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

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

** Both authors contributed equally*

† Both authors share last authorship

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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/cutoffs 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 2-50% [5, 6] for anxiety symptoms and 0-33% [7, 8] for depressive symptoms. Only a few studies investigated prevalence of anxiety and depressive disorders, which ranged respectively from 3-7% [9, 10] and 1-17% [10, 11] .

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. [4]

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. [16], included studies till 2009, investigating psychosocial functioning and quality of life. They found an increased incidence of anxiety and depressive disorders, varying from 25-73%, 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, two 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 cutoff for elevated symptoms reported by the authors. Disagreement regarding extracted data was re-

solved 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. [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 include 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).

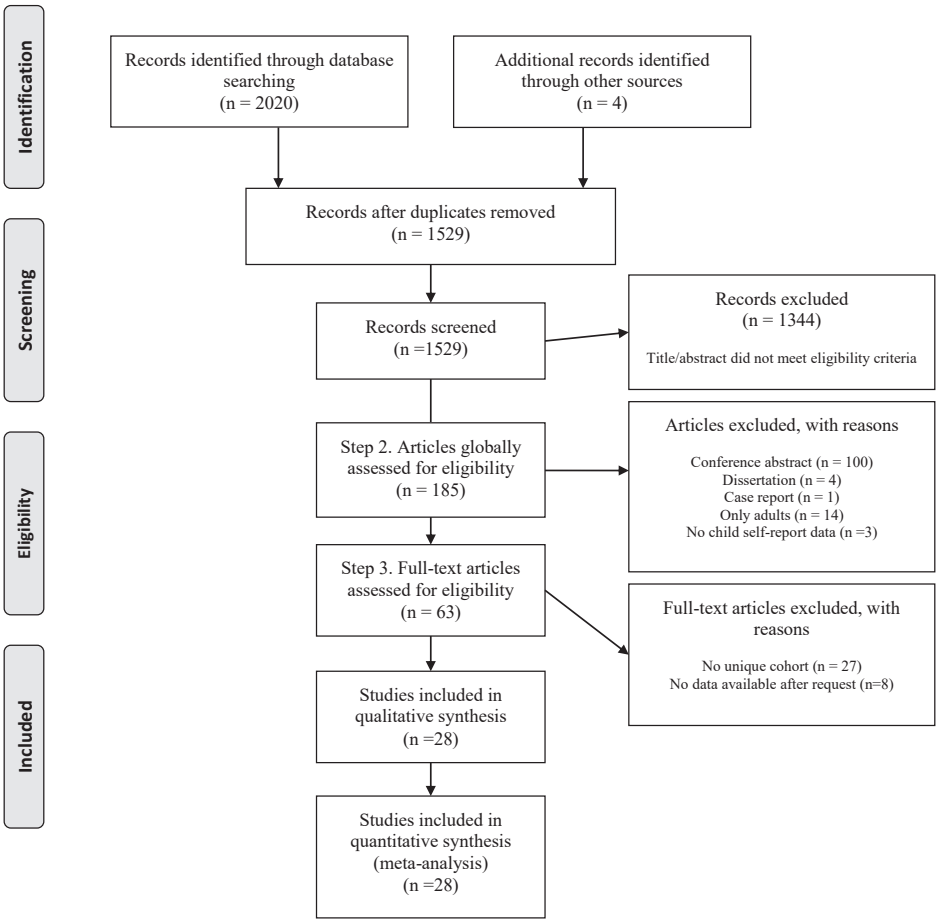

Figure 1 | PRISMA flow diagram

RESULTS

Study selection

During the database search 2020 records were found, 4 additional studies were identified through other sources (i.e. reference lists of included records). 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 8 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.

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, which 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, 9 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]. 25 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 (PGA) [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 (cutoff 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[7] §	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[11] §	2733	54	63	13,8 (<18)	-	16/27	Anxiety	ICD codes	-	-	4,8	-	-
							Depression	ICD codes	-	-	-	-	0,9
Arvanitis 2016[30] §	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[33] §	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[35] §	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[36] §	21	52	57	13,9 (6-20¶)	33,3	13/27	Depression	Q	ChilD-S (Total score ≥11)	-	-	19,1	-
Iturralde 2017[37] §	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	-	-	-

Table 1 | *Overview of study characteristics and prevalence rates (continued)*

Study	Sample size	% Male	% CD	Mean age (range†)	% Active disease	Quality score	Outcome	Method Q or I‡	Instrument (cutoff for elevated symptoms)	Prevalence (%)				
										Anxiety symptoms	Anxiety disorders	Depressive symptoms	Depressive disorders	
Giannakopoulos 2016[40§]	85	41	67	13,2 (8-18)	50,6	11/27	Depression	Q	CDI (Total score ≥15)	-	-	14,0	-	
Szigethy 2007[41 §]	156	-	-	14,3 (11-17)	-	12/27	Depression	Q	CDI (Total score ≥9)	-	-	23,1	-	
Szigethy 2014[42 §]	765	-	-	- (9-17)	-	13/27	Depression	Q	CDI (Total score ≥10)	-	-	32,0	-	
							Depression	I	K-SADS	-	-	-	10,5	
Thompson 2012[43 §]	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[48 §]	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[50 §]	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	-	

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.

Notes: 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; § data after request provided by the (corresponding) author; ¶ all included patients were <18; $ data received of patients <18.

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, $ß$ = .004, p = .699) and gender (% male, $ß$ = .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 9 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.

Author and year		Statistics per study			Prevalence rate and 95% Confidence interval
		Prevalence rate	Lower limit	Upper limit	
Mackner et al 2005[5]	1/50	0,020	0,000	0,084	
Reigada et al 2015[6]	46/93	0,495	0,393	0,596	
Reigada et al 2011[8]	8/36	0,222	0,099	0,374	
Arvanitis et al 2016[30]	46/276	0,167	0,125	0,213	
Jelenova et al 2016[35]	4/23	0,174	0,042	0,360	
Kilroy et al 2011[39]	31/79	0,392	0,287	0,503	
Watson et al 2017[42]	4/71	0,056	0,012	0,124	
Reigada et al 2016[47]	23/86	0,267	0,179	0,367	
Walter et al 2016[49]	24/161	0,149	0,098	0,209	
Reigada et al 2017[50]	18/280	0,064	0,038	0,096	
Total		0,164	0,068	0,273	

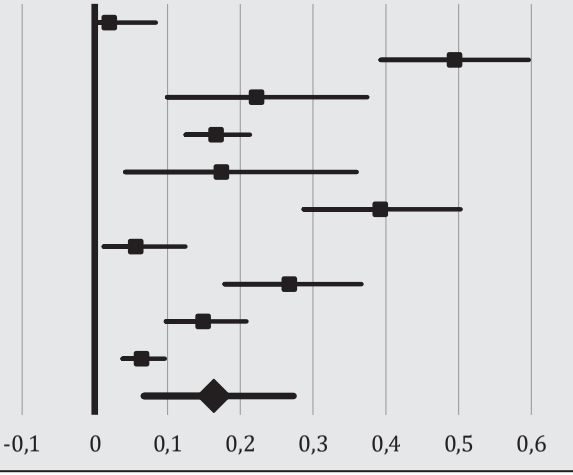

Figure 2a | Forest plot prevalence rate anxiety symptoms

Note. Sample sizes can differ from those mentioned in Table 1, due to missing data on the outcome measure.

Author and year		Statistics per study			Prevalence rate and 95% Confidence interval
		Prevalence rate	Lower limit	Upper limit	
Loftus et al 2011[9]	81/2144	0,038	0,030	0,046	
Engelmann et al 2015[10]	3/47	0,064	0,008	0,156	
Barnes et al 2017[11]	121/2733	0,044	0,037	0,052	
Total		0,042	0,036	0,048	

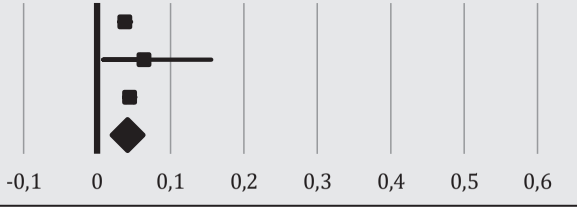

Figure 2b | Forest plot prevalence rate anxiety disorders
Note. Sample sizes can differ from those mentioned in Table 1, due to missing data on the outcome measure.

Author and year		Statistics per study			Prevalence rate and 95% Confidence interval
		Prevalence rate	Lower limit	Upper limit	
Mackner et al 2005[5]	0/50	0,000	0,000	0,034	
Reed-Knight et al 2012[7]	0/31	0,000	0,000	0,055	
Reigada et al 2011[8]	12/36	0,333	0,187	0,497	
Arvanitis et al 2016[30]	10/276	0,036	0,017	0,062	
Marcus et al 2009[31]	1/70	0,014	0,000	0,060	
Castaneda et al 2013[32]	11/34	0,324	0,175	0,492	
Van Tilburg et al 2015[33]	51/189	0,270	0,209	0,336	
Jayanath et al 2014[34]	6/26	0,231	0,086	0,415	
Jelenova et al 2016[35]	4/24	0,167	0,040	0,347	
Mahlmann et al 2017[36]	4/21	0,190	0,046	0,391	
Iturralde et al 2017[37]	2/23	0,087	0,002	0,245	
Herzog et al 2013[38]	1/110	0,009	0,000	0,039	
Giannakopoulos et al 2016[40]	12/85	0,141	0,074	0,224	
Szigethy et al 2007[41]	36/156	0,231	0,168	0,300	
Szigethy et al 2014[42]	245/765	0,320	0,288	0,354	
Thompson et al 2012[43]	50/191	0,262	0,202	0,327	
Watson et al 2017[44]	6/71	0,085	0,029	0,162	
Schuman et al 2013[45]	24/122	0,197	0,131	0,272	
Reed-Knight et al 2014[46]	10/78	0,128	0,062	0,213	
Ryan et al 2013[48]	4/112	0,036	0,008	0,080	
Walter et al 2016[49]	8/161	0,050	0,021	0,089	
Reigada et al 2017[50]	7/280	0,025	0,009	0,047	
Total		0,150	0,064	0,248	

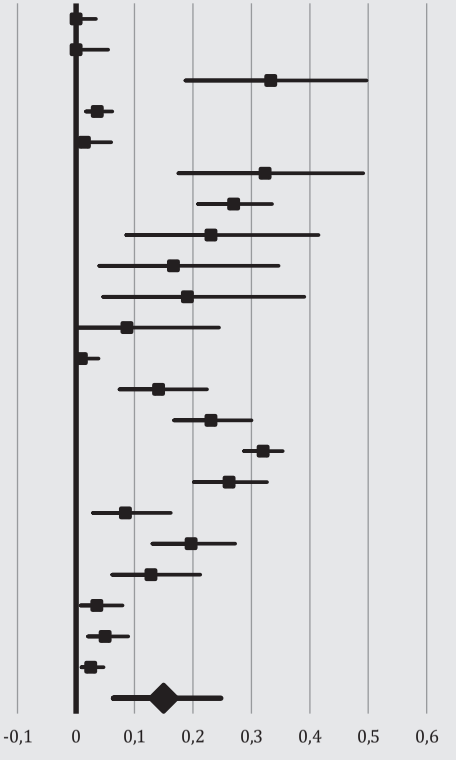

Figure 2c | Forest plot for the meta-analysis on the prevalence rate of depressive symptoms
Note. Sample sizes can differ from those mentioned in Table 1, due to missing data on the outcome measure.

Author and year		Statistics per study			Prevalence rate and 95% Confidence interval
		Prevalence rate	Lower limit	Upper limit	
Loftus et al 2011[9]	118/2144	0,055	0,046	0,065	
Engelmann et al 2015[10]	8/47	0,170	0,074	0,293	
Barnes et al 2017[11]	28/2733	0,010	0,007	0,014	
Szigethy et al 2014[42]	80/765	0,105	0,084	0,127	
Total		0,034	0	0,093	

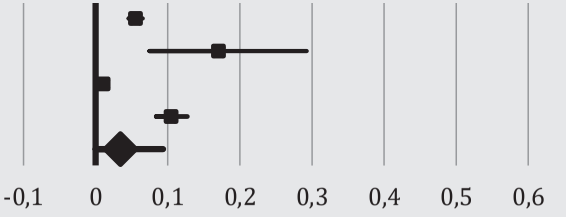

Figure 2d | Forest plot prevalence rate depressive disorders
Note. Sample sizes can differ from those mentioned in Table 1, due to missing data on the outcome measure.

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 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 cutoffs. 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 cor-

ticosteroids, 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. Firstly, although all studies used validated instruments to assess anxiety or depressive symptoms, numerous different instruments were used, not all validated in paediatric IBD. Different cutoffs for the same instruments were used, and some used raw total scores, while others used (varying) T-scores. For example, for the CDI, cutoff scores ranged from 9 [42] to 19 [38] or 20 [35] and for the SCARED, cutoff 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 cutoffs for each instrument. In addition, only 4 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.

Secondly, 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%). Thirdly, 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.

Fourthly, 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, 2 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. Firstly, knowing about this high heterogeneity is very important. Secondly, 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 and colleagues [17] and include using the same validated screening measures and clinical diagnostic measures (psychiatric interview) with the same comparable cutoffs, 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 cutoffs, 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 cutoffs. More studies are necessary to determine the prevalence of anxiety/depressive disorders using a standardized psychiatric interview following DSM criteria. In order 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).

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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"

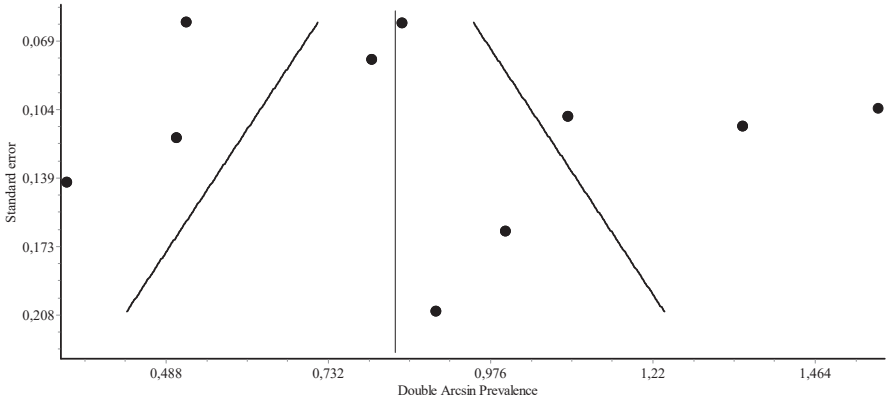
Appendix 2. Quality/risk of bias checklist

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)

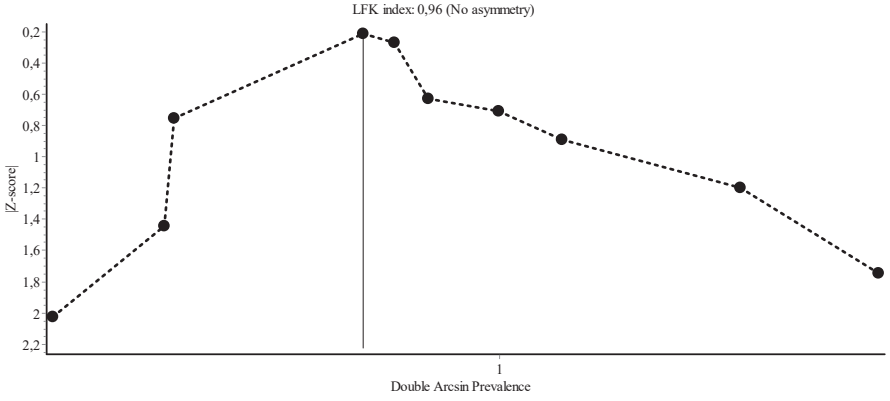
Maximum score: 27

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

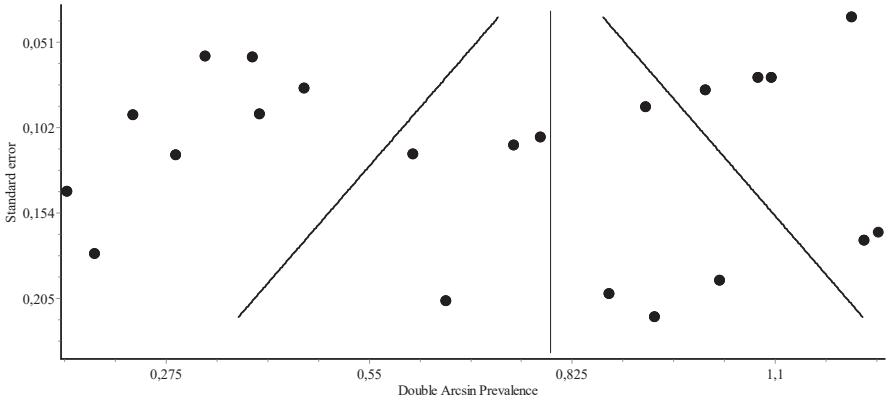
Appendix 3. Funnel and Doi plots for anxiety and depressive symptoms



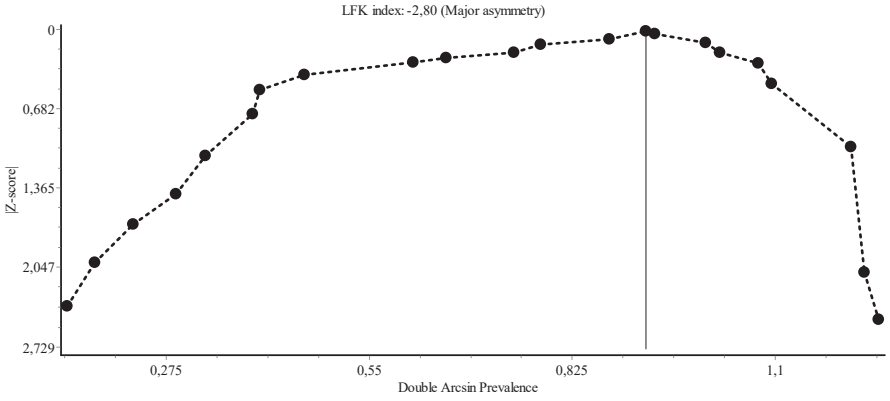
a) Funnel plot anxiety symptoms



b) Doi plot anxiety symptoms
Abbreviations: LFK= Luis Furuya-Kanamori index



c) Funnel plot depressive symptoms



d) Doi plot anxiety symptoms
Abbreviations: LFK= Luis Furuya-Kanamori index