Summary

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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