (Table S1).[14] The interview contained 10 questions regarding medication use, missed medication and the experienced burden of the medication regimen. Patients could receive one point per question, with a maximum score of 10. Prescriptions for supplements, such as calcium or iron, were not included in the assessment of medication adherence. Low adherence was indicated by a score below six, medium by a score of six to eight and high by a score of eight or more. At enrolment, patients retrospectively graded the transition process on a 10-point scale, where one was very poor and 10 was excellent and these scores are recorded in Table 1. A total score below five indicated a failed transition, five or six was

moderately successful and above six was successful. For the analysis we combined failed and moderately successful transition into the unsuccessful transition category, to reflect that improvements were needed in this group. We then compared those findings with the group of subjects who had a successful transition.

Table 1. Transition Yourself Score

Items	Score	Frequency (n=35), n (%)
Time to first outpatient visit to adult gastroenterologist		
Unknown or after 12 months	0	1 (2.9)
After 6-12 months	1	3 (8.6)
Within 3-6 months	2	31 (88.6)
Non-attendance rates at outpatient clinic < 12 months after transfer		
>25%	0	2 (5.7)
10-25%	1	3 (8.6)
None / <10%	2	30 (85.7)
Medication adherence		
Low adherence	0	4 (11.4)
Medium adherence	1	17 (48.6)
High adherence	2	5 (14.3)
No medication prescribed[A]		9 (25.7)
Quality of transition (grade 0-10) [B]		
< 5.5	0	0
5.5-7	1	11 (31.4)
>7	2	24 (68.6)
Total score:		
Failed transition	<4	2 (5.7)
Moderate successful transition	5 or 6	11 (31.4)
Successful transition	>6	22 (62.9)

Notes: [A] These patients were given two points in total transition score. B as experienced by the transferred patient

IBD-yourself

IBD-yourself is questionnaire that was previously developed and validated by our research group to explore knowledge about IBD and self-efficacy.[12] It covers a number of domains, such as knowledge of IBD, diagnostic tests and medication use. Higher scores indicated higher overall levels of self-efficacy. As the number of questions could differ between patients, we just provided scores for each domain and no total score (Table S2).[12]

Clinical outcome one year after transfer

Data regarding relapses, disease related complications, admissions, surgery and pregnancies were retrieved from medical charts. Clinical relapse was defined as a relapse with a change in treatment strategy and, or, hospital admission.

Statistical analysis

Statistical analyses were completed using SPSS 18.0 for Windows (SPSS Inc, Chicago, USA). Significance was set at $p<0.05$. Descriptive statistics were calculated as percentages for discrete data and medians with interquartile ranges (IQR) for continuous data. The chi-square test or Fisher's exact test was used to analyse categorical data. Correlation between the IBD-yourself and transition success was examined using Spearman's correlation coefficient and the Mann-Whitney *U* test.

RESULTS

Patients' characteristics

There were 35 adult patients who gave their informed consent, with a median age of 21.9 years and interquartile range (IQR) of 21.1-22.6. Of the 50 patients who took part in the 2008 study, two declined participation, one patient had died from a metastasised rectal adenocarcinoma due to Hermansky Pudlak syndrome and 12 patients had been lost to follow up. The clinical and demographic characteristics are shown in Table 2, in the column total. The baseline characteristics of the 35 participants and 15 non-participants did not differ (data not shown), except for educational status. Of the non-participants, 80% had low educational status compared to 46% of the participants.

Outcome of transition at one year after transfer

Almost 90% of the patients visited the adult outpatient clinic in the first three to six months after transfer. In addition, 85% of the patients missed less than 10% of their outpatient visits in the first year after transfer. Most patients had medium medication adherence. Almost 70% of patients valued the quality of their transition as good, scoring it above a seven. When we used the total Transition Yourself Score, the transition was successful in 22/35 (63%) patients, moderately successful in 11 (31%) and failed in two patients (6%) (Table 1). A female patient with Crohn's disease failed the transition as she did not adhere to her medication, did not appear for her first appointment and presented more than one year after transfer in the emergency department with a clinical relapse. The other patient was a male patient with Crohn's disease who was transferred to a community hospital, but was lost to follow up after transfer.

Table 2. Patient characteristics

	Total (n=35)	Unsuccessful transition¥ (n=13)	Successful transition (n=22)	p value§
Age at diagnosis (years), (median, IQR)	13 (12-15)	14 (11.5-15.0)	13 (12.0-15.0)	0.875
Months in transition clinic before transfer (median, IQR)	13 (5-18)	10 (5.0-18.0)	13 (4.8-17.8)	0.811
Disease duration at transfer (median, IQR)	7 (7-10)	4.1 (3.0-6.9)	4.5 (2.9-6.1)	0.864
Years after transfer at inclusion in study				1.0
<2	2 (5.7%)	1 (7.7%)	1 (4.5%)	
2-4	20 (57.1%)	7 (53.8%)	13 (59.1%)	
4-6	13 (37.1%)	5 (38.5%)	8 (36.4%)	
Gender (male), no (%)	15 (42.9%)	3 (23.1%)	12 (54.5%)	0.070
Disease type, CD, no (%)	24 (68.6%)	9 (69.2%)	15 (68.2%)	1.0
Medication at transfer‡				0.840
Aminosalicylates	9 (25.7%)	3 (23.1%)	6 (27.2%)	
Immunomodulators	25 (71.4%)	9 (69.2%)	16 (72.7%)	
Anti-TNF	12 (34.2%)	5 (38.5%)	7 (31.8%)	
Prednisone	2 (5.7%)	1 (7.7%)	1 (4.5%)	
No medication	1 (2.9%)	0	1 (4.5%)	
Active disease during transfer	5 (14.3%)	4 (30.8%)	1 (4.5%)	0.052
Relapse within first year after transfer	10 (28.6%)	5 (38.5%)	5 (22.7%)	0.444
Educational level				0.467
Low	16 (45.7%)	7 (53.8 %)	9 (40.1%)	
Medium	13 (37.2%)	3 (23.1%)	10 (45.5%)	
High	6 (17.1%)	3 (23.1%)	3 (13.6%)	

Notes: ‡ Some patients were prescribed more than one kind of medication ¥ moderately successful and failed transition § successful versus unsuccessful transition. Percentages are displayed as column percentages

Factors influencing outcome of transition

The clinical and demographic characteristics did not differ significantly between the group with successful and unsuccessful transition (Table 2). In the group with unsuccessful transition. 80% had active disease before their transfer to adult care and this approached significance (p=0.052). Female patients were more likely than males to have an unsuccessful transfer (p=0.069) (data not shown).

Relation between adolescent self-efficacy and successful transition

Spearman's correlation showed a significant correlation for the outcome of transition and the IBD-yourself domain that covered actual behaviour in medication use (r=0.397, p=0.025, n= 35). In parallel, adolescents with a successful transition had significantly higher scores in the domain of actual behaviour in medication use (Mann Whitney *U* test: U=60.0, z=-2.208, p=0.027). As shown in Table 3, the scores of each IBD-yourself domain were divided in three groups, namely low, medium and high. A non-significant trend was seen in seven of the domains, with more patients having a high score in the successful transition group.

Clinical outcome at one year after transfer

Of the 35 patients, 10 patients (29%) had a relapse with clinical consequences in the first year after transfer. In 50% of these patients, the outcome of their transition was scored as either moderately successful or unsuccessful. In contrast, the transition was unsuccessful in 30% of patients without relapsing disease. No significant differences were found between the patients with or without relapse with respect to the outcome of their transition, therapy adherence and missed outpatient clinic visits (data not shown). Of the 35 patients, two underwent surgery, namely resection of the remaining colon after hemi-colectomy and

Table 3. IBD- yourself and outcome of transition

Domains IBD Yourself	Unsuccessful transition (failed&moderate) (n=13), n (%)	Successful transition (n=22), n (%)
Self-efficacy in knowledge of IBD (n=35)		
12-14 points	2 (15.4%)	1 (4.5%)
15-17 points	6 (46.2%)	12 (54.5%)
18-20 points	5 (38.5%)	9 (40.9%)
Self-efficacy in knowledge of diagnostic tests (n=35)		
14-17 points	2 (15.4%)	4 (18.2%)
18-21 points	7 (53.5%)	8 (36.4%)
22-24 points	4 (30.8%)	10 (45.5%)
Self-efficacy in knowledge of medication (n=27)		
17-22 points	4 (40.0%)	4 (23.5%)
23-27 points	4 (40.0%)	6 (35.3%)
28-32 points	2 (20.0%)	7 (41.2%)
Actual behaviour medication use (n=32)*		
7-10 points	1 (10.0%)	2 (9.1%)
11-14 points	7 (70.0%)	3 (13.6%)
15-17 points	2 (20.0%)	17 (77.3%)
Self-efficacy in skills for independent outpatient clinic visits (n=35)		
12-20 points	2 (15.4%)	3 (13.6%)
21-28 points	5 (38.5%)	9 (40.9%)
29-36 points	6 (46.2%)	10 (45.5%)
Actual behaviour outpatient clinic (n=26)		
4-6 points	10 (90.9%)	9 (60.0%)
7-8 points	1 (9.1%)	6 (40.0%)
Self-efficacy in coping with IBD (n=34)		
5-8 points	1(8.3%)	1 (4.5%)
9-12 points	4 (33.3%)	6 (27.3%)
13-16 points	7 (58.3%)	15 (68.2%)
Self-efficacy in knowledge of transition process (n=31)		
32-42 points	3 (25.0%)	2 (10.5%)
43-52 points	4 (33.3%)	8 (42.1%)
53-62 points	5 (41.7%)	9 (47.4%)
Self-efficacy in transfer readiness (n=34)		
4-6 points	10 (76.9%)	14 (66.7%)
7-8 points	3 (23.1%)	(33.3%)

*p<0.05

resection of perianal skintags, one Crohn's disease patient developed a perianal fistula and received antibiotics and two patients developed a new extra intestinal manifestation (arthralgia). One patient became pregnant during anti-tumour necrosis factor treatment and delivered a healthy baby. None of the patients developed a malignancy during the study period.

DISCUSSION

Our study showed that in our IBD transition clinic, transition was successful in 63% of patients and moderately successful in 31% of patients. This modest success ratio indicates that there is room for improvement in our IBD transition strategy, both in general and in individual patients.

To our knowledge, only one previous study has described the outcome of transition in IBD care.[15] Non-adherence rates were in accordance with our cohort, but higher rates of hospitalisation and disease complications were found after transfer. However, it is not clear at what point in the transition process this was assessed.

The outcome of transition has also been described in paediatric patients with other chronic diseases with success varying from 42-53% of patients.[16-19] All these studies used a restricted definition of success, namely attending the first one or two visits in adult care. In our clinic the transition process starts early, at the age of 16, with early involvement of the adult gastroenterologist. This could explain the relatively higher rates of successful transition in our cohort compared to the cohorts of patients with other chronic diseases.

A scoring system for the outcome of transition in IBD is currently not available and we decided to develop such an instrument, the Transition Yourself Score. In 2015, a ranking list with key elements and indicators of successful transition in general was published.[13] This list, together with previous literature, supports the elements of the Transition Yourself Score.[13, 19-21] A qualitative evaluation by the patient was included because patient experiences are of essential importance, reflect continuity of care and should be taken into account.[13]

We hypothesised that patient or disease related factors can influence the outcome of transition as well as the actual transition clinic. Our study indicated that female patients and patients with an active disease before transfer might be at risk for unsuccessful transition.

Unsuccessful transition may have serious consequences, such as non-adherence, hospitalisation or surgery. To our knowledge, there have not been any studies that have measured successful transition and correlated these to the clinical outcomes after transfer. Unfortunately, because of the limited size of our study, we were not able to do that either.

As discussed earlier, it has been suggested that self-efficacy is a prerequisite for self-management and transfer readiness.[10, 11] Whitfield et al.[22] investigated self-efficacy in adolescent IBD patients and found that mean self-efficacy scores were higher in older

patients, but not in patients with longer disease duration. Remarkably, communication with the doctor did not improve with age and about 80% of patients above 18 years of age reported that they were not independent when it came to disease management tasks. Unfortunately, this study did not assess if patients actually used the skills they claimed to possess. It could be that self-efficacy does not always correlate with actual behaviour. Our study showed that actual behaviour could be associated with transition success. Since the publication of the IBD-yourself, another self-efficacy scale for adolescents and young adults has been developed and validated, but studies using this scale have not yet been published.[23]

This study had several limitations: the recruitment from a single centre, the retrospective nature and the small sample size limited the statistical analysis and generalisability. In addition, recall bias could have influenced the patients' recollections of the item quality of the transition process, since some patients participated several years after their transfer. Moreover, socioeconomic status was higher in participants than non-participants, which could have influenced the results of our study. Furthermore, the Transition Yourself Score needs to be validated and IBD-yourself needs to be compared to other measures of self-efficacy for further validation. Lastly, the generalisability may be limited because of country specific transition approaches, but the general elements chosen to classify the success of transition can be tailored to each local situation.

CONCLUSION

Despite these limitations, this study was the first to evaluate the outcome of transition in IBD by using a new score, the Transition Yourself Score. We showed that, after attending our IBD transition clinic, 63% of patients had a successful transition. The IBD-yourself, which measured self-efficacy, did not predict a successful transition, which can question the importance of self-efficacy. We stress the importance of not only assessing self-efficacy or self-management, but also the outcome of transition and clinical disease course after transfer. If predictors for a successful transition can be identified, then transition programmes can be optimised. The Transition Yourself Score is a simple tool to assess the efficacy of transition programmes, but it needs to be validated.

REFERENCES

1 Baumgart DC, Bernstein CN, Abbas Z, 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):639-644.

2 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol*. 2004;18(3):509-523.

3 Goodhand J, Hedin CR, Croft NM, Lindsay JO. Adolescents with IBD: the importance of structured transition care. *J Crohns Colitis*. 2011;5(6):509-519.

4 Bollegala N, Brill H, Marshall JK. Resource utilization during pediatric to adult transfer of care in IBD. *J Crohns Colitis*. 2013;7(2):e55-60.

5 Cole R, Ashok D, Razack A, Azaz A, Sebastian S. Evaluation of Outcomes in Adolescent Inflammatory Bowel Disease Patients Following Transfer From Pediatric to Adult Health Care Services: Case for Transition. *J Adolesc Health*. 2015;57(2):212-217.

6 Trivedi I, Keefer L. The Emerging Adult with Inflammatory Bowel Disease: Challenges and Recommendations for the Adult Gastroenterologist. *Gastroenterol Res Pract*. 2015;2015:260807.

7 Wright EK, Williams J, Andrews JM, et al. Perspectives of paediatric and adult gastroenterologists on transfer and transition care of adolescents with inflammatory bowel disease. *Intern Med J*. 2014;44(5):490-496.

8 Escher JC. Transition from pediatric to adult health care in inflammatory bowel disease. *Dig Dis*. 2009;27(3):382-386.

9 Bandura A. Self-efficacy. In: Ramachaudran ed. Encyclopedia of human behavior,Vol. 4. New York: Academic Press, 1994:71-81.

10 Marks R, Allegrante JP, Lorig K. A review and synthesis of research evidence for self-efficacy-enhancing interventions for reducing chronic disability: implications for health education practice (part II). *Health Promot Pract*. 2005;6(2):148-156.

11 van Staa A, van der Stege HA, Jedeloo S, Moll HA, Hilberink SR. Readiness to transfer to adult care of adolescents with chronic conditions: exploration of associated factors. *J Adolesc Health*. 2011;48(3):295-302.

12 Zijlstra M, De Bie C, Breij L, et al. Self-efficacy in adolescents with inflammatory bowel disease: a pilot study of the "IBD-yourself", a disease-specific questionnaire. *J Crohns Colitis*. 2013;7(9):e375-385.

13 Suris JC, Akre C. Key elements for, and indicators of, a successful transition: an international Delphi study. *J Adolesc Health*. 2015;56(6):612-618.

14 Mackner LM, Crandall WV. Oral medication adherence in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2005;11(11):1006-1012.

15 Bennett AL, Moore D, Bampton PA, Bryant RV, Andrews JM. Outcomes and patients' perspectives of transition from paediatric to adult care in inflammatory bowel disease. *World J Gastroenterol*. 2016;22(8):2611-2620.

16 Reid GJ, Irvine MJ, McCrindle BW, et al. Prevalence and correlates of successful transfer from pediatric to adult health care among a cohort of young adults with complex congenital heart defects. *Pediatrics*. 2004;113:e197-205.

17 Gleeson H, Davis J, Jones J, O'Shea E, Clayton PE. The challenge of delivering endocrine care and successful transition to adult services in adolescents with congenital adrenal hyperplasia: experience in a single centre over 18 years. *Clin Endocrinol (Oxf)*. 2013;78(1):23-28.

18 Hazel E, Zhang X, Duffy CM, Campillo S. High rates of unsuccessful transfer to adult care among young adults with juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*. 2010;8:2.

19 Jensen PT, Karnes J, Jones K, et al. Quantitative evaluation of a pediatric rheumatology transition program. *Pediatr Rheumatol Online J*. 2015;13:17.

20 Fredericks EM, Dore-Stites D, Well A, et al. Assessment of transition readiness skills and adherence in pediatric liver transplant recipients. *Pediatr Transplant*. 2010;14(8):944-953.

21 Andemariam B, Owarish-Gross J, Grady J, Boruchov D, Thrall RS, Hagstrom JN. Identification of risk factors for an unsuccessful transition from pediatric to adult sickle cell disease care. *Pediatr Blood Cancer*. 2014;61(4):697-701.

22 Whitfield EP, Fredericks EM, Eder SJ, Shpeen BH, Adler J. Transition readiness in pediatric patients with inflammatory bowel disease: patient survey of self-management skills. *J Pediatr Gastroenterol Nutr*. 2015;60(1):36-41.

23 Izaguirre MR, Taft T, Keefer L. Validation of a Self-efficacy Scale for Adolescents and Young Adults With Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr*. 2017;65(5):546-550.

SUPPLEMENTARY TABLES

Table S1. Questions adherence interview

1	Did you forget to take your IBD medication (pills, tablets, enemas or suppositories) in the past two weeks or did you forget your last planned infusion/injection? (Yes=0, No=1)
2	Did you skip your medication in the past two weeks because you think they do not help or even make you feel worse? (Yes=0, No=1)
3	When you are not at home, do you bring along your IBD medication? (Yes=1, No=0)
4	Sometimes medication is not taken on purpose (for other reasons than forgetting), did that happen to you past two weeks? (Yes=0, No=1)
5	Did you take your medication(s) for IBD yesterday? And (if you get infusions or take injections): did you receive your most recent planned infusion/injection? (Yes=1, No=0)
6	Do you sometimes skip your medication(s) when you feel good and have no symptoms of your disease? (Yes=0, No=1)
7	Are you bothered by the fact that you have to take medication? (yes=0, no=1)
8	Do you find it hard to remember to take or inject your medication or go to the hospital for your infusion? (Yes=0, No=1)
9	Do you receive help from somebody else in remembering to take your medication or plan your infusions? (yes=0, no=1)
10	When you run out of medication, do you actively arrange a new prescription (yes=1, no=0)

Table S2. Domains and scoring IBD-yourself (20)

	Domain	Number of questions	Score range
1	VAS on general independency	1	0-100
2	VAS on perceived disease burden	1	0-100
3	Self-efficacy in knowledge of IBD	5	0-20
4	Self-efficacy in knowledge of diagnostic tests	6	0-24
5	Self-efficacy in medication use	8	0-32
6	Actual behaviour regarding medication use	4	0-20
7	Self-efficacy in skills for independent outpatient clinic visits	9	0-36
8	Actual behaviour at the outpatient clinic	4	0-8
9	Self-efficacy in coping with IBD	4	0-16
10	Self-efficacy in knowledge of transition process	14	0-70
11	Self-efficacy in transfer readiness	2	0-8

CHAPTER 11

Health care transition outcomes in inflammatory bowel disease: a multinational delphi study

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ABSTRACT

Background

Transition programs are designed to prepare adolescent Inflammatory Bowel Disease (IBD) patients for transfer to adult care. It is still unclear which outcome parameters define 'successful transition'. Therefore, this study aimed to identify outcomes important for success of transition in IBD.

Methods

A multinational Delphi study in patients, IBD-nurses and paediatric and adult gastroenterologists was conducted. In Stage 1, panellists commented on an outcome list. In Stage 2, the refined list was graded from 1-9 (least-very important), by an expert and a patient panel. In stage 3, the expert panel ranked important outcomes from 1 to 10 (least-most important). Descriptive statistics and Mann-Whitney-U tests were performed.

Results

The final item list developed in Stage 1 was tested by the expert (n=74 participants,52.7% paediatrics) and patient panel (n=61, aged 16-25 y, 49.2% male). Respectively, 10 and 11 items were found to be important by the expert and patient panel. Both panels agreed on 8 of these items, of which 6 reflected self-management skills. In Stage 3, the expert panel formed a top-10 list. The three most important items were: decision making regarding IBD (mean score 6.7), independent communication (mean score 6.3) and patient satisfaction (mean score 5.8).

Conclusion

This is the first study identifying outcomes that IBD-health care providers and patients deem important factors for successful transition. Self-management skills were considered more important than IBD-specific items. This is a first step to further define success of transition in IBD and subsequently evaluate the efficacy of different transition models.

INTRODUCTION

In up to 25% percent of patients inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis [UC]) manifests during late childhood or adolescence.[1,2] As IBD is a lifelong disease all of these patients will need to undergo transfer of paediatric to adult care. To optimise this transfer and minimise adverse outcomes, it is advised to have a transition period where patients (and parents) are prepared for the actual transfer.[3,4] Transition is defined as the purposeful planned movement and preparation of adolescents and young adults with chronic medical conditions from child-centred to adult-oriented healthcare systems.[5] In the transition process the patient, parent, paediatric gastroenterologist, adult gastroenterologist and IBD-nurse have specific tasks.[3,6] Patients should acquire (disease) knowledge, autonomy and self-management.[7-11] Parents need to allow their adolescent child more independence. Physicians and nurses should support the transition process, be knowledgeable of adolescents' developmental and health issues and prepare adolescents for the changes that will be encountered in the adult health care system.[6,12,13] Transitional programs are designed to facilitate all these processes [12,14,15] and prepare the individual patient for his/her transfer by helping to increase knowledge as well as to reach a higher level of self-management.

As summarised in the UK guideline on transition in patients with chronic digestive diseases, inadequate transition arrangements have been associated with adverse outcomes across several medical conditions, such as diabetes[16], heart disease[17] and sickle cell disease.[18] In IBD, studies investigating the impact of structured transition are scarce. Studies showed that the lack of a structured transition service negatively impacted adherence[19,20] and attendance[19,20], and was associated with a higher hospitalisation and surgery rate.[19] On the other hand, structured transition programmes have been shown to result in better disease related outcomes[21,22], improved self- and disease knowledge and improved quality of life.[22,23]

Although many different models for transitional care have been proposed in IBD (e.g. [4,12,14,24]), there is no evidence that one particular model is more effective than others.[3] In addition, a clear definition on success of transition in IBD is lacking.[12,19,25] Two recent studies identified general, non-disease specific indicators for success of transition in adolescent medicine. Outcomes such as quality of life, continuity of care, self-management, therapy knowledge and adherence were recognised as important outcomes for success of transition.[26,27] Continuity of care is considered a core issue[27], this was also emphasised in a systematic review that showed engagement in adult care (attending first (two) visits) and retention in adult care (continuing to attend scheduled clinic appointments) were often used in studies investigating transition in chronically ill adolescents.[28]

In another recent study, in IBD patients, their parents and paediatric health care providers, were asked to select 5 of items from the Transition Readiness Assessment Questionnaire (TRAQ), thought to be important for successful transition. All three stakeholders had a different selection of items[29], but all selected items related to adherence,

communication with the doctor, calling in case of problems or adverse reactions to medication.[29]

As emphasised in the European Crohn's and Colitis Organisation (ECCO) topical review on transitional care in IBD, it is important to identify objective outcome measures that can be used to define successful transition in IBD.[3] Therefore, the primary aim of this study was to identify outcomes that health care providers working with IBD patients think are important for success of transition in IBD, using a Delphi procedure in 3 types of health care providers working with IBD patients. Our secondary aim was to compare the outcomes identified by health care providers to outcomes selected by a patient panel, which was recruited in second instance.

MATERIALS AND METHODS

To identify health care transition outcomes for IBD, we conducted a three-stage Delphi[30-33] process, a commonly used method for reaching consensus. The survey consisted of three rounds, which were designed and distributed using an online survey programme (SurveyMonkey). At each stage, all experts were contacted via e-mail explaining the task to be done, and a web link was included to complete the questionnaire. At each round, participants were given 2 weeks to send in their reply. Every two weeks a reminder was sent to all participant who had not yet replied. After 3 reminders, the web link was closed. We decided to give only factual feedback after each round, to avoid influencing panellists' opinion.[34] The study started July 2016 and ended March 2018.

Delphi Panel

The Delphi panel was composed based on a practical approach. To achieve international consensus, experts in the field of IBD from around the world were invited to participate. Our main aim was to create a balanced panel of all health care providers working with IBD patients in the transition process. Therefore, paediatric gastroenterologists, (adult) gastroenterologists, paediatric and adult IBD nurses were invited. The first step in composing the Delphi Panel was inviting all members of the 'Paediatric IBD Porto and Interest Groups of European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)' and the authors of the European Crohn's and Colitis Organisation Topical Review on transitional care in IBD.[3] The 'Paediatric IBD Porto Group' is a group of 36 paediatric IBD experts from the (ESPGHAN) whose goals are to generate collaborative international research and to provide a leadership role concerning current diagnosis and management of IBD in children. The IBD Interest Group is an open growing group of 48 ESPGHAN members at the time of the study who participate in all activities generated by the Porto group such as collaborative studies and guidelines preparation. Both groups mostly consist of paediatric gastroenterologist from Europa as well as Israel and some from North America. A total of 91

panellists were invited and were asked to participate as well as invite a paediatric IBD-nurse, adult gastroenterologist and adult IBD nurse, from their own hospital. From the 91 invited panellists 31 (34%) agreed to participate. The 31 panellists invited another 43 physicians or nurses and vouched for their credentials. In addition, the website of the hospital where they worked was also checked to double check their credentials. This resulted in 74 panellists (here-after 'Expert panel or panellists'; Figure 1).

After completing the Delphi stages in the expert panel, we concluded that also including the perspective of the adolescent and young adult patients would be of great added value. Therefore, we proceeded to include adolescent and young adult patients, hereafter defined as 'patient panel or patients'. The patients were recruited from two sources: (a) an ongoing study into transition at the IBD outpatient transition clinic in the Erasmus Medical Centre in Rotterdam (the study was approved by the Medical Ethics Committee and patients provided informed consent), and (b) young adult IBD patients from the Dutch Crohn and Colitis patient organisation. All patients were given three weeks to complete the survey and provided information with regard to their sex, age, disease duration and disease type. The patient panel participated in stage 2 only, but were asked after completing stage 2 if they thought an item was missing.

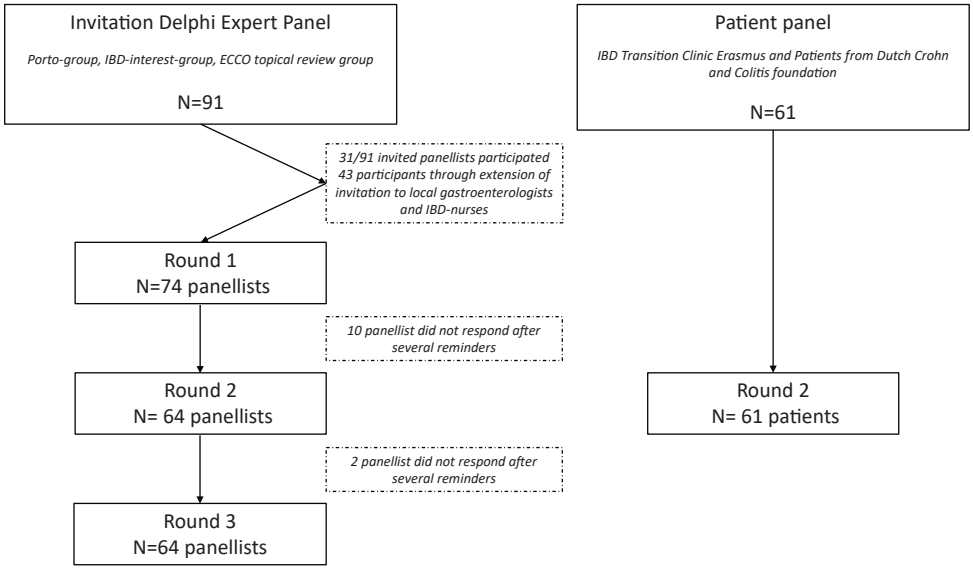


Figure 1. Flowchart composition Delphi panel

Stage 1

In this first stage, a literature review[4,19,20,26-28,35,36] was performed and a list with items related to outcome of transition was created. This list was sent to the research team, and was discussed in a joined meeting. The 23-item list was sent to all 74 participants of the expert panel (Figure 2A). In stage 1, participants were asked to comment on the list, for example to state if they thought an item should be removed from the list (for reasons of not being associated to outcome of transition), merged with another item, or rephrased. Additionally, participants were invited to add new items to the list. Lastly, all panellists were asked to complete a short form to collect demographic characteristics, such as their name, academic degree(s), department, position and details about the hospital where they work (name, city, country and hospital type (community vs tertiary hospital)).

The research team analysed all responses from stage 1, at first each member evaluated the responses individually, and in a meeting consensus was reached. Criteria to accept items were (a) suggestions to refine or specify items if it improved clarity or (b) every new suggested item related to outcome of transition. Items were rejected or deleted if (a) they were not related to outcome of transition (but to for example organisation or availability or the IBD transition clinic) or (b) showed large similarity with an item already on the list. Similar outcomes were categorised into themes. Country-specific items were deleted, as our aim was to achieve international consensus.

Stage 2

In the second stage, participants were given a brief summary of the results of stage 1, indicating that some items were deleted, rephrased or reformulated, and explaining that the new item list with outcomes of transition consisted of 26 items (Figure 2B). In stage 2, the panellists were asked to rate each item on a scale from 1 (least important outcome of transition) to 9 (very important outcome of transition). At all times, participants could contact the research team to comment or clarify. Before start of the study, the research team agreed to use the 'Rand UCLA criteria for agreement', often used in Delphi studies [26,37], to categorize the outcomes as important, equivocal or not important. A threshold for retaining transition outcomes was established, based on the overall level of agreement among participants. Outcomes were labelled important when they had a mean of 7-9 without disagreement, outcomes rated 4 to 6 were considered equivocal, and outcomes rated 1 to 3 were rated as not important. Disagreement was defined as 30% of ratings are in lower third (rating 1-3) and 30% upper third (7-9).[38] Two members of the research team (GB and JCE) analysed the responses and calculated means for each outcome and determined whether disagreement was present. This stage was also completed by the adolescent and young adult patient panel, recruited in second instance.

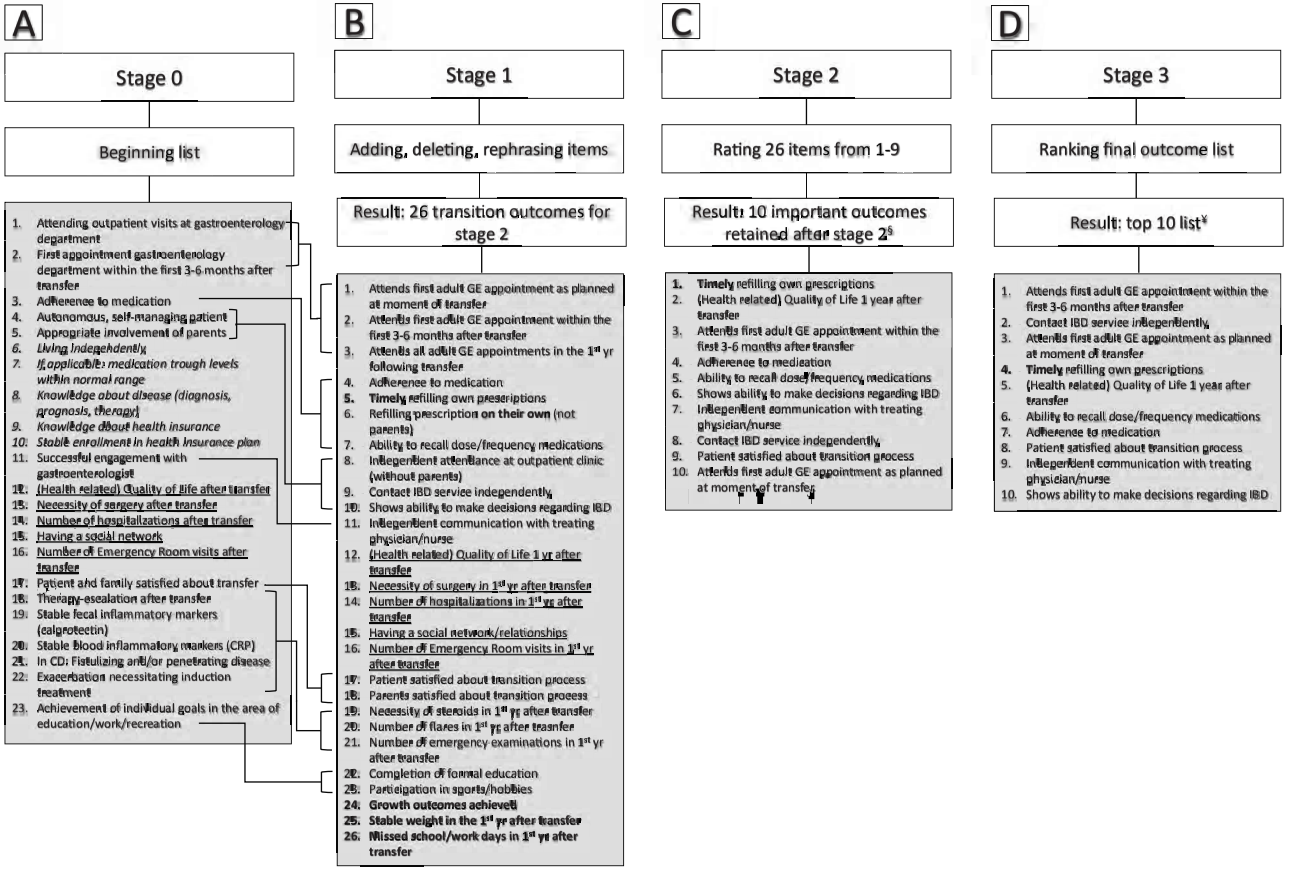


Figure 2. Summary 3 stage Delphi procedure

Notes: panel A: italic: removed items, underlined: items not changed in stage 1. Panel B: bold items are newly suggested items. Panel C: § order of the items based on lowest (1) to highest (10) mean score Table 3. panel D: ¥ 10 reflecting most important, 1 least important.

Stage 3

In the third stage, the expert panel was given a brief summary of the results of stage 2, indicating that using the Rand UCLA criteria, the item list with 26 items was reduced to ten. In stage 3, this list with 10 important outcomes was sent to the panel with the request to rank the items from 1 to 10, with '1' meaning least important outcome of transition, and '10' reflecting essential outcome of transition. It was emphasised that each item could receive only 1 position between 1-10. Thus, the expert panel was now instructed to rank the important items from stage 2 in a top 10 list, forcing them to re-prioritise the items and state which ones they consider most important.

Statistical analysis

Descriptive statistics were used to summarise the panellists' opinions for closed questions at each round. Data were analysed with SPSS 23 (IBM) and were conducted blind to the names of the participants. Open comments were analysed qualitatively and clustered into main themes. For stage 2, according to the 'Rand UCLA criteria for agreement' mean scores were calculated per item, and proportions were given to determine disagreement. Because of a non-normal distribution of the data, subgroups (e.g. patients panel vs expert panel or paediatric vs adult providers) were compared using a Mann Whitney U test. Holms correction for multiple testing was used[39], a corrected p-value below $p<0.05$ was considered significant.

RESULTS

Delphi Panel

A total of 74 participants, from 17 countries, agreed to participate in the Delphi expert panel. Seventy seven percent of the experts came from Europe (n=57; Austria n=2, Croatia n=1, Czech Republic n=2, Denmark n=3, England n=18, Finland n=1, Germany n=2, Greece n=2, Hungary n=2, Italy n=1, Lithuania n=1, Scotland n=7, Spain n=1, the Netherlands n=14), the other participants came from Israel (n=8), Canada (n=3) and the United States (n=6) (Table 1). Participants belonged to one of the four core groups: paediatric gastroenterologist, paediatric IBD nurse, gastroenterologist or adult IBD nurse. The clinical research fellow was a medical doctor (MD) working in paediatrics ('paediatric gastroenterologist group'), the transition manager had a Bachelor of Science in adolescent care ('paediatric nurse group') and the fellow paediatric gastroenterology was an MD working in paediatrics ('paediatric gastroenterologist group'). Of the 74 panellists, 40.5% were male, 91.9% worked in a tertiary hospital, 52.7% worked in the paediatric department and 30% of panellists were IBD nurses (Table 1).

Table 1. Demographic characteristics expert panel (n=74)

		N. %
Gender	Male, %	40.5
Hospital Type	Community Hospital	6 (8.1)
	Tertiary Hospital	68 (91.9)
Department	Paediatrics	39 (52.7)
	Gastroenterology	29 (39.2)
	Internal Medicine	6 (8.1)
Position	Paediatric Gastroenterologist	28 (37.8)
	Paediatric IBD nurse	10 (13.6)
	Gastroenterologist	22 (29.7)
	Adult IBD nurse	11 (14.9)
	Clinical research fellow	1 (1.4)
	Transition manager	1 (1.4)
	Fellow paediatric Gastroenterology	1 (1.4)
Continent of origin	Europe	57 (77.0)
	North America	9 (12.2)
	Asia	8 (10.8)

Patient Panel (only participating in stage 2)

A total of 61 adolescent and young adult patients were recruited. 67.2% originated from the IBD-transition clinic in the Erasmus Medical Centre, 49.2% was male and mean age was 18.7 years (Table 2).

Table 2. Demographics patient panel (n=61)

		N. % or Median (IQR)
Recruited from	Dutch Crohn and Ulcerative Colitis Patient organisation	20 (32.8)
	IBD Transition Clinic Erasmus Medical Centre	41 (67.2)
Age (years)	Range	16.5-24.7
	Median (IQR)	18.7 (18.1-20.1)
Gender	Male	30 (49.2)
Disease duration (years)	Range	1-18
	Median (IQR)	5.0 (3.0-7.0)
Disease type	Crohn's disease	34 (55.7)
	Ulcerative Colitis	23 (37.7)
	IBD unclassified	4 (6.6)

Abbreviations: IQR: interquartile range

Stage 1

All 74 panellists included in the expert panel responded to stage 1. Many panellists responded with suggestions for rephrasing of items already on the list, such as timely medication refill, refilling own prescriptions. Using the suggestions from the panellists, several items were rephrased, split into more parts or specified (see Figure 2A and B). Five items were removed from the list (italic items Figure 2A) for the following reasons: Items 7, 9 and 10 were removed because of their country- and patient-specific nature. In addition, items 6 and 9 were removed because they were not considered to reflect outcome of transition, and other items reflecting autonomy and knowledge were already on the list. Three new items were suggested by the panel and added to the list: growth target achieved, stable weight and missed school/work days (items 24-26 Figure 2B). The new list consisted of 26 items (Figure 2B). Some panellists also suggested items only reflecting disease related knowledge and organisation of the transition process (e.g. good collaboration of paediatric and adult gastroenterologist), and these were not used to refine the list with outcomes.

Stage 2

Of the 74 panellists in the expert panel, 64 (86.5%) responded to stage 2, rating each item with a number from 1-9 (9=most important outcome for transition). Of the 64 remaining participants, 14 were IBD-nurses (21.8%), 28 (43.8%) paediatric gastroenterologists and 22 (34.4%) gastroenterologists. Nine out of 10 non-responders worked in a tertiary hospital (one paediatric gastroenterologist, seven IBD nurses, one research fellow, one transition manager).

Table 3 shows the mean ratings for each of the 26 items for both the expert and the patient panel. For the expert panel, 10 items had a mean score above 7 without disagreement, indicating important outcomes. Top-5 outcomes at this stage were (starting with the most important item): Attends first adult GE appointment as planned (mean 7.92, Standard Deviation [SD] 1.4), patient satisfied about transition process (mean 7.89, SD 1.5), contacting IBD service independently (mean 7.81, SD 1.1), independent communication (mean 7.79, SD 1.2) and shows ability to make decisions regarding IBD (mean 7.59, SD 1.2). The least important outcomes were 'necessity surgery', 'independent attendance outpatient clinic', 'participation sports/hobbies', 'necessity steroids', and 'stable weight'. Continent of origin did not influence grading. Female members of the expert panel gave a significantly higher grade to the items 'patient satisfaction' (mean males 7.2(SD 1.6); mean females 8.4 (SD 1.0); p 0.008), 'Parental satisfaction' (mean males 6.1(SD 1.9); mean females 7.6(SD 1.3); p 0.008), and 'Growth outcomes achieved' (mean males 5.1(SD 2.3); mean females 7.0(SD 2.6); p 0.024).

For the patient panel, 11 of the 26 items had a mean score above 7 without disagreement. The top five outcomes were (starting with the most important item): independent communication (mean 8.39, SD 0.8), shows ability to make decisions regarding IBD (mean 8.16, SD 1.3), adherence to medication, (mean 8.08, SD 1.6), ability to recall

dose/frequency medication (mean 7.92, SD 1.5) and timely refilling own prescriptions (mean 7.82, SD 1.7). Least important outcomes were: 'necessity of surgery', 'necessity of steroids', number of 'hospitalisations', 'ER visits' or 'flares' (Table 3). No additional items related to success of transition were suggested by the patient panel. Sex did not influence grading within the patient panel (data not shown).

Comparing the grades from expert (n=64) and the patient (n=57) panel (Table 3), showed that both the patient and the expert panel identified the same 8 items as important (mean grades for these items were quite similar (<1 point difference between both groups). Additionally, the patient panel found 'attends all GE appointments in first year following transfer', 'parents satisfied with transition' and 'refilling prescriptions on own' important, and the expert panel considered 'attend first GE appointment as planned' and 'within the first 3-6 months after transfer' important. For some of the 'non-important' items (mean < 7) differences between both panels were large: disease related outcomes (Items 13,14,16,19-21) and 'school/work absence' (item 26) received a significantly lower mean score by the patient panel (range 2.6-3.3) compared to the expert panel (range 5.5-6.6).

Comparing the different providers within the expert panel (adult (n=32) vs paediatric (n=32) health care providers; paediatric (n=28) vs adult (n=22) gastroenterologists; nurses (n=13) to physicians (n=50)) did not show significant differences after correction for multiple testing.

Stage 3

Of the 64 experts, 62 responded to stage 3. Table 4 and Figure 2D display the top-10 ranking of the important outcomes from stage 2. For the panel as a whole 'ability to make decisions regarding IBD' (mean 6.7, SD 2.7), 'independent communication' (Mean 6.3, SD 2.8) and 'patient satisfaction' (mean 5.8, SD 2.4) were the top-3 outcomes, whereas 'attends first GE appointment within the first 3-6 months after transfer' (mean 4.4, SD 3.2), 'contact IBD service independently' (mean 5.2, SD 2.4) or 'attends first GE appointment as planned' (5.4, SD 3.6), received lower scores (Table 4). Differences for the 3 provider types are shown in Table 4. Comparing the different providers within the expert panel (adult (n=32) vs paediatric (n=28) health care providers (see supplementary Figure 1); paediatric (n=28) vs adult (n=22) gastroenterologists; nurses (n=12) to physicians (n=50)) did not show significant differences after correction for multiple testing.

Table 3. Mean importance ratings# of all 26 items from stage 2

Item number		Mean score (SD) expert panel (n=64)	% with a score 1.2 or 3‡	Mean score (SD) patient panel (n=61)	% with a score 1.2 or 3‡	Corrected p-value
1	Attends first adult GE appointment as planned at moment of transfer	**7.92 (1.4)**	1.6	6.98 (2.0)	4.9	0.036*
2	Attends first adult GE appointment within the first 3-6 months after transfer	**7.12 (2.0)**	7.8	6.62 (2.1)	11.5	1.000
3	Attends all adult GE appointments in the 1st year following transfer	6.76 (1.9)	6.3	**7.23 (2.1)**	6.6	0.649
4	Adherence to medication	**7.48 (1.8)**	3.1	**8.08 (1.6)**	3.3	0.09
5	Timely refilling own prescriptions	**7.02 (1.5)**	1.6	**7.82 (1.7)**	3.3	0.002*
6	Refilling prescription on their own (not parents)	6.91 (1.6)	4.7	**7.33 (2.0)**	6.6	0.390
7	Ability to recall dose/frequency medications	**7.56 (1.5)**	3.1	**7.92 (1.5)**	1.6	0.480
8	Independent attendance at outpatient clinic (without parents)	5.94 (2.2)	17.2	5.20 (2.8)	32.8	1.000
9	Contact IBD service independently	**7.81 (1.1)**	0	**7.77 (1.6)**	1.6	1.000
10	Shows ability to make decisions regarding IBD	**7.59 (1.2)**	1.6	**8.16 (1.3)**	0	0.055
11	Independent communication with treating physician/nurse	**7.79 (1.2)**	0	**8.39 (0.8)**	0	0.036*
12	(Health related) Quality of Life 1 year after transfer	**7.11 (1.5)**	1.6	**7.39 (1.9)**	6.6	1.000
13	Necessity of surgery in 1st year after transfer	5.56 (2.4)	23.4	2.66 (2.1)	72.1	< 0.0001*
14	Number of hospitalizations in 1st year after transfer	6.36 (2.3)	12.5	3.08 (2.3)	62.3	< 0.0001*
15	Having a social network/relationships	6.39 (1.9)	10.9	6.46 (2.8)	19.7	1.000
16	Number of Emergency Room visits in 1st year after transfer	6.59 (2.2)	10.9	3.05 (2.5)	65.6	< 0.0001*
17	Patient satisfied about transition process	**7.89 (1.5)**	1.6	**7.56 (1.9)**	6.6	1.000
18	Parents satisfied about transition process	6.92 (1.8)	6.3	**7.28 (1.9)**	6.6	1.000
19	Necessity of steroids in 1st year after transfer	6.02 (2.5)	18.8	2.64 (2.1)	68.9	< 0.0001*
20	Number of flares in 1st year after transfer	6.43 (2.3)	14.1	3.15 (2.4)	63.9	< 0.0001*
21	Number of emergency examinations in 1st year after transfer	6.36 (2.1)	10.9	3.21 (2.2)	59.0	< 0.0001*
22	Completion of formal education	6.17 (2.2)	14.1	6.70 (2.9)	19.7	0.238
23	Participation in sports/hobbies	5.97 (2.0)	14.1	5.90 (2.8)	23.0	1.000
24	Growth outcomes achieved	6.16 (2.6)	18.8	5.41 (2.8)	27.9	1.000
25	Stable weight in the 1st year after transfer	6.06 (1.9)	9.4	5.72 (2.5)	23.0	1.000
26	Missed school/work days in 1st year after transfer	6.67 (1.8)	6.3	4.10 (2.7)	47.5	< 0.0001*

Abbreviations: GE: gastroenterology

Notes: # participants rated each item from 1-9 ‡ No disagreement was found (30% of ratings in lower third (rating 1-3) and 30% upper third (7-9)). Bold represents mean score 7-9. * corrected p-value using Holms correction for multiple testing < 0.05

Table 4. Top 10 ranking of stage 3 outcomes all 62 participants and per provider type

Top 10- all 62 participants	Mean (SD)	Top 10- pediatric gastroenterologists (n=28)	Mean (SD)	Top 10-gastroenterologists (n=22)	Mean (SD)	Top 10- IBD- Nurses (n=12)	Mean (SD)
Attends first adult GE appointment within the first 3-6 months after transfer	4.37 (3.2)	Attends first adult GE appointment within the first 3-6 months after transfer	4.11 (3.2)	Attends first adult GE appointment within the first 3-6 months after transfer	4.14 (2.7)	Adherence to medication	4.17 (3.2)
Contact IBD service independently	5.15 (2.4)	Timely refilling own prescriptions	5.04 (2.8)	Attends first adult GE appointment as planned at moment of transfer	4.5 (3.5)	Timely refilling own prescriptions	4.42 (1.9)
Attends first adult GE appointment as planned at moment of transfer	5.40 (3.6)	Ability to recall dose/frequency medications	5.39 (2.6)	Contact IBD service independently	4.91 (1.9)	Contact IBD service independently	4.58 (3.0)
Timely refilling own prescriptions	5.42 (2.7)	(Health related) Quality of Life 1 year after transfer	5.43 (3.1)	Adherence to medication	5.27 (2.4)	Attends first adult GE appointment within the first 3-6 months after transfer	5.42 (3.8)
(Health related) Quality of Life 1 year after transfer	5.44 (3.3)	Contact IBD service independently	5.57 (2.5)	(Health related) Quality of Life 1 year after transfer	5.32 (3.7)	Ability to recall dose/ frequency medications	5.50 (1.7)
Ability to recall dose/frequency medications	5.53 (2.8)	Attends first adult GE appointment as planned at moment of transfer	5.79 (3.7)	Patient satisfied about transition process	5.41 (2.7)	(Health related) Quality of Life 1 year after transfer	5.67 (3.2)
Adherence to medication	5.55 (2.3)	Patient satisfied about transition process	5.93 (2.4)	Ability to recall dose/ frequency medications	5.77 (2.3)	Patient satisfied about transition process	6.00 (2.1)
Patient satisfied about transition process	5.76 (2.4)	Independent communication with treating physician/nurse	6.00 (2.9)	Independent communication with treating physician/nurse	6.27 (2.9)	Shows ability to make decisions regarding IBD	6.00 (2.7)
Independent communication with treating physician/nurse	6.31 (2.8)	Adherence to medication	6.32 (2.7)	Timely refilling own prescriptions	6.45 (2.7)	Attends first adult GE appointment as planned at moment of transfer	6.17 (3.8)
Shows ability to make decisions regarding IBD	6.65 (2.7)	Shows ability to make decisions regarding IBD	6.68 (2.6)	Shows ability to make decisions regarding IBD	6.95 (2.7)	Independent communication with treating physician/nurse	7.08 (2.4)

Abbreviations: GE: gastroenterology
Note: most important outcomes, with highest importance rank are on the lower part of the list.

DISCUSSION

The primary objective of this study was to identify outcomes that three types of health care providers responsible for the care of IBD patients (gastroenterologists, paediatric gastroenterologists, and IBD-nurses) thought were important for success of transition in IBD patients. Our secondary aim was to compare these outcomes to the outcomes selected by a patient panel recruited in second instance, i.e. who only participated in stage 2 of this Delphi study. In stage 2, ten and 11 out of 26 items were identified as important by the expert (n=64) and the patient panel (n=61), respectively (Stage 2, Table 3). Surprisingly, results show that both the expert and patient panel thought the same items were important for success of transition: 8 items were identified as important in both the patient and the expert panel. Of these, 6 items concerned self-management skills and autonomy (e.g. independent communication, medication adherence), while the other 2 items were more general: Health related Quality of Life and patient satisfaction about transition process. In addition, both panels thought that attendance to adult GE appointments was important, but gave slightly different grades (difference < 1 point) to the relevant items (items 1-3, Table 3). Similarly, 'satisfaction of parents about transition process' was considered important in both panels, and almost reached the threshold for importance in the expert panel. Likewise, 'independent attendance at outpatient clinic' received a low grade (<6) by both the expert and the patient panel, possibly reflecting that both value or at least do not disapprove the presence of parents.

Only the expert panel provided a top-10 ranking (=stage 3) of the important items, and this showed that from the 10 important items, decision-making, independent communication and patient satisfaction were considered most important for success of transition in IBD patients. Comparing the top-10 of different providers did not show significant differences.

Remarkably, not one of the IBD/disease-specific items (e.g.surgery, inflammatory markers) were found to be important. The patient panel gave even lower grades than the expert panel. This is in accordance with previous studies discussing successful transition in other chronic diseases such as congenital heart defects[40], rheumatological diseases[41,42], and congenital adrenal hyperplasia.[43] In all these studies successful transition was not defined by disease-specific items, but by attendance to the first (one or two) visits of the adult health care provider. This seems a restricted definition of success. However, continuity of care is seen as a core outcome of transition[27], and is often studied as outcome of transition[28]. Incorporating disease outcomes in the definition of successful transition can be complicated considering the heterogeneous course of chronic diseases such as IBD as well as the case mix that occurs when patients with a severe course are seen in (academic) centers.[6] Philpott et al. (2018) therefore plea for including patient-driven outcomes in the definition of successful transition, such as trust in the adult health care system and autonomy.[6]

In IBD, several studies investigated outcomes of transition. A study by Bollegala *et al.* retrospectively compared outcomes 1 year before vs 1 year after transfer (n=95, no structured transition program) and report fewer outpatient clinic visits and more non-compliance, but no differences in other aspects of health care utilisation.[20] Furthermore, a survey by Bennett *et al*. showed no differences in compliance, complications, surgery, hospitalization rate or number of flares between 46 IBD patients who had transferred to adult care (without a structured transition program) and 36 age-matched patients who received care in adult setting from the beginning.[44] At last, Cole et al. showed that patients who did not attend a transition service, more often needed surgery, hospitalization, and had higher non-attendance and lower treatment adherence than patients that did attend a transition service.[19] These studies suggest that clinical outcomes might be different for patients that followed a structured transition program and those who did not, with possibly better outcomes after structured transition. However, at this point, it is unknown whether absence from the transition program itself is a risk factor for adverse outcomes or if absence is just a surrogate marker of patients that are not able to attend the transition program due to a complicated course of IBD.

So far, a definition of successful transition in IBD has not been formulated. Previously, our research group designed a score measuring success of transition in IBD (the Transition Yourself score).[45] The score comprised four elements: time to first outpatient visit to adult gastroenterologist, adherence to visits at the gastroenterology outpatient clinic, adherence to medication and qualitative evaluation of transition by the patient. The Transition Yourself Score was developed based on literature review and a focus group review with IBD experts, but has not yet been validated. In addition to validating the score, our research group considered it important to ask the opinion of a larger IBD expert panel in identifying items reflecting success of transition and also ask patients' opinion.

Two recent studies used a Delphi study to identify general, non-disease specific indicators for success of transition in adolescent medicine.[26,27] First, Fair et al. included 117 experts, mainly from the US (88%), and 70% paediatric professionals. In the final stage, 10 important outcomes were found: Achieving optimal QoL, self-managing own condition, understanding characteristics and complications of condition, knowing names and purposes of medication, adherence to medication, attending most medical appointments, having a medical home, avoidance unnecessary hospitalizations, understanding health insurance, and having a social network. Second, Suris and Akre included 37 adolescent health workers (mainly physicians) from 15 countries. Items found to be important for success of transition were: patient not lost to follow up, no missed consultations, trusting relationship with provider, attention for self-management, first visit adult care within the first 3-6 months after transfer, number of ER visits, patient/family satisfied transfer, maintaining stable disease or improvement.[26]

The selected items in both studies partly resemble the important items identified in this study. However, some of the items are described in general words, e.g. 'managing

your own condition', which covers several items from our item list. Due to this lack of specificity, it remains unclear which specific items are valued most by the panellists in the previous studies. Furthermore, only Suris and Akre's list included a disease related item: stable disease or disease improvement. In our expert and patient panel disease specific parameters received low grades. Moreover, disease knowledge was included in the final outcome list by Fair *et al.* We chose not to include knowledge of disease in our refined list for stage 1, because items implying disease knowledge were already on the list.

Strengths and limitations

This study was strengthened by the appropriate use of the Delphi procedure, and the use of a large multinational expert panel, including health care providers from 17 countries. Secondly, formation of the Delphi panel was initiated by inviting two pre-existing expert groups with a leadership role and expertise in the care of adolescent IBD patients to form the Delphi Panel. Extension of this invitation eventually led to the inclusion of 74 paediatric gastroenterologists, gastroenterologists and IBD nurses from both the paediatric and adult department. Thirdly, in second instance also a patient panel was composed to provide the patient perspective in grading the 26 items in stage 2. Lastly, the expert panel was balanced with 50% of panellists from both the paediatric and adult department.

The study was limited by a low response rate in the first invitation round (34%), although 31 opinion leaders in IBD with great experience in transition did participate, and the final panel consisted of 74 members. In addition, the majority of experts worked in Europe, which may reflect a Western perspective. Second, 90% of panellists worked in tertiary hospitals, although this is a limitation, it makes sense considering the fact that most paediatric IBD patients are treated in tertiary hospitals.[46] Third, although using the widely accepted RAND UCLA criteria for agreement, items with a mean below 7 were now labelled 'not important', which could be judged as too stringent. Fourth, it would have been better if the patient panel was included from the beginning of the study, so that all three Delphi stages would have been completed by all participants at the same time. Fifth, the subgroup analyses performed within the expert panel had relatively low number of participants. Finally, to assure clarity of all items in the list, we chose to specify the items as much as possible. As a consequence, sometimes several items concerned the same topic, but had a different emphasis (e.g. 3 items about medication adherence (item 4-6 Figure 2B).

Conclusion

This is the first study investigating outcomes reflecting successful transition in IBD patients using a multinational expert panel and comparing the results to a patient panel. Experts and patients agreed to a great extent: 8 out of 26 items were found to be important for success of transition, of which 6 items concerned self-management skills/autonomy. Remarkably, no IBD-specific item was found important. The three most important outcomes in the top-10 list from the expert panel were independent decision-making, independent communication

and patient satisfaction and did not differ between paediatric gastroenterologists, gastroenterologist and IBD-nurses. Identifying these outcomes can facilitate the definition of successful transition and subsequently the construction of an objective score measuring success of transition. After validation, this score could be used to test the efficacy of the different transition programs, in order to improve transitional care worldwide.

REFERENCES

1 Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol* 2004;18:509-23.

2 Adamiak T, Walkiewicz-Jedrzejczak D, Fish D*, et al.* Incidence, clinical characteristics, and natural history of pediatric ibd in wisconsin: A population-based epidemiological study. *Inflamm Bowel Dis* 2013;19:1218-23.

3 van Rheenen PF, Aloi M, Biron IA*, et al.* European crohn's and colitis organisation topical review on transitional care in inflammatory bowel disease. *J Crohns Colitis* 2017;11:1032-8.

4 Brooks AJ, Smith PJ, Cohen R*, et al.* Uk guideline on transition of adolescent and young persons with chronic digestive diseases from paediatric to adult care. *Gut* 2017;66:988-1000.

5 Blum RW, Garell D, Hodgman CH*, et al.* Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the society for adolescent medicine. *J Adolesc Health* 1993;14:570-6.

6 Philpott JR, Kurowski JA. Challenges in transitional care in inflammatory bowel disease: A review of the current literature in transition readiness and outcomes. *Inflamm Bowel Dis* 2019;25(1):45-55.

7 van Groningen J, Ziniel S, Arnold J, Fishman LN. When independent healthcare behaviors develop in adolescents with inflammatory bowel disease. *Inflamm Bowel Dis* 2012;18:2310-4.

8 Fishman LN, Ziniel SI, Adrichem ME, Fernandes SM, Arnold J. Provider awareness alone does not improve transition readiness skills in adolescent patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2014;59:221-4.

9 Trivedi I, Keefer L. The emerging adult with inflammatory bowel disease: Challenges and recommendations for the adult gastroenterologist. *Gastroenterol Res Pract* 2015;2015:260807.

10 Fishman LN, Barendse RM, Hait E, Burdick C, Arnold J. Self-management of older adolescents with inflammatory bowel disease: A pilot study of behavior and knowledge as prelude to transition. *Clin Pediatr (Phila)* 2010;49:1129-33.

11 Wright EK, Williams J, Andrews JM*, et al.* Perspectives of paediatric and adult gastroenterologists on transfer and transition care of adolescents with inflammatory bowel disease. *Intern Med J* 2014;44:490-6.

12 Goodhand J, Hedin CR, Croft NM, Lindsay JO. Adolescents with ibd: The importance of structured transition care. *J Crohns Colitis* 2011;5:509-19.

13 Brooks AJ, Smith PJ, Lindsay JO. Monitoring adolescents and young people with inflammatory bowel disease during transition to adult healthcare. *Frontline Gastroenterol* 2018;9:37-44.

14 Escher JC. Transition from pediatric to adult health care in inflammatory bowel disease. *Dig Dis* 2009;27:382-6.

15 Dabadie A, Troadec F, Heresbach D*, et al.* Transition of patients with inflammatory bowel disease from pediatric to adult care. *Gastroenterol Clin Biol* 2008;32:451-9.

16 Nakhla M, Daneman D, To T, Paradis G, Guttmann A. Transition to adult care for youths with diabetes mellitus: Findings from a universal health care system. *Pediatrics* 2009;124:e1134-41.

17 Wray J, Frigiola A, Bull C, Adult Congenital Heart disease Research N. Loss to specialist follow-up in congenital heart disease; out of sight, out of mind. *Heart* 2013;99:485-90.

18 Andemariam B, Owarish-Gross J, Grady J*, et al.* Identification of risk factors for an unsuccessful transition from pediatric to adult sickle cell disease care. *Pediatr Blood Cancer* 2014;61:697-701.

19 Cole R, Ashok D, Razack A, Azaz A, Sebastian S. Evaluation of outcomes in adolescent inflammatory bowel disease patients following transfer from pediatric to adult health care services: Case for transition. *J Adolesc Health* 2015;57:212-7.

20 Bollegala N, Brill H, Marshall JK. Resource utilization during pediatric to adult transfer of care in ibd. *J Crohns Colitis* 2013;7:e55-60.

21 Crowley R, Wolfe I, Lock K, McKee M. Improving the transition between paediatric and adult healthcare: A systematic review. *Arch Dis Child* 2011;96:548-53.

22 Mackie AS, Islam S, Magill-Evans J*, et al.* Healthcare transition for youth with heart disease: A clinical trial. *Heart* 2014;100:1113-8.

23 McDonagh JE, Southwood TR, Shaw KL, British Society of P, Adolescent R. The impact of a coordinated transitional care programme on adolescents with juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2007;46:161-8.

24 de Silva PS, Fishman LN. Transition of the patient with ibd from pediatric to adult care-an assessment of current evidence. *Inflamm Bowel Dis* 2014;20:1458-64.

25 Leung Y, Heyman MB, Mahadevan U. Transitioning the adolescent inflammatory bowel disease patient: Guidelines for the adult and pediatric gastroenterologist. *Inflamm Bowel Dis* 2011;17:2169-73.

26 Fair C, Cuttance J, Sharma N*, et al.* International and interdisciplinary identification of health care transition outcomes. *JAMA Pediatr* 2016;170:205-11.

27 Suris JC, Akre C. Key elements for, and indicators of, a successful transition: An international delphi study. *J Adolesc Health* 2015;56:612-8.

28 Rachas A, Lefeuvre D, Meyer L*, et al.* Evaluating continuity during transfer to adult care: A systematic review. *Pediatrics* 2016;138(1).

29 Gray WN, Reed-Knight B, Morgan PJ*, et al.* Multi-site comparison of patient, parent, and pediatric provider perspectives on transition to adult care in ibd. *J Pediatr Nurs* 2018;39:49-54.

30 Hsu CC, Sandford BA. The delphi technique: Making sense of consensus. *Practical Assessment Research and Education.* 2007:12:1-8.

31 Dewa LH, Murray K, Thibaut B*, et al.* Identifying research priorities for patient safety in mental health: An international expert delphi study. *BMJ Open* 2018;8:e021361.

32 Russell D, Atkin L, Betts A*, et al.* Using a modified delphi methodology to gain consensus on the use of dressings in chronic wounds management. *J Wound Care* 2018;27:156-65.

33 Snelson E, Ramlakhan S. Which observed behaviours may reassure physicians that a child is not septic? An international delphi study. *Arch Dis Child* 2018: 103: 864-867.

34 Hasson F, Keeney S, McKenna H. Research guidelines for the delphi survey technique. *J Adv Nurs* 2000;32:1008-15.

35 Oswald DP, Gilles DL, Cannady MS*, et al.* Youth with special health care needs: Transition to adult health care services. *Matern Child Health J* 2013;17:1744-52.

36 Sattoe JNT, Hilberink SR, van Staa A. How to define successful transition? An exploration of consensus indicators and outcomes in young adults with chronic conditions. *Child Care Health Dev* 2017;43:768-73.

37 Elwyn G, O'Connor A, Stacey D*, et al.* Developing a quality criteria framework for patient decision aids: Online international delphi consensus process. *BMJ* 2006;333:417.

38 Fitch K, Bernstein S, Aguilar MD*, et al.* The RAND/UCLA appropriateness method user's manual. Santa Monica: Rand; 2001. https://www.rand.org/pubs/monograph_reports/MR1269.html. Accessed February 2019.

39 Holms S. A simple sequential rejective method procedure. *Scandinavian Journal of Statistics* 1979;6:65-70.

40 Reid GJ, Irvine MJ, McCrindle BW*, et al.* Prevalence and correlates of successful transfer from pediatric to adult health care among a cohort of young adults with complex congenital heart defects. *Pediatrics* 2004;113:e197-205.

41 Hazel E, Zhang X, Duffy CM, Campillo S. High rates of unsuccessful transfer to adult care among young adults with juvenile idiopathic arthritis. *Pediatr Rheumatol Online J* 2010;8:2.

42 Jensen PT, Karnes J, Jones K*, et al.* Quantitative evaluation of a pediatric rheumatology transition program. *Pediatr Rheumatol Online J* 2015;13:17.

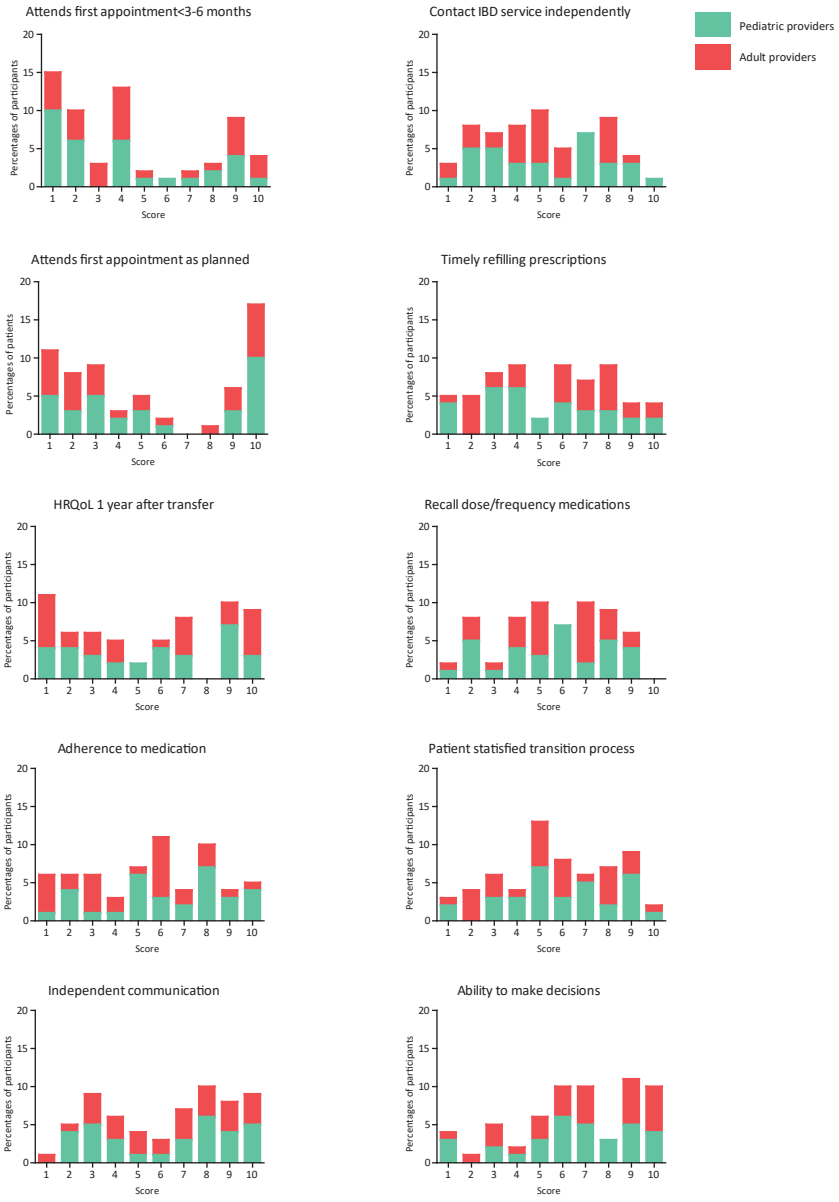
43 Gleeson H, Davis J, Jones J, O'Shea E, Clayton PE. The challenge of delivering endocrine care and successful transition to adult services in adolescents with congenital adrenal hyperplasia: Experience in a single centre over 18 years. *Clin Endocrinol (Oxf)* 2013;78:23-8.

44 Bennett AL, Moore D, Bampton PA, Bryant RV, Andrews JM. Outcomes and patients' perspectives of transition from paediatric to adult care in inflammatory bowel disease. *World J Gastroenterol* 2016;22:2611-20.

45 van den Brink G, van Gaalen MAC, Zijlstra M*, et al.* Self-efficacy did not predict the outcome of the transition to adult care in adolescents with inflammatory bowel disease. *Acta Paediatr* 2019: 108(2):333-338 .

46 de Bie CI, Buderus S, Sandhu BK*, et al.* Diagnostic workup of paediatric patients with inflammatory bowel disease in europe: Results of a 5-year audit of the eurokids registry. *J Pediatr Gastroenterol Nutr* 2012;54:374-80.

SUPPLEMENTARY FIGURES



Supplementary Figure 1. Top-10 outcomes stage 3: Paediatric versus adult providers

Note: Ranking 1 (least important) to 10 (most important); Providers includes physicians as well as nurses

PART III

General discussion and Summary

CHAPTER 12

General discussion

The studies in this thesis are focused on two themes relevant to adolescent and young adult IBD patients (also called young IBD patients): I) psychosocial problems, especially anxiety and depression and effectiveness of cognitive behavioural therapy (CBT) on medical and psychosocial outcomes, and II) transition to adult care. In **Chapter 2** we performed a systematic review with meta-analysis regarding the prevalence of anxiety and depression in paediatric IBD. **Chapter 3** gave an introduction of HAPPY-IBD, our multicentre randomised trial investigating the effectiveness of cognitive behavioural therapy (CBT) on psychological outcomes and clinical disease course in young IBD patients with subclinical symptoms of anxiety and/or depression. **Chapter 4 and 5** described the results of stage I of HAPPY-IBD: the screening of 374 Dutch adolescents and young adults with IBD on anxiety and/or depression and discussion of prevalence rates and risk factors. **Chapter 6 and 7** reported on the short and long-term psychological results: the effectiveness of a disease specific CBT on anxiety, depression and Health Related Quality of Life in young IBD patients. **Chapter 8** focussed on the effect of CBT on clinical disease course and inflammatory markers and **Chapter 9** explored the brain-gut axis in IBD and investigated plasma protein profiles in IBD patients with anxiety/depression.

Chapter 10 and 11 studied the outcome of transition in IBD patients. In **Chapter 10** we proposed a composite score measuring success of transition and in **Chapter 11** a more thorough approach was used to identify outcomes reflecting successful transition by asking the opinion of a large expert and patient panel in a multinational Delphi study, as a first step towards defining successful transition and developing a validated transition success score.

In this discussion the findings of our studies are discussed in three parts 1) anxiety and depression in paediatric IBD, 2) our multicentre randomised trial HAPPY and 3) transition. For each part, main findings are discussed in the light of current clinical practices and evidence, and recommendations for future research are given.

ANXIETY AND DEPRESSION IN YOUNG PATIENTS WITH IBD

Prevalence of anxiety and depression in paediatric IBD

Studies investigating anxiety and depression in paediatric IBD have reported greatly varying prevalence rates (anxiety symptoms 2[1]-50%[2]; depressive symptoms 0[3]-33%[4]). Only a few studies investigated the prevalence of anxiety and depressive disorders. To gain more insight into the prevalence of anxiety and depression in paediatric IBD we performed a systematic review with a meta-analysis **(Chapter 2)** including all available studies published between 1994-2017. Of the 28 studies included, most investigated anxiety (n=10) or depressive (n=22) symptoms, only a few reported on anxiety (n=3) or depressive (n=4) disorders. Pooled prevalence estimates for anxiety and depressive symptoms were respectively 16.4% (95%

confidence interval [CI] 6.8-27.3%) and 15.0% (95% CI 0-9.3%). For anxiety and depressive disorders this was much lower, respectively 4.2% and 3.4%.

Pooled prevalence rates of anxiety and depressive symptoms were higher compared to a community sample of Dutch adolescents[5], but lower compared to meta-analyses in paediatric diabetes and asthma (range 27-33%).[6,7] In addition, prevalence rates were also lower than reported in a recent systematic review in adult IBD (anxiety symptoms 35.1%; depressive symptoms 21.6%).[8] The differences in prevalence rates between children and adults could be explained by the higher prevalence of anxiety/depression in adults in the general population[9, 10] and the possibly increased disease burden in adults due to a longer and more complicated disease course of IBD. However, it is necessary to be careful comparing pooled prevalence rates to each other, considering the great variation in the used instruments and cut-offs.

Studies investigating which factors influence prevalence rates of anxiety and depressive symptoms, focused on disease type and clinical disease activity.[8] In our study, we investigated whether disease type, clinical disease activity or gender influenced prevalence rates and only found that studies with a higher percentage of active disease had a higher rate of depressive symptoms. To what extent factors such as disease duration, medication use, disease phenotype impact the prevalence of anxiety and depression in paediatric IBD, should be investigated in future studies.

As in other systematic reviews investigating prevalence of anxiety and depression, heterogeneity in study designs complicated meta-analysis in our study and forced us to be cautious in drawing firm conclusions. By performing this meta-analysis we gained the insight that for cross-cultural comparison of studies, future studies should use uniform screening measures, with the same comparable cut-offs.[11] In addition, future systematic reviews would benefit if studies presented data separately for possible influencing factors such as disease type, clinical disease activity and different types of medication.

Stage I HAPPY-IBD: screening anxiety and depression

After finishing our systematic review, prevalence rates from our own multicentre trial in the South West region of the Netherlands became available. HAPPY-IBD is one of the first studies investigating both the prevalence of anxiety and depression in young IBD patients. We decided to study anxiety and depression simultaneously, because it is known that anxiety can precede depression and that they often present concomitantly.[12] In addition, combining adolescents and young adult patients in research is important[13], considering they are at a unique (transitional) stage in their emotional, cognitive and social development. Our study showed surprisingly high prevalence rates **(Chapter 3):** of the 372 patients, 177 (47.6%) patients experienced elevated symptoms of anxiety and/or depression. Anxiety symptoms (28.3%) were more prevalent than depressive symptoms (2.9%), but also many patients suffered from both (15.8%). An innovative aspect, and also a major strength of our study, was that we measured severity of the elevated psychological symptoms using a psychiatric

interview in 134/177 patients. Clinical, severe symptoms were found in 46 (34.3%) patients (50% anxiety disorder, 10.8% depressive disorder, 32% both). Mild, subclinical symptoms were present in 88 (65.6%) patients.

Compared to previous studies, our cohort had a higher prevalence of anxiety symptoms[2, 4, 14], whereas the prevalence of depressive symptoms seemed to be lower.[4, 15, 16] Few studies report on the prevalence of combined anxiety and depressive symptoms. The lower prevalence of depressive symptoms, could be explained by the relatively low cut-offs of the CDI questionnaire used in previous studies (9[15] or 10[17], versus 13 in our study), which actually correspond to scores within the average range.[18] Secondly, the higher percentage of patients with active disease in the other studies could also explain the higher rates of depressive symptoms. Nevertheless, in our cohort with 75% of patients in clinical remission, high prevalence rates of anxiety symptoms and combined anxiety and depressive symptoms were found.

Insight in risk factors for anxiety and depression is necessary to help health care professionals identify those at risk. Active disease has repeatedly been shown to associate with anxiety and depressive symptoms.[2, 8, 11, 15, 19, 20] This was also confirmed in our cohort, and emphasises that disease control is important for physical and mental health. In addition, we also showed female gender to be a predictor for anxiety/depressive symptoms.[20, 21] Contrary to other studies, we have not found an association with socio-economic status[22], steroid use[23] or perianal disease.[24]

Considering the high prevalence of anxiety/depressive symptoms in IBD patients and the fact that they are often not recognised in a consultation in the outpatient clinic, it is likely that these problems are often missed and remain untreated.[25, 26] However, considering the impact of psychological symptoms on patients' lives, on the experienced disease burden and health care utilisation[19, 23, 27-30] , it is important to identify those suffering from psychological symptoms. The only way to identify patients in need is to screen IBD patients regularly on anxiety and depression.

Implement screening in clinical practice

In the current international guidelines for paediatric[31, 32] and adult[33-37] patients with IBD, screening for psychological problems is not (yet) part of standard care for IBD patients. Current international guidelines for adolescents with other chronic diseases, such as diabetes and cystic fibrosis (CF), recommend to screen yearly for at least anxiety and depression.[38-40] Screening at the outpatient clinic can be done using (digital) questionnaires (at home or in the waiting room) or by the doctor/nurse during clinic visits. Many questionnaires are available measuring depression or anxiety in paediatric patients[41], of which a selection is available and validated in Dutch and/or in IBD. *H*owever, the disadvantage of many of these questionnaires is that they are often long and time consuming. Shorter validated questionnaires measuring anxiety/depression, such as the Patient Health Questionnaire (PHQ-9; 9 questions) for depression[42], and the Generalized Anxiety Disorder-7 (GAD-7; 7

questions)[43] are available (also in Dutch), but were originally designed for adult patients. However, in recent years, they are increasingly used in adolescents in secondary/tertiary care[44-46], and have also been used in paediatric IBD.[47]

Instruments measuring anxiety/depression with only two or three questions, and therefore suitable for screening by a physician/nurse during the outpatient clinic visit are scarce. Short versions of the PHQ-9, (the PHQ-2) or the GAD-7 (GAD-2), or the SCARED (SCARED-5) are available, but are not sufficiently validated in adolescents (in secondary/tertiary care).[48-50]

To our knowledge, only one study previously investigated implementation of psychological screening in paediatric IBD patients. Iturralde et al. (2017) studied the implementation of screening for depression in three paediatric subspecialty clinics in the USA (IBD; n=32), cystic fibrosis (CF; n=27) and diabetes (DM; n=50). Patients were screened using the PHQ-9, positives screens (total score ≥ 11 or suicidal thoughts) received a same day behavioural health assessment. In total 16 patients screened positively on the PHQ-9 (IBD n=5; CF n=3; DM n=8) and received a referral for mental health services. The study demonstrated that screening was feasible (did not interrupt patient flow) and acceptable to both patients and health care providers.[47]

In summary, the importance of screening for psychological problems in young IBD patients is not (yet) recognised in international guidelines. However, the recently updated Dutch guideline for children and adolescents with IBD (www.richtlijnendatabase.nl: IBD) does recommend to screen paediatric patients yearly for anxiety and depression. The best way to conduct this screening at, or during, the outpatient clinic is not yet clear. Sufficiently validated short screening tools for children and adolescents with IBD are not available yet. Promising tools could be the PHQ-9/PHQ-2, GAD-7/GAD-2, which are also incorporated in the screening guidelines for adolescents and (young) adults with cystic fibrosis[39] and suggested for use in IBD patients.[51]

Future directions

To gain better insight into the prevalence and risk factors for anxiety and depression in (paediatric) IBD, future studies should use uniform screening measures, with the same comparable cut-offs. In addition, to clarify the association with other risk factors and anxiety/depression, such as disease type, clinical disease activity and medication (e.g. anti –TNF), future studies need to present prevalence rates separately for these factors. Furthermore, many studies, especially in paediatric IBD, used cross-sectional designs to identify disease-related risk factors for anxiety/depression. Longitudinal observational designs are necessary to study the associations of disease related factors and anxiety/depression over time. Lastly, studies investigating screening for psychological symptoms in (paediatric) IBD are warranted to determine the best screening method (instrument, frequency, necessary follow-up) and cost-effectiveness.

HAPPY-IBD: RANDOMISED CONTROLLED TRIAL INVESTIGATING THE EFFICACY OF COGNITIVE BEHAVIOURAL THERAPY ON PSYCHOLOGICAL SYMPTOMS AND CLINICAL DISEASE COURSE

Effect of cognitive behavioural therapy (CBT) on (subclinical) anxiety and depression

Within HAPPY-IBD we investigated the effect of CBT in IBD patients with mild/subclinical anxiety/depression, because studies have shown that these symptoms are prevalent[52-54] and that subclinical symptoms can evolve into clinical disorders.[52, 55-57] We showed that after 3 **(Chapter 6)** and after 6 and 12 months **(Chapter 7)** there was no difference in the course of anxiety and depressive symptoms for patients in both the CBT+CAU group ("CBT") and the CAU group: an improvement in anxiety and depressive symptoms was seen in all patients. Our results indicate that CBT added to care as usual (CAU) did not perform better than standard medical care in improving subclinical anxiety/depressive symptoms.

There are several explanations for our findings. At first, all patients, including patients in the CAU group, received multiple questionnaires and interviews assessing psychological health. This increased attention for psychological health could have elicited increased awareness, (unintended) psychoeducation and positively affected mental health in all patients.[58, 59] Second, our cohort consisted of patients with subclinical anxiety and/or depressive symptoms, and IBD mostly in clinical remission (±75% remission, ± 20% mildly active disease). For these patients, mere participation in the trial may have been enough to improve psychological symptoms and to prevent the development of clinical/severe anxiety/depression.

Compared to other studies, HAPPY-IBD is the first to investigate the effect of CBT in young IBD patients with subclinical anxiety and/or depression and to study both medical and psychological outcomes. Previous studies in adolescents have focused only on (sub) clinical depression[60, 61], for clinical anxiety only a small pilot study is available.[62] Studies by Szigethy et al. have shown a reduction in depressive symptoms[61] and depressive severity[60] following the same disease-specific CBT.

It could be that CBT has a greater effect on psychological outcomes in IBD patients with severe (clinical) anxiety and/or depression and at least moderately active bowel disease, although no studies are available yet that support this hypothesis. Even in adult IBD patients, no studies are available investigating the effectiveness of CBT in (sub)clinical depression or anxiety.[63] However, in one study investigating the effect of CBT in patients with "low mental quality of life", approximately 70% of patients had Hospital Anxiety And Depression scale (HADS)-scores indicative of an anxiety or depressive disorder. The study demonstrated that CBT was effective in reducing anxiety and depressive symptoms.[64] Unfortunately, studies investigating the effect of CBT on psychological health in IBD patients with at least moderately active disease and suffering from (sub)clinical anxiety/depression are not available.[63]

In general cohorts of IBD patients, unselected for anxiety or depression, several studies were done on the effect of CBT in IBD patients. A study in 185 adolescents with IBD tested the effectiveness of a 3-session CBT protocol (versus education support condition), and found that CBT decreased school absences and improved HRQOL, but did not find an effect on anxiety/depression. Two recent systematic reviews also reported no effect of CBT on anxiety and depression in adult IBD.[63, 65] Results of other psychotherapies on anxiety/depression in unselected patients showed mixed results, with little or no (long term) effect on anxiety and depression.[37, 63, 65, 66] It is therefore argued that psychotherapy should only be offered to selected patients, with identified needs.[67, 68]

Effect of Cognitive Behavioural Therapy (CBT) on clinical disease course

Within the brain-gut axis a bidirectional relationship is hypothesised between psychological symptoms and (intestinal) inflammation. Psychological treatment may improve clinical symptoms, but also intestinal and systemic inflammation in IBD.

Within HAPPY-IBD we investigated whether CBT (in addition to care as usual, CAU) influenced clinical disease course **(Chapter 8)**. We showed that time to first relapse, (pooled) clinical disease activity, CRP and faecal calprotectin did not differ significantly between patients in the CBT and the CAU group during the first year after treatment randomisation. Exploratory analyses in 10-18-year-old patients suggested a different course of faecal calprotectin and CRP between groups, with a slight increase in the CAU group, which could suggest a positive influence on intestinal inflammation on the longer term.

We believe our findings can be explained by the fact that in the current trial, both groups equally improved in anxiety/depressive symptoms and HRQOL after 3[69] and 6-12 months (Stapersma et al., submitted). Concurrently, it is not surprising that we did not find a difference in clinical, inflammatory bowel disease-related outcomes between both groups. We would however expect clinical outcome (including longer time to relapse / lower frequency of relapse) to improve within both groups (as both groups improved in anxiety and depressive symptoms over time).[69] Low baseline clinical disease activity could also explain why we did not find an improvement in clinical or inflammatory activity.

The only comparable study in paediatric as well as adult IBD, investigated the effect of CBT (versus supportive nondirective therapy) in 217 adolescents with IBD and minor/major depression and found an improvement in depressive severity, HRQOL and pooled clinical disease activity after 3 months in both groups. However, this improvement in clinical disease activity was rather small (±10 points on the PCDAI /PUCAI).[60] Other studies reporting on the effect of CBT on clinical disease course in IBD did not select patients on anxiety/depression, and included paediatric[70] or adult IBD[68, 71-73] patients in clinical remission or with mildly active disease. No difference in remission[68, 72] or relapse rates[70], clinical disease activity[60, 68, 72, 73] or CRP-levels[40, 41] between CBT and the control condition were reported.

As mentioned, it could be that CBT is more effective in improving disease course (reducing inflammation) in patients with more severe anxiety/depression, although only

few studies provide support for this.[60, 64] Similarly, CBT could have a greater influence on disease course in patients with at least moderately active disease. Unfortunately, studies investigating disease course in IBD patients with at least moderately active disease are not available. Lastly, it is possible that CBT has an effect on other measures of disease course or disease burden, such as disability, healthcare use (e.g. visits to the Emergency Room), school absenteeism or fatigue.[74]

Brain-gut axis in IBD: the relationship between psychological symptoms and (intestinal) inflammation at a molecular level

HAPPY-IBD provided us with the unique opportunity to investigate the relationship between anxiety and/or depression and (systemic) inflammation **(Chapter 9)**, and we were the first to use a large unbiased inflammatory protein panel (including 92 proteins). Distinctive inflammatory protein signatures associated with a) symptoms of anxiety b) symptoms of depression, c) presence versus absence of anxiety and/or depression and d) response to CBT in IBD. Within these, Leukemia inhibitory factor receptor (LIF-R) and chemokine CCL4 were upregulated in patients with psychological symptoms and decreased after CBT, and possibly candidate proteins reflecting response to psychotherapy.

Previous studies investigating the relationship between anxiety and/or depression and (systemic) inflammation are scarce: one study previously reported on the association between IBD, anxiety/depression and plasma proteins, but investigated a limited selection of proteins (Interleukin (IL)-1β, IL-6, CRP). [75] In addition, only one study described an effect of a psychological intervention (one session hypnotherapy) on Tumor Necrosis Factor (TNF-α), IL-6 and IL-13 levels.[76]

In contrast, multiple studies investigated cytokine levels in anxiety and depression in otherwise healthy adolescents and adults, or the effect of psychotherapy on inflammation in adult IBD. All studies used small (biased) protein panels. Associations between anxiety and/or depression and IL-1β, IL-2, IL-6, IL-8, CRP, Interferon-gamma (IFN-γ), Tumor Necrosis Factor (TNF-α), and chemokines MCP-1 (CCL2), CCL3, CCL11, CXCL4, CXCL7 were reported.[77-86] Systematic reviews investigating the effect of psychotherapy on inflammation did not show any robust associations.[87, 88]

In conclusion, using an innovative and unbiased approach with a large protein panel, we found distinct plasma protein signatures associating with anxiety and/or depression or response to CBT in IBD patients mostly in remission. Several proteins not previously investigated in anxiety and depression (in IBD) were now analysed, providing a novel perspective on possibly involved proteins. Future studies using large unbiased protein panels are necessary to confirm our findings and to investigate whether protein signatures are different for several subgroups (e.g. Crohn's disease versus ulcerative colitis; responders versus non-responders to psychotherapy).

Future directions

As shown, a full protocol of 10 sessions of CBT did not show to be beneficial for IBD patients in remission or with mildly active disease but suffering from subclinical anxiety and depression: CBT did not perform better in improving psychological or clinical outcomes than CAU. Considering we were the first to include IBD patients with anxiety and/or depression ánd investigate both psychological and clinical outcomes, more studies with comparable study designs are needed to confirm our findings. Furthermore, additional studies are needed to gain insight in the best approach for IBD patients with (sub)clinical anxiety/depression.

- Observational studies investigating the natural course of subclinical psychological symptoms in IBD, taking into account the clinical course of disease, are needed to provide insight into the necessity of an intervention;
- RCTs comparing different psychological interventions with varying treatment modalities (e.g. computerised CBT) and intensity (e.g. 3 session protocol) are required to determine the most effective treatment strategy;
- To investigate if there are subgroups of IBD patients that would benefit from a full protocol of CBT, studies including IBD patients with more severe (clinical) anxiety/depression and with at least moderately active disease are warranted;
- Lastly, future studies should also include (patient reported) outcomes related to burden of disease, irritable bowel symptoms and treatment adherence, to investigate if CBT affects more 'subjective' outcomes, because these outcomes are known to impact health care utilisation and clinical outcomes.

TRANSITION

Success of transition

As IBD is a lifelong disease, all patients will need to undergo transfer of paediatric to adult care. Transfer to adolescent care can be challenging due to several reasons, including the differences between paediatric and adult care. Therefore, a transition process is advised, in which all stakeholders (patients, parents, paediatric and adult gastroenterologists and specialised nurses) have specific tasks. For patients, the most important tasks are to learn responsibility for their own health, acquire (disease) knowledge, autonomy and self-management.[89-91] A clear definition of success of transition, or a scoring system measuring success of transition in IBD is not yet available.[89, 92, 93]

As a first step in exploring success of transition, we developed a tool in 2014, the Transition Yourself Score, to measure success of transition **(Chapter 10)**. The score was based on previous literature and a focus group meeting with IBD experts and consisted of four items: time to the first gastroenterology outpatient clinic visit, outpatient clinic non-attendance rates, adherence to medication and a qualitative evaluation of transition by the

patient. Applying the score on our cohort of 35 IBD patients, we found that transition was successful in 63% of cases, moderately successful in 31% and failed in 6%.

We have not psychometrically tested the Transition Yourself Score yet, because we felt the need to use a more thorough and objective approach to identify objective outcome measures that can be used to define successful transition in IBD.[94] Therefore, we developed a three stage Delphi study asking a large expert and patient panel about outcomes they thought were important for success transition **(Chapter 11)**. The expert panel consisted of paediatric gastroenterologist, adult gastroenterologist and IBD nurses. The study started with 26 items, of these, 10 and 11 out of 26 items were identified as important by the expert (n=64) and the patient panel (n=61) respectively. Surprisingly, the opinion of both the expert and patient panel was quite similar: 8 items were identified as important by both the patient and the expert panel. Of these, 6 items concerned self-management skills and autonomy (e.g. independent communication, medication adherence), while the other 2 items were more general: Health related Quality of Life and patient satisfaction about transition process. Remarkably, disease-specific items (such as surgery, inflammatory markers) were not found to be important, which has also been reported in studies discussing successful transition in other chronic diseases.[95-98]

Few studies investigated outcome of transition in IBD. No robust conclusions can be drawn, considering the fact that all studies used different designs and outcomes.[93, 99, 100] Two recent Delphi studies identified general, non-disease specific outcomes for success of transition in adolescent medicine (so including experts from several subspecialties). Our findings partly resemble the selected outcomes in these studies.[101, 102]

Future directions

With our Delphi study we took the first step in identifying outcomes that both experts and patients find important for success of transition. These findings should be confirmed in other (international) expert and patient panels. In addition, future research should focus on providing a clear definition of successful transition and develop and validate an objective score measuring success of transition. After validation, this score should be used to test the efficacy of the different IBD transition programs, in order to improve transitional care worldwide.

REFERENCES

1 Mackner LM, Crandall WV. Long-term psychosocial outcomes reported by children and adolescents with inflammatory bowel disease. *Am J Gastroenterol*. 2005;100(6):1386-1392.

2 Reigada LC, Hoogendoorn CJ, Walsh LC, et al. Anxiety symptoms and disease severity in children and adolescents with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2015;60(1):30-35.

3 Reed-Knight B, McCormick M, Lewis JD, Blount RL. Participation and attrition in a coping skills intervention for adolescent girls with inflammatory bowel disease. *J Clin Psychol Med Settings*. 2012;19(2):188-196.

4 Reigada LC, Bruzzese JM, Benkov KJ, et al. Illness-specific anxiety: implications for functioning and utilization of medical services in adolescents with inflammatory bowel disease. *J Spec Pediatr Nurs*. 2011;16(3):207-215.

5 Netherlands Youth Institute: Facts and figures anxiety and depressive problems. In: https://www.nji.nl/nl/Depressie-Probleemschets-Cijfers-Cijfers-over-angst--en-stemmingsproblemen. Accessed May 2018.

6 Buchberger B, Huppertz H, Krabbe L, Lux B, Mattivi JT, Siafarikas A. Symptoms of depression and anxiety in youth with type 1 diabetes: A systematic review and meta-analysis. *Psychoneuroendocrinology*. 2016;70:70-84.

7 Lu Y, Mak KK, van Bever HP, Ng TP, Mak A, Ho RC. Prevalence of anxiety and depressive symptoms in adolescents with asthma: a meta-analysis and meta-regression. *Pediatr Allergy Immunol*. 2012;23(8):707-715.

8 Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review. *J Psychosom Res*. 2016;87:70-80.

9 Angst J, Merikangas KR, Preisig M. Subthreshold syndromes of depression and anxiety in the community. *J Clin Psychiatry*. 1997;58 Suppl 8:6-10.

10 Karsten J, Hartman CA, Smit JH, et al. Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. *Brit J Psychiat*. 2011;198(3):206-212.

11 Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. *Inflamm Bowel Dis*. 2016;22(3):752-762.

12 Garber J, Weersing VR. Comorbidity of Anxiety and Depression in Youth: Implications for Treatment and Prevention. *Clin Psychol.* 2010;17(4):293-306.

13 Nass SJ, Beaupin LK, Demark-Wahnefried W, et al. Identifying and addressing the needs of adolescents and young adults with cancer: summary of an Institute of Medicine workshop. *Oncologist*. 2015;20(2):186-195.

14 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):275-279.

15 Szigethy E, Levy-Warren A, Whitton S, 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.

16 Reed-Knight B, Lobato D, Hagin S, et al. Depressive symptoms in youth with inflammatory bowel disease compared with a community sample. *Inflamm Bowel Dis*. 2014;20(4):614-621.

17 Srinath AI, Goyal A, Zimmerman LA, et al. Predictors of abdominal pain in depressed pediatric inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2014;20(8):1329-1340.

18 Twenge JM, Nolen-Hoeksema S. Age, gender, race, socioeconomic status, and birth cohort differences on the children's depression inventory: a meta-analysis. *J Abnorm Psychol*. 2002;111(4):578-588.

19 Brooks AJ, Rowse G, Ryder A, Peach EJ, Corfe BM, Lobo AJ. Systematic review: psychological morbidity in young people with inflammatory bowel disease - risk factors and impacts. *Aliment Pharmacol Ther*. 2016;44(1):3-15.

20 Byrne G, Rosenfeld G, Leung Y, et al. Prevalence of Anxiety and Depression in Patients with Inflammatory Bowel Disease. *Can J Gastroenterol Hepatol*. 2017;2017:6496727.

21 Walter JG, Kahn SA, Noe JD, Schurman JV, Miller SA, Greenley RN. Feeling Fine: Anxiety and Depressive Symptoms in Youth with Established IBD. *Inflamm Bowel Dis*. 2016;22(2):402-408.

22 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):2301-2309.

23 Navabi S, Gorrepati VS, Yadav S, et al. Influences and Impact of Anxiety and Depression in the Setting of Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2018;24(11):2303-2308.

24 Ananthakrishnan AN, Gainer VS, Cai T, et al. Similar risk of depression and anxiety following surgery or hospitalization for Crohn's disease and ulcerative colitis. *Am J Gastroenterol*. 2013;108(4):594-601.

25 Klag T, Mazurak N, Fantasia L, et al. High Demand for Psychotherapy in Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2017;23(10):1796-1802.

26 Bennebroek Evertsz F, Thijssens NA, Stokkers PC, et al. Do Inflammatory Bowel Disease patients with anxiety and depressive symptoms receive the care they need? *J Crohns Colitis*. 2012;6(1):68-76.

27 Singh H, Nugent Z, Brownell M, Targownik LE, Roos LL, Bernstein CN. Academic Performance among Children with Inflammatory Bowel Disease: A Population-Based Study. *J Pediatr*. 2015;166(5):1128-1133.

28 De Boer AG, Bennebroek Evertsz F, Stokkers PC, et al. Employment status, difficulties at work and quality of life in inflammatory bowel disease patients. *Eur J Gastroenterol Hepatol*. 2016;28(10):1130-1136.

29 Reigada LC, Satpute A, Hoogendoorn CJ, et al. Patient-reported Anxiety: A Possible Predictor of Pediatric Inflammatory Bowel Disease Health Care Use. *Inflamm Bowel Dis*. 2016;22(9):2127-2133.

30 Burisch J, Jess T, Martinato M, Lakatos PL, EpiCom E. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis*. 2013;7(4):322-337.

31 Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care- an Evidence-Based Guideline from ECCO and ESPGHAN. *J Pediatr Gastroenterol Nutr*. 2018.

32 Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis*. 2014;8(10):1179-1207.

33 Gionchetti P, Dignass A, Danese S, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. *J Crohns Colitis*. 2017;11(2):135-149.

34 Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis*. 2017;11(1):3-25.

35 Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis*. 2017;11(6):649-670.

36 Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis*. 2017;11(7):769-784.

37 Torres J, Ellul P, Langhorst J, et al. European Crohn's and Colitis Organisation Topical Review on Complementary Medicine and Psychotherapy in Inflammatory Bowel Disease. *J Crohns Colitis*. 2019.

38 Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care*. 2005;28(1):186-212.

39 Quittner AL, Abbott J, Georgiopoulos AM, et al. International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. *Thorax*. 2016;71(1):26-34.

40 Monaghan M, Singh C, Streisand R, Cogen FR. Screening and identification of children and adolescents at risk for depression during a diabetes clinic visit. *Diabetes Spectrum*. 2010;23:25-31.

41 Thabrew H, McDowell H, Given K, Murrell K. Systematic Review of Screening Instruments for Psychosocial Problems in Children and Adolescents With Long-Term Physical Conditions. *Glob Pediatr Health*. 2017;4:2333794X17690314.

42 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.

43 Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097.

44 Allgaier AK, Pietsch K, Fruhe B, Sigl-Glockner J, Schulte-Korne G. Screening for depression in adolescents: validity of the patient health questionnaire in pediatric care. *Depress Anxiety*. 2012;29(10):906-913.

45 Richardson LP, McCauley E, Grossman DC, et al. Evaluation of the Patient Health Questionnaire-9 Item for detecting major depression among adolescents. *Pediatrics*. 2010;126(6):1117-1123.

46 Mossman SA, Luft MJ, Schroeder HK, et al. The Generalized Anxiety Disorder 7-item scale in adolescents with generalized anxiety disorder: Signal detection and validation. *Ann Clin Psychiatry*. 2017;29(4):227-234A.

47 Iturralde E, Adams RN, Barley RC, et al. Implementation of Depression Screening and Global Health Assessment in Pediatric Subspecialty Clinics. *J Adolesc Health*. 2017;61(5):591-598.

48 Sudhanthar S, Thakur K, Sigal Y, Turner J. Improving validated depression screen among adolescent population in primary care practice using electronic health records (EHR). *BMJ Qual Improv Rep*. 2015;4(1).

49 Richardson LP, Rockhill C, Russo JE, et al. Evaluation of the PHQ-2 as a brief screen for detecting major depression among adolescents. *Pediatrics*. 2010;125(5):e1097-1103.

50 Ramsawh HJ, Chavira DA, Kanegaye JT, Ancoli-Israel S, Madati PJ, Stein MB. Screening for adolescent anxiety disorders in a pediatric emergency department. *Pediatr Emerg Care*. 2012;28(10):1041-1047.

51 Szigethy EM, Allen JI, Reiss M, et al. White Paper AGA: The Impact of Mental and Psychosocial Factors on the Care of Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol.*2017;15(7):986-997.

52 Bosman RC, Ten Have M, de Graaf R, Muntingh AD, van Balkom AJ, Batelaan NM. Prevalence and course of subthreshold anxiety disorder in the general population: A three-year follow-up study. *J Affect Disord*. 2019;247:105-113.

53 Lewinsohn PM, Shankman SA, Gau JM, Klein DN. The prevalence and co-morbidity of subthreshold psychiatric conditions. *Psychol Med*. 2004;34(4):613-622.

54 Bertha EA, Balazs J. Subthreshold depression in adolescence: a systematic review. *Eur Child Adolesc Psychiatry*. 2013;22(10):589-603.

55 Klein DN, Shankman SA, Lewinsohn PM, Seeley JR. Subthreshold depressive disorder in adolescents: predictors of escalation to full-syndrome depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2009;48(7):703-710.

56 Shankman SA, Lewinsohn PM, Klein DN, Small JW, Seeley JR, Altman SE. Subthreshold conditions as precursors for full syndrome disorders: a 15-year longitudinal study of multiple diagnostic classes. *J Child Psychol Psychiatry*. 2009;50(12):1485-1494.

57 Hill RM, Pettit JW, Lewinsohn PM, Seeley JR, Klein DN. Escalation to Major Depressive Disorder among adolescents with subthreshold depressive symptoms: evidence of distinct subgroups at risk. *J Affect Disord*. 2014;158:133-138.

58 Arrindell WA. Changes in waiting-list patients over time: data on some commonly-used measures. Beware! *Behav Res Ther*. 2001;39(10):1227-1247.

59 McCambridge J. From question-behaviour effects in trials to the social psychology of research participation. *Psychol Health*. 2015;30(1):72-84.

60 Szigethy E, Bujoreanu SI, Youk AO, 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):726-735.

61 Szigethy E, Kenney E, Carpenter J, et al. Cognitive-behavioral therapy for adolescents with inflammatory bowel disease and subsyndromal depression. *J Am Acad Child Adolesc Psychiatry*. 2007;46(10):1290-1298.

62 Reigada LC, Benkov KJ, Bruzzese JM, et al. Integrating illness concerns into cognitive behavioral therapy for children and adolescents with inflammatory bowel disease and co-occurring anxiety. *J Spec Pediatr Nurs*. 2013;18(2):133-143.

63 Gracie DJ, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2(3):189-199.

64 Bennebroek Evertsz F, Sprangers MAG, Sitnikova K, et al. Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: A multicenter randomized controlled trial. *J Consult Clin Psychol*. 2017;85(9):918-925.

65 Tarricone I, Regazzi MG, Bonucci G, et al. Prevalence and effectiveness of psychiatric treatments for patients with IBD: A systematic literature review. *J Psychosom Res*. 2017;101:68-95.

66 McCombie AM, Mulder RT, Gearry RB. Psychotherapy for inflammatory bowel disease: a review and update. *J Crohns Colitis*. 2013;7(12):935-949.

67 Mikocka-Walus A, Andrews JM, Bampton P. Cognitive Behavioral Therapy for IBD. *Inflamm Bowel Dis*. 2016;22(2):E5-6.

68 Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-Behavioural Therapy for Inflammatory Bowel Disease: 24-Month Data from a Randomised Controlled Trial. *Int J Behav Med*. 2017;24(1):127-135.

69 Stapersma L, van den Brink G, van der Ende J, et al. Effectiveness of Disease-Specific Cognitive Behavioral Therapy on Anxiety, Depression, and Quality of Life in Youth With Inflammatory Bowel Disease: A Randomized Controlled Trial. *J Pediatr Psychol*. 2018;43(9):967-980.

70 Levy RL, van Tilburg MA, Langer SL, et al. Effects of a Cognitive Behavioral Therapy Intervention Trial to Improve Disease Outcomes in Children with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2016;22(9):2134-2148.

71 McCombie A, Gearry R, Andrews J, Mulder R, Mikocka-Walus A. Does Computerized Cognitive Behavioral Therapy Help People with Inflammatory Bowel Disease? A Randomized Controlled Trial. *Inflamm Bowel Dis*. 2016;22(1):171-181.

72 Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-behavioural therapy has no effect on disease activity but improves quality of life in subgroups of patients with inflammatory bowel disease: a pilot randomised controlled trial. *BMC Gastroenterol*. 2015;15:54.

73 Schoultz M, Atherton I, Watson A. Mindfulness-based cognitive therapy for inflammatory bowel disease patients: findings from an exploratory pilot randomised controlled trial. *Trials*. 2015;16:379.

74 Keerthy D, Youk A, Srinath AI, et al. Effect of Psychotherapy on Health Care Utilization in Children With Inflammatory Bowel Disease and Depression. *J Pediatr Gastroenterol Nutr*. 2016;63(6):658-664.

75 Abautret-Daly A, Dempsey E, Riestra S, et al. Association between psychological measures with inflammatory anddisease-related markers of inflammatory bowel disease. *Int J Psychiatry Clin Pract*. 2017;21(3):221-230.

76 Mawdsley JE, Jenkins DG, Macey MG, Langmead L, Rampton DS. The effect of hypnosis on systemic and rectal mucosal measures of inflammation in ulcerative colitis. *Am J Gastroenterol*. 2008;103(6):1460-1469.

77 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):447-455.

78 Hou R, Baldwin DS. A neuroimmunological perspective on anxiety disorders. *Hum Psychopharmacol*. 2012;27(1):6-14.

79 O'Donovan A, Hughes BM, Slavich GM, et al. Clinical anxiety, cortisol and interleukin-6: evidence for specificity in emotion-biology relationships. *Brain Behav Immun*. 2010;24(7):1074-1077.

80 Liukkonen T, Rasanen P, Jokelainen J, et al. The association between anxiety and C-reactive protein (CRP) levels: results from the Northern Finland 1966 birth cohort study. *Eur Psychiatry*. 2011;26(6):363-369.

81 Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171-186.

82 Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457.

83 Al-Hakeim HK, Al-Rammahi DA, Al-Dujaili AH. IL-6, IL-18, sIL-2R, and TNFalpha proinflammatory markers in depression and schizophrenia patients who are free of overt inflammation. *J Affect Disord*. 2015;182:106-114.

84 Pallavi P, Sagar R, Mehta M, et al. Serum cytokines and anxiety in adolescent depression patients: Gender effect. *Psychiatry Res*. 2015;229(1-2):374-380.

85 Lamers F, Milaneschi Y, Smit JH, Schoevers RA, Wittenberg G, Penninx B. Longitudinal Association Between Depression and Inflammatory Markers: Results From the Netherlands Study of Depression and Anxiety. *Biol Psychiatry*. 2019;95(10):829-837.

86 Leighton SP, Nerurkar L, Krishnadas R, Johnman C, Graham GJ, Cavanagh J. Chemokines in depression in health and in inflammatory illness: a systematic review and meta-analysis. *Mol Psychiatry*. 2018;23(1):48-58.

87 Lopresti AL. Cognitive behaviour therapy and inflammation: A systematic review of its relationship and the potential implications for the treatment of depression. *Aust N Z J Psychiatry*. 2017;51(6):565-582.

88 O'Toole MS, Bovbjerg DH, Renna ME, Lekander M, Mennin DS, Zachariae R. Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans: A systematic review and meta-analysis. *Brain Behav Immun*. 2018;74:68-78.

89 Goodhand J, Hedin CR, Croft NM, Lindsay JO. Adolescents with IBD: the importance of structured transition care. *J Crohns Colitis*. 2011;5(6):509-519.

90 Philpott JR, Kurowski JA. Challenges in Transitional Care in Inflammatory Bowel Disease: A Review of the Current Literature in Transition Readiness and Outcomes. *Inflamm Bowel Dis*. 2019;25(1):45-55.

91 Brooks AJ, Smith PJ, Lindsay JO. Monitoring adolescents and young people with inflammatory bowel disease during transition to adult healthcare. *Frontline Gastroenterol*. 2018;9(1):37-44.

92 Leung Y, Heyman MB, Mahadevan U. Transitioning the adolescent inflammatory bowel disease patient: guidelines for the adult and pediatric gastroenterologist. *Inflamm Bowel Dis*. 2011;17(10):2169-2173.

93 Cole R, Ashok D, Razack A, Azaz A, Sebastian S. Evaluation of Outcomes in Adolescent Inflammatory Bowel Disease Patients Following Transfer From Pediatric to Adult Health Care Services: Case for Transition. *J Adolesc Health*. 2015;57(2):212-217.

94 van Rheenen PF, Aloi M, Biron IA, et al. European Crohn's and Colitis Organisation Topical Review on Transitional Care in Inflammatory Bowel Disease. *J Crohns Colitis*. 2017;11(9):1032-1038.

95 Reid GJ, Irvine MJ, McCrindle BW, et al. Prevalence and correlates of successful transfer from pediatric to adult health care among a cohort of young adults with complex congenital heart defects. *Pediatrics*. 2004;113(3 Pt 1):e197-205.

96 Hazel E, Zhang X, Duffy CM, Campillo S. High rates of unsuccessful transfer to adult care among young adults with juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*. 2010;8:2.

97 Jensen PT, Karnes J, Jones K, et al. Quantitative evaluation of a pediatric rheumatology transition program. *Pediatr Rheumatol Online J*. 2015;13:17.

98 Gleeson H, Davis J, Jones J, O'Shea E, Clayton PE. The challenge of delivering endocrine care and successful transition to adult services in adolescents with congenital adrenal hyperplasia: experience in a single centre over 18 years. *Clin Endocrinol (Oxf)*. 2013;78(1):23-28.

99 Bollegala N, Brill H, Marshall JK. Resource utilization during pediatric to adult transfer of care in IBD. *J Crohns Colitis*. 2013;7(2):e55-60.

100 Bennett AL, Moore D, Bampton PA, Bryant RV, Andrews JM. Outcomes and patients' perspectives of transition from paediatric to adult care in inflammatory bowel disease. *World J Gastroenterol*. 2016;22(8):2611-2620.

101 Fair C, Cuttance J, Sharma N, et al. International and Interdisciplinary Identification of Health Care Transition Outcomes. *JAMA Pediatr*. 2016;170(3):205-211.

102 Suris JC, Akre C. Key elements for, and indicators of, a successful transition: an international Delphi study. *J Adolesc Health*. 2015;56(6):612-618.

CHAPTER 13

Summary
Samenvatting

SUMMARY

The general aim of this thesis was to investigate two themes relevant to adolescent and young adult IBD patients: 1) psychosocial problems (especially anxiety and depression) and effectiveness of cognitive behavioural therapy (CBT) on medical and psychosocial outcomes, and 2) transition from paediatric to adult care.

PART I concerns anxiety and depression in paediatric IBD and the effectiveness of a disease specific CBT protocol examined in a randomised controlled trial (RCT). **Chapter 2** presents a systematic review and meta-analysis investigating the prevalence of anxiety and depression in paediatric IBD patients. A total of 28 studies were included (n=8107, 51.3% male, 67.1% Crohn's disease, mean age 14.3 years). Of importance is the distinction between psychological symptoms and disorders: disorders reflect severe symptoms that cause significant impairment in daily life and are diagnosed based on an interview using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. Symptoms are usually measured with self-report questionnaires, and patients with elevated symptoms (who do not meet all criteria of a disorder) suffer from milder (or so-called subclinical) symptoms, but do not experience such a significant impairment in their daily life as patients with a diagnosed disorder. Of the 28 included studies, most investigated anxiety (n=10) or depressive (n=22) symptoms, while only a few reported on anxiety (n=3) or depressive (n=4) disorders. Pooled prevalence estimates for anxiety and depressive symptoms were respectively 16.4% and 15.0% . For anxiety and depressive disorders this was much lower, respectively 4.2% and 3.4%. Meta-regression showed that studies with a higher percentage of patients with active disease had a higher rate of depressive symptoms. Comparing with pooled prevalence rates in adult IBD, the found prevalence rates in paediatric IBD patients were much lower. We discussed several explanations for this difference, of which one is the lower number of studies available in paediatric IBD and the highly varying use of instruments and cut-off scores. This forced us to be careful drawing firm conclusions and we strongly advise that future studies use the same instruments ánd cut-off scores to gain better insight into prevalence rates.

In **Chapter 3** we present the study protocol of HAPPY-IBD, our multicentre randomised controlled trial (RCT) investigating the effectiveness of a disease specific cognitive behavioural therapy (CBT) on psychological outcomes ánd clinical disease course in young (10-25-year-old) IBD patients with subclinical symptoms of anxiety and/or depression. In the RCT patients are randomised to either CBT+ Care as usual, or to CAU only.

Chapter 4 and 5 describe the results from the first stage of HAPPY-IBD: the screening of 374 Dutch adolescents and young adult with IBD on anxiety and depression using self-report questionnaires and a psychiatric interview for patients with elevated symptoms. In **Chapter 4** we showed that 47.4% of patients suffered from anxiety and/or depressive symptoms. Mild (subclinical) and severe (clinical) anxiety and/or depressive symptoms were

present in respectively 23.6% and 12.4%. Clinical disease activity, faecal calprotectin and erythrocyte sedimentation rate were significantly higher in patients with severe psychological symptoms. In addition, we found a much higher prevalence of anxiety symptoms (28.3%) compared to depressive symptoms (2.9%) or to both anxiety and depressive symptoms (15.8%). Active disease significantly predicted depressive symptoms. Female gender and a shorter disease duration were significantly associated with the presence of anxiety and/or depressive symptoms. Considering the high prevalence of anxiety and/or depressive symptoms we strongly recommend to screen young IBD patients for anxiety/depression when they visit the outpatient clinic.

In **Chapter 5** we aim to explore the associations of psychological factors (illness perceptions, coping, anxiety, depression) with health related quality of life (HRQOL), controlling for demographic (gender, age, socio-economic status) and clinical factors (disease type, clinical disease activity). Using multiple regression analyses, we showed that negative illness perceptions and depression were negatively associated to HRQOL.

Chapter 6 is the first chapter reporting on stage 2 of HAPPY-IBD; the randomised controlled trial, where we included 70 patients who were randomised to either CBT+CAU or CAU only. **I**n **Chapter 6** we showed that after 3 months (directly after completing 10 sessions of CBT), overall, patients in both groups either remained stable or improved in their symptoms of anxiety and depression according to their reliable change index (RCI). Exploratory linear mixed model analyses showed that all patients improved in their symptoms of anxiety or depression and improved in HRQOL.

In **Chapter 7** the long-term effectiveness of CBT on anxiety, depression, HRQOL and other psychological outcomes such as social functioning, coping, illness perceptions and sleep problems were discussed. On the long term, results showed a similar pattern: in both the CBT +CAU and the CAU group a similar proportion of patients improved in anxiety and depressive symptoms. In addition, both groups improved on anxiety, depression, HRQOL, social functioning, coping and illness perception. Two explanations are given for this lack of difference: the extra attention (questionnaires, interviews) that patients in the CAU received by merely participating in the RCT could have been enough to improve their subclinical symptoms of anxiety and/or depression. In addition, giving a full protocol of CBT to IBD patients with subclinical anxiety/depression and mostly in clinical remission seems unnecessary.

In **Chapter 8** we focused on the effect of CBT on clinical disease course. We showed that there was no difference between the CBT+CAU and the CAU group in the time to first relapse or relapse frequency in the first year after randomisation. In addition, CBT did not influence (pooled) clinical disease activity scores, and inflammatory markers (faecal calprotectin, C-reactive protein). We emphasised that these results are not surprising considering both groups equally improved in anxiety/depressive symptoms and hypothesise that CBT may be more effective in patients with more severe anxiety/depression and active disease.

In **Chapter 9** we explored the brain-gut axis in IBD: the bidirectional relationship between psychological stress and (intestinal) inflammation and the possibility to improve intestinal/systemic inflammation by treating anxiety/depression. Using an innovative and unbiased approach with a large protein panel, we found distinct plasma protein signatures associating with anxiety and/or depression in IBD patients mostly in remission. These immune signatures were altered in patients receiving CBT. Several proteins not previously investigated in anxiety and depression (in IBD) were now analyzed, providing a novel perspective on possibly involved proteins. Leukemia Inhibitory Factor-Receptor (LIF-R) and Chemokine (C-C motif) ligand 4 (CCL4) seemed promising candidate proteins responsive to psychotherapy, as they were associated to both the presence of anxiety and/or depressive symptoms and decreased after CBT.

Chapter 10 (in PART II) is the first of two chapters investigating outcome of transition. Here we propose a composite score measuring success of transition (Transition Yourself Score) consisting of the following items: adherence to visits at the gastroenterology outpatient clinic, adherence to medication and qualitative evaluation of the transition process by the patient. Failed transition was defined as a total score below 5. In our cohort of 35 patients, transition was successful in 63% of cases, moderately successful in 31% and failed in 6%. In addition, we demonstrated that self-efficacy, using the IBD-yourself questionnaire, was not predictive of success of transition.

In **Chapter 11** we used a more thorough approach in identifying outcomes reflecting successful transition, a step to further define success of transition in IBD. In a three-stage multinational Delphi study the opinion of a large expert (n=74) and patient panel (n=61) was asked. Analyses showed that, using the RAND UCLA criteria for agreement, 10 and 11 items were found to be important for success of transition by respectively the expert and patient panel. Remarkably, both panels agreed on 8 of these items, and 6 of the 8 items reflected self-management skills. The top-10 list formed by the expert panel in stage 3 showed that 'decision making regarding IBD', 'independent communication', and 'patient satisfaction about the transition process' were the three most important items.

In **Chapter 12 (PART III)** the main findings of our studies and their scientific and clinical implications are discussed and recommendations for future research are given.

With respect to anxiety and depression in paediatric IBD: we conclude that future studies using uniform screening measures (and cut-offs) are necessary to gain better insight into the prevalence of anxiety and depression. Based on the high prevalence we found in our patient cohort, we believe that it is justified and necessary to screen young IBD patients for anxiety/depression. For IBD patients in remission or with mildly active disease, but suffering from subclinical anxiety/depression, a full protocol of CBT did not seem beneficial. The best approach for this patient groups remains a question for the future. Furthermore, studies

investigating the effect of CBT in IBD patients with more severe (clinical) anxiety/depression and with at least moderately active disease are warranted.

With our transition research, we took the first steps in defining success of transition in IBD. Future studies should confirm our findings, formulate a definition of successful transition and develop a score measuring success of transition.

SAMENVATTING

Het doel van dit promotieonderzoek was om twee onderwerpen te bestuderen die belangrijk zijn voor adolescenten en jongvolwassen patiënten met Inflammatory Bowel Disease (chronisch Inflammatoire Darmziekten: ziekte van Crohn en Colitis Ulcerosa): 1) psychosociale problemen (specifiek angst en depressie) en de effectiviteit van cognitieve gedragstherapie (CGT) op medische en psychosociale uitkomsten, en 2) transitie van de kindergeneeskundige zorg naar de volwassenen zorg.

PART I bespreekt angst en depressie bij kinderen en adolescenten met IBD en de effectiviteit van een ziekte specifiek CGT protocol dat onderzocht werd in een gerandomiseerd gecontroleerd onderzoek (RCT). In **Hoofdstuk 2** presenteren we een systematisch literatuuronderzoek met meta-analyse naar het voorkomende (de prevalentie) van angst en depressie bij kinderen en adolescenten met IBD. In totaal werden 28 studies geïncludeerd (totaal aantal patiënten (n)= 8107, 51.3% man, 67.1% Ziekte van Crohn, gemiddelde leeftijd 14.3 jaar). Van belang is het verschil tussen psychologische symptomen en stoornissen: stoornissen beschrijven ernstige symptomen die een belangrijke beperking geven in het dagelijks leven en worden gediagnosticeerd met een psychiatrisch interview gebaseerd op de Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. Psychologische symptomen worden doorgaans gemeten met zelfrapportage vragenlijsten, patiënten met verhoogde symptomen (die niet voldoen aan alle criteria voor een stoornis) hebben last van mildere (of subklinische) symptomen, maar ervaren een minder grote beperking in het dagelijks leven dan patiënten met een gediagnosticeerde stoornis. Van de 28 geïncludeerde studies, onderzochten de meeste angst (n=10) of depressieve (n=22) symptomen, enkele studies onderzochten angst (n=3) of depressieve (n=4) stoornissen. De geschatte gepoolde prevalentie van angst-en depressieve symptomen was respectievelijk 16.4% en 15.0%. Voor angst-en depressieve stoornissen was dit een stuk lager, respectievelijk 4.2% en 3.4%. Meta-regressie analyse toonde dat studies waarin een hoger percentage patiënten actieve ziekte had, een hogere prevalentie van depressieve symptomen gevonden werd. Vergeleken met gepoolde prevalenties van angst/depressie in volwassen IBD-patiënten, zijn de gevonden prevalenties bij kinderen/jongeren met IBD een stuk lager. Verschillende verklaringen voor dit verschil werden besproken, waarvan één het kleinere aantal beschikbare studies is in kinderen met IBD, met daarbij een groot aantal verschillende instrumenten met verschillende cutoff scores. Om deze redenen zijn we voorzichtig met het trekken van conclusies en adviseren we dat onderzoeken in toekomst dezelfde instrumenten met dezelfde cutoff scores gaan gebruiken, om een beter inzicht te krijgen in de prevalenties.

In **Hoofdstuk 3** presenteren we het onderzoeksprotocol van HAPPY-IBD, onze multicenter gerandomiseerde gecontroleerde studie (RCT) die het effect van een ziekte specifieke CGT op zowel psychologische uitkomsten als het ziektebeloop onderzoekt in jonge (10-25 jaar) IBD-patiënten met subklinische angst en/of depressie symptomen. In de

RCT worden patiënten gerandomiseerd (dat wil zeggen op basis van toeval geloot) aan of Cognitieve Gedragstherapie (CGT) + reguliere medische zorg (RMZ), of aan RMZ alleen.

Hoofdstuk 4 en 5 beschrijven de resultaten van de eerste fase van HAPPY-IBD: het screenen van 374 Nederlandse adolescenten en jongvolwassenen met IBD op angst en depressie met zelfrapportage vragenlijsten en een psychiatrisch interview bij patiënten met verhoogde symptomen. In **Hoofdstuk 4** tonen we dat 47.4% van de patiënten last had van angst en/of depressie symptomen. Milde (subklinische) en ernstige (klinische) angst en/of depressieve symptomen waren aanwezig bij respectievelijk 23.6% en 12.4% van de patiënten. Klinische ziekteactiviteit, fecaal calprotectine en de bezinking (BSE) waren significant hoger bij patiënten met ernstige psychologische symptomen. Daarnaast vonden we een hogere prevalentie van angstsymptomen (28.3%) vergeleken met depressieve symptomen (2.9%) of gecombineerde angst-én depressieve symptomen (15.8%). Actieve ziekte was een significante voorspeller voor het hebben van depressieve symptomen. Het vrouwelijk geslacht en een kortere ziekteduur waren geassocieerd met de aanwezigheid van angst en/of depressieve symptomen. Gezien de hoge prevalentie van angst en/of depressieve symptomen adviseren wij met klem om jonge IBD-patiënten te screenen op angst en depressie wanneer zij de polikliniek bezoeken.

In **Hoofdstuk 5** exploreren we de relatie tussen psychologische factoren (ziektepercepties, coping, angst, depressie) en ziekte-specifieke kwaliteit van leven (KvL), gecorrigeerd voor demografische (geslacht, leeftijd, sociaal-economische status) en klinische factoren (ziekte type, klinische ziekteactiviteit). Door middel van multipele regressieanalyses lieten we zien dat negatieve ziektepercepties en depressie negatief geassocieerd zijn met ziektespecifieke KvL.

Hoofdstuk 6 is het eerste hoofdstuk dat rapporteert over fase 2 van HAPPY-IBD: het gerandomiseerde gecontroleerde onderzoek (RCT), waarin 70 patiënten werden geïncludeerd die gerandomiseerd werden aan of CBT+RMZ of RMZ alleen. In **Hoofdstuk 6** toonden we dat, over het geheel genomen, patiënten in beide groepen na 3 maanden (direct na het voltooien van 10 sessies CGT) ofwel stabiel bleven of verbeterden in angst/depressie symptomen. Exploratieve lineaire mixed model analyses toonden dat alle patiënten verbeterden wat betreft hun symptomen van angst of depressie en verbeterden in ziektespecifieke KvL. In **Hoofdstuk 7** wordt de effectiviteit van CBT op angst, depressie, ziektespecifieke KvL en andere psychologische uitkomsten zoals sociaal functioneren, ziektepercepties en slaapproblemen op lange termijn besproken. Resultaten op de lange termijn toonde eenzelfde patroon: in zowel de CGT+RMZ als de RMZ groep, was het deel van de patiënten dat verbeterden in angst/depressieve symptomen gelijk. Daarnaast was er in beide groepen evenveel verbetering in angst, depressie, ziektespecifieke KvL, sociaal functioneren, coping en ziektepercepties. Twee verklaringen werden gegeven voor het niet vinden van een verschil tussen beide groepen: de extra aandacht (vragenlijsten, interviews) die patiënten in de RMZ groep kregen door alleen mee te doen aan de RCT, zou al genoeg kunnen zijn om te verbeteren in subklinische angst/depressie symptomen. Daarnaast lijkt het

onnodig om IBD-patiënten met subklinische angst/depressie symptomen, en grotendeels in remissie, een uitgebreid CBT protocol te geven.

In **Hoofdstuk 8** richtten we ons op het effect van CGT op het beloop van de darmontsteking. We lieten zien dat de tijd tot de eerste opvlamming of het aantal opvlammingen niet verschillend was tussen de CGT+RMZ en de RMZ groep in het eerste jaar na randomisatie. Daarnaast zagen we dat CGT geen invloed had op klinische ziekteactiviteit scores en inflammatoire markers (fecaal calprotectine en C-reactief proteine). We benadrukten dat deze resultaten niet verassend waren gezien het feit dat beide groepen evenveel verbeterden in angst/depressie symptomen en veronderstellen dat CGT wellicht effectiever is bij patiënten met ernstigere angst/depressie symptomen en bij patiënten met een actieve darmontsteking.

In **Hoofdstuk 9** onderzochten we de hersen-darm-as in IBD: de wederzijdse relatie tussen psychologische stress en (intestinale) inflammatie, en de mogelijkheid om intestinale/systemische inflammatie te verbeteren door angst/depressie te behandelen. Met behulp van een vernieuwende en objectieve analysemethode met een groot eiwit panel, vonden we dat karakteristieke plasma eiwit profielen geassocieerd waren met angst en/of depressie bij IBD-patiënten die op dat moment geen klachten hadden van hun darmontsteking (darmziekte in klinische remissie). CGT zorgde voor verandering van deze eiwitprofielen. Verschillende eiwitten, niet eerder onderzocht in relatie tot angst/depressie (in IBD-patiënten) werden nu geanalyseerd, en bieden een nieuw perspectief op mogelijk betrokken eiwitten. Leukemia Inhibitory Factor-Receptor (LIF-R) en Chemokine (C-C motif) ligand 4 (CCL4) lijken veelbelovende kandidaat eiwitten die veranderen na psychotherapie, gezien het feit dat ze geassocieerd waren met de aanwezigheid van angst en/of depressieve symptomen en daalde na CGT.

Hoofdstuk 10 (PART II) is de eerste van twee hoofdstukken die de uitkomst/succes van transitie onderzoekt. In dit hoofdstuk introduceren we een samengestelde score die succes van transitie meet (Transition Yourself Score) en bestaat uit de volgende items: verschijnen op afspraken op de Maag Darm Lever (MDL) polikliniek, therapietrouw en een kwalitatieve evaluatie van het transitieproces door de patiënt. Mislukte transitie werd gedefinieerd als een totaalscore onder 5. In ons cohort met 35 patiënten bleek transitie succesvol bij 63% van de patiënten, redelijk succesvol bij 31% en mislukt bij 6% van de patiënten. Daarnaast lieten we zien dat zelfredzaamheid, gemeten met de IBD-Yourself vragenlijst, geen voorspeller was voor succes van transitie.

In **Hoofdstuk 11** gebruikten we een grondigere methode om uitkomsten die succes van transitie weerspiegelen te identificeren, als volgende stap om succes van transitie verder te definiëren. Door middel van een Delphi procedure in 3 fasen, vroegen we de mening van een groot expert (n=74) en patiënten (n=61) panel. Analyse met behulp van de RAND ULCA criteria voor overeenstemming toonde dat respectievelijk 10 en 11 items belangrijk werden geacht voor succes van transitie volgens het expert en patiënten panel. Opmerkelijk was dat beide panels het eens waren over 8 van deze items, en dat 6 van de 8

zelfmanagement vaardigheden betroffen. De top-10 gevormd door het expert panel in fase 3 toonde dat 'zelfstandig beslissingen maken omtrent IBD', 'zelfstandig communiceren', en 'patiënt tevreden over transitieproces' de drie belangrijkste items waren.

In **Hoofdstuk 12 (PART III)** worden de belangrijkste bevindingen van onze studies bediscussieerd en aanbevelingen voor toekomstig onderzoek gedaan.

Wat betreft angst en depressie bij kinderen en jongeren met IBD, concluderen we dat toekomstige onderzoeken dezelfde instrumenten met dezelfde cutoff scores moeten gebruiken, om een beter inzicht te krijgen in de prevalenties. Gezien de hoge prevalentie van angst en/of depressieve symptomen gevonden in onze patiëntengroep, adviseren wij met klem om jonge IBD-patiënten te screenen op angst en depressie.

Voor IBD-patiënten die weinig/geen klachten hebben van hun darmontsteking, maar wel subklinische angst en/of depressieklachten, lijkt een uitgebreid CGT protocol niet nodig. De beste behandelmethode voor deze patiëntengroep blijft een vraag voor de toekomst. Daarnaast zijn studies nodig die het effect van CGT onderzoeken bij IBD-patiënten met ernstige (klinische) angst/depressie en minstens matig actieve ziekte.

Met ons onderzoek naar transitie hebben we de eerste stappen genomen om succes van transitie in IBD te definiëren. Onze bevindingen moeten bevestigd worden in toekomstig onderzoek, daarnaast is een definitie van succesvolle transitie nodig, evenals een objectieve score die succes van transitie kan meten.

PART IV
Appendices

List of abbreviations
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LIST OF ABBREVIATIONS

ADIS-C/P	Anxiety Disorders Interview Schedule for Children/Parents
ADRS	Adolescent Depression Rating Scale
BDI-II	Beck Depression Inventory-second edition
B-IPQ	Brief Illness Perceptions Questionnaire
CAU	Care as Usual
CBT	Cognitive Behavioural Therapy
CCL	C-C Motif Chemokine
CXCL	C-X-C Motif Chemokine
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDI	Child Depression Inventory
CDRS-R	Child Depression Rating Scale – Revised
CERQ	Cognitive Emotion Regulation Questionnaire
CRP	C-Reactive Protein
CSM	Common Sense Model
ECCO	European Crohn's and Colitis Organisation
EIM	Extra-Intestinal Manifestations
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
FC	Fold Change
GE	Gastroenterology
HADS-A	Hospital Anxiety and Depression Scale – Anxiety scale
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HPA	Hypothalamic-pituitary-adrenal
HRQoL	Health-Related Quality of Life
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IBD-U	Inflammatory Bowel Disease Unclassified
IFN-y	Interferon gamma
IL	Interleukin
IQR	Interquartile Ranges
LIF-R	Leukemia Inhibitory Factor Receptor
LOD	Lower limit Of Detection
LRT	Likelihood Ratio Test
LFK	Luis Furuya-Kanamori
MCP	Monocyte Chemoattractant Protein
PARS	Paediatric Anxiety Ratings Scale

PASCET	Primary and Secondary Control Enhancement Therapy
PCA	Principal Component Analysis
PCDAI	Paediatric Crohn's Disease Activity
pMAYO	Partial Mayo
PUCAI	Paediatric Ulcerative Colitis Activity Index
RCT	Randomized Controlled Trial
RCI	Reliable Change Index
SCARED	Screen for Child Anxiety Related Emotional Disorders
SEM	Standard Error of Measurement
SES	Socio-Economic Status
SLCBT	Social Learning and Cognitive Behavioral Therapy
TNF	Tumor Necrosis Factor
TSNE	T-Distributed Stochastic Neighbor Embedding
TRAQ	Transition Readiness Assessment Questionnaire
UC	Ulcerative Colitis

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Gertrude van den Brink was born on 28 November 1986 in Utrecht, the Netherlands. She attended pre-university education at the Koningin Wilhelmina College (KWC) in Culemborg and received her certificate in 2004. Thereafter, Gertrude studied Education and Child studies for 1 year at the University of Utrecht and started her medical training at the University of Maastricht in 2005. In 2011, after receiving her medical degree, she worked as a paediatric resident (ANIOS) at the Groene Hart Ziekenhuis in Gouda and the Erasmus MC-Sophia Children's hospital. Working in a research-oriented hospital made her enthusiastic about medical research. In 2014, Dr. Hankje Escher (paediatric gastroenterologist) and Dr. Lisbeth Utens (clinical psychologist) gave her the opportunity to start a PhD project investigating psychosocial problems in adolescents and young adults with inflammatory bowel disease. In September 2019 she will start her training to become a General practitioner (GP) at the Leids Universitair Medisch Centrum (LUMC), combined with post-doc research. Gertrude is married with Jos Knoester and lives together with their daughter Thirza (2017) and son Jesse (2019).

LIST OF PUBLICATIONS

van den Brink G, Costes LMM, Tindemans I, Stapersma L, Rizopolous D, van der Woude CJ, Raatgeep HRC, Utens EMGJ, 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*

van den Brink G , Stapersma L, Bom AS, Rizopolous D, van der Woude CJ, Stuyt RJL, Szigethy EM, Escher JC, Utens EMWJ, Hendriks DM, Van der Burg JAT, Beukers R, Korpershoek TA, Theuns-Valks SDM, Utens EMWJ, Escher JC. Effect of Cognitive Behavioural therapy on clinical disease course in adolescents and young adults with Inflammatory bowel disease and subclinical anxiety and/or depression: Results of a randomised trial. *Inflamm Bowel Dis.* 2019 May 3 [Epub ahead of print]

van den Brink G, van Gaalen MAC, Zijlstra M, de Ridder L, van der Woude CJ, Escher JC. Health Care Transition outcomes in Inflammatory Bowel Disease: an international Delphi study. *J Crohns Colitis.* 2019 Feb 14 [Epub ahead of print]

Stapersma L, **van den Brink G ,** van der Ende J, Szigethy EM, Bodelier AG, 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. *Int J Behav Med.* Jun 2019 [Epub ahead of print]

Stapersma L, **van den Brink G** , van der Ende J, Szigethy EM, Groenweg M, de Bruijne FH, Hillegers MHJ, Escher JC, Utens EMWJ. Psychological outcomes of a cognitive behavioral therapy for youths with inflammatory bowel disease: results of a randomized controlled trials at 6 and 12 months follow-up. *In Revision*

van den Brink G , Stapersma L, Szigethy EM, Escher JC, Utens EMWJ. Systematic review with meta-analysis: anxiety and depression in children and adolescents with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;48(5):496-506

van den Brink G, Stapersma L, Szigethy EM, Escher JC, Utens EMWJ. Editorial: anxiety and depression in inflammatory bowel disease - authors' reply. *Aliment Pharmacol Ther.* 2018;48(6):687-688.

van den Brink G, van Gaalen MAC, Zijlstra M, de Ridder L, van der Woude CJ, Escher JC. Self-efficacy did not predict the outcome of the transition to adult care in adolescents with inflammatory bowel disease. *Acta Paediatr.* 2019;108(2):333-338

van den Brink G, Stapersma L, Vlug LE, Rizopolous 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. *Aliment Pharmacol Ther.* 2018;48(3):358-369.

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. *J Pediatr Psychol.* 2018;43(9):967-98029.

van den Brink G, van der Woude CJ, de Ridder L, van Gaalen MA, Escher JC. [Transition from paediatric to adult care: management of adolescents with inflammatory bowel disease]. *Ned Tijdschr Geneeskd.* 2016;160:D578. Dutch.

van den Brink G, Stapersma L, El Marroun H, Henrichs J, Szigethy EM, Utens EM,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 multicenter randomised controlled trial (HAPPY-IBD). *BMJ Open Gastroenterol.* 2016 Mar 2;3(1):e000071.

G. van den Brink, J.O. Wishaupt, J.C. Douma, N.G. Hartwig, F.G.A. Versteegh, Bordetella pertussis: An Underreported Pathogen In Pediatric Respiratory Infections. *BMC Infect Dis.* 2014;30;14:526.

PHD PORTFOLIO

Name PhD student: G. van den Brink
Erasmus MC Department: Pediatric Gastroenterology
PhD period: April 2014 – December 2018
Promotors: Prof. Dr. J.C. Escher / Prof Dr. E.M.W.J. Utens

PhD Training program	Year	Workload
General courses		
EndNote and PudMed (and other databases) courses	May 2014	1.0 ECTS
BROK ('Basiscursus Regelgeving Klinisch Onderzoek', NFU BROK academy)	November 2014	1.0 ECTS
Integrity in Science	January 2015	0.3 ECTS
Basic Introduction Course on SPSS	November 2015	1.0 ECTS
Biostatistical Methods I: Basis Principles part A	March 2016	2.0 ECTS
Specific courses		
Summer Course Immunology (Research Master Infection & Immunity)	September 2015	3.0 ECTS
Regression Analysis	August 2016	1.4 ECTS
Repeated measurements	April 2018	1.4 ECTS
EBRO Course (Richtlijnontwikkling, Federatie Medisch Specialisten)	November 2017	0.4 ECTS
Seminars and Workshops		
Sophia Research Days *(oral presentation 2018)*	2014-2018	1.6 ECTS
Erasmus MC PhD Day	2014-2017	1.6 ECTS
Yearly Young ICC symposium	2014-2018	1.0 ETCS
ECCO 2016 Educational course Pediatric IBD	March 2016	0.3 ECTS
ESPGHAN 2nd IBD Masterclass, Rotterdam	November 2016	0.8 ECTS
ESPGHAN masterclass on gastrointestinal immunity	November 2017	1.0 ECTS
Attended conferences		
PIBD Rotterdam 2014	September 2014	1.0 ECTS
ECCO 2016 Amsterdam	March 2016	1.0 ECTS
Attended conferences with presentations		
ESPGHAN 2019 Glasgow *(poster presentation)*	June 2019	1.0 ECTS
ECCO 2019 Copenhagen *(poster presentation*	March 2019	1.0 ECTS
ECCO 2015 Barcelona *(poster presentation)*	February 2015	1.0 ECTS
ESPGHAN IBD Clinical Observation Program Rotterdam (*oral presentation)*	December 2015	1.0 ECTS
PIBD Barcelona 2017 *(E-poster, and poster presentation)*	September 2017	1.0 ECTS
NVGE Eindhoven 2017 *(oral presentation)*	October 2017	0.3 ECTS
ECCO 2018 (*poster presentation)*	February 2018	1.0 ECTS
ESPGHAN 2018 *(poster presentation)*	May 2018	1.0 ECTS
KICC symposium *(oral presentation)*	January 2019	1.0 ECTS
Local research meetings		
Lab- clinic research meetings (2/month) with yearly presentations	2014-2018	2.0 ECTS
Regional Paediatric Gastroenterology meeting AMC-VUmc-LUMC	September 2014	0.2 ECTS
Clinical & Research Meeting Pediatric Psychology	October 2014	0.2 ECTS

PhD Teaching	Year	Workload
Lecturing		
Lectures for Pediatric Nurses 2/year	2015-2018	1.2 ECTS
Lecture for IBD Nurse specialists	May 2018	0.7 ECTS
Lecture for education advisors working with IBD patients	February 2019	0.4 ECTS
Supervising Master's thesis		
L. Vlug, medical student, Erasmus University	2017	2.0 ECTS
A. Bom, medical student, Erasmus University	2018	2.0 ECTS
Other	**Year**	**Workload**
Meetings for updating guideline paediatric IBD	2016-2018	1.6 ECTS
Outpatient clinic, department paediatric gastroenterology	2014-2018	2.0 ECTS
Reviewer of articles for international scientific journals	2015-2018	1.0 ECTS

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