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# General discussion



## GENERAL DISCUSSION

### Aims of the present thesis and main results

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

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

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

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

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

The abovementioned findings will be discussed more extensively below.

## Psychological aspects of IBD in youth

### Anxiety and depression in youth with IBD

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

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

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

#### 1) Disease factors

##### *Clinical disease activity*

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

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

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

#### *Other disease factors*

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

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

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

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

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

## 2) Demographic factors

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

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

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

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

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

#### Other psychological factors of IBD in youth

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

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

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

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

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

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

### **Interrelationships between disease and psychological factors**

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

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

### **Disease-specific CBT for youth with IBD**

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

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

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

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

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

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

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

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

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

### **Strengths and limitations**

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

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

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

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

## Future research

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

### Future research – psychological problems in IBD

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

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

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

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

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

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

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

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

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

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

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

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

### **Clinical implications and Recommendations**

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

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