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

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

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

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

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

INTRODUCTION

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

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

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

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

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

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

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

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

MATERIALS AND METHODS

Design

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

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

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

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

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

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

Procedure

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

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

Measures

Demographic characteristics

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

Clinical characteristics

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

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

Anxiety and depression

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

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

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

Severity of anxiety and depression

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

Health-related quality of Life

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

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

Statistical analysis

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

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

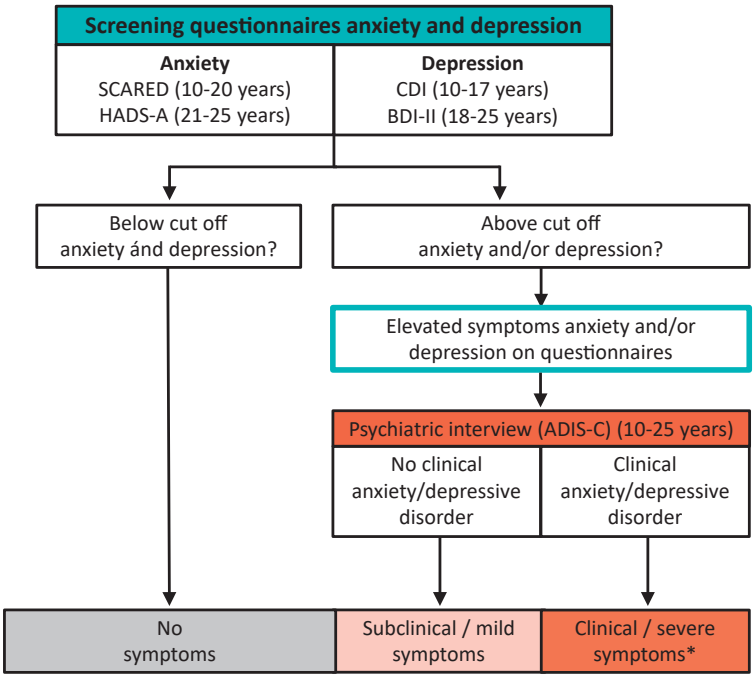

Figure 1 | Flowchart screening anxiety/depression
Abbreviations: SCARED= Screen for Child Anxiety Related Emotional Disorders; HADS-A= Hospital Anxiety and Depression Scale – Anxiety scale; CDI= Child Depression Inventory; BDI-II= Beck Depression Inventory-second edition ADIS-C= Anxiety Disorders Interview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

To identify risk factors for symptoms of anxiety and depressive symptoms (aim 2), we conducted four regression analyses with the following outcomes. I: absence/presence of anxiety/depressive symptoms, II: severity of anxiety/depressive symptoms, III: absence/presence of anxiety symptoms and IV: absence/presence of depressive symptoms. Analysis III and IV were performed to investigate risk factors specific for anxiety or depressive symptoms. For analysis I, III and IV a binomial logistic regression and for analysis II an multinomial logistic regression was conducted. Subgroup analysis was performed for patients 10-17 and 18-25 years. In the regression analysis, the 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) and the computing environment R for multiple imputation (R Development Core Team, 2016. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients characteristics

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

Prevalence of anxiety and depression

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

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

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

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

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

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

Abbreviations: SD= standard deviation, IQR= interquartile range, CD= Crohn's Disease, UC: ulcerative colitis, IBD-U: IBD-unclassified.
Notes: [†]UC includes IBD-U patients [‡]L1: ileocecal, L2: colonic, L3: ileocolonic, L4a: upper gastrointestinal tract proximal and L4b distal from Treitz ligament [§]E1: proctitis, E2: left sided colitis distal of splenic flexure, E3: extensive colitis distal of hepatic flexure, E4: pancolitis [¶]prednisone (oral and intravenous) and budesonide (oral) [¥]aminosalicylate or corticosteroid enemas [||]EIM: involving skin (31.5%), eyes (1.75%), liver and biliary tracts (10.5%), joints (33.3%) and bones (28.1%)

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

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

Health-related quality of life

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

Prevalence of mild and severe anxiety/depressive symptoms

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

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

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

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

Multiple regression analysis: risk factors for anxiety and depressive symptoms

Risk factors for anxiety/depressive symptoms

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

Risk factors for mild and severe anxiety/depressive symptoms

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

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

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

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

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

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

Abbreviations: IQR= interquartile range

Risk factors for anxiety symptoms

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

Risk factors for depressive symptoms

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

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

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

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

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

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

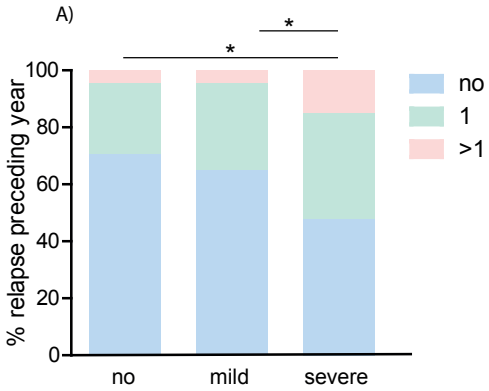

Figure 2a (left) | Patients with severe anxiety/depressive symptoms had more relapse preceding year compared to patients with mild or no anxiety/depressive symptoms
Note: * $p<0.05$

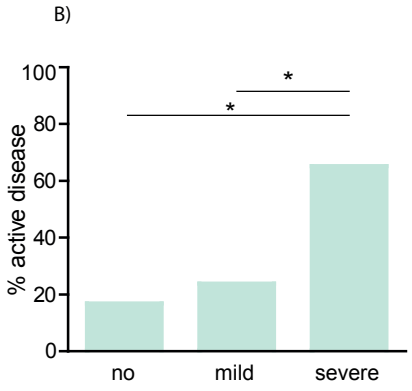

Figure 2b (right) | A higher percentage of active disease was found patients with severe anxiety/depressive symptoms compared to patients with mild or no anxiety/depressive symptoms
Note: * $p<0.05$

DISCUSSION

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

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

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

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

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

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

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

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

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

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