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Changes in health-related quality of life over a 1-year follow-up period in children with inflammatory bowel disease

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Abstract
Purpose Little is known about disease-specific health-related quality-of-life (HRQoL) changes over time in paediatric patients with inflammatory bowel disease (IBD), and about their associations with baseline medical characteristics.
Methods In this study, 153 paediatric patients with IBD from the multicentre prospective Swiss IBD cohort study were included at baseline. Of these, 90 patients were analysed at a 1-year follow-up. Medical data were extracted from hospital records, while HRQoL data were measured using the standardized, self-report disease-specific IMPACT-III questionnaire.
Results The IBD diagnosis of the included children was made an average of 2.0 years before their baseline assessment. Over the 1-year follow-up period, a significant increase in overall HRQoL and in the HRQoL domain 'physical functioning' was evident. On multivariate analysis, overall HRQoL changes over time were predicted by baseline HRQoL, baseline disease activity, and disease activity changes over time. HRQoL improvements were significantly associated with decreases in physician-assessed disease activity. Children reporting a low baseline HRQoL and children with inactive or mildly-active disease experienced greater improvements.
Conclusions Children with more severe baseline disease activity had the greatest risk for HRQoL deterioration over the 1-year follow-up period. However, among possible factors that might influence HRQoL changes over time, the child's medical characteristics explained only a small proportion of their variability in our sample. We, therefore, recommend that researchers and clinicians focus on factors that are not incorporated within the multidimensional HRQoL concept if they seek to gain better insights into factors that influence HRQoL changes over time in children with IBD.

Keywords Health-related quality of life · Psychological adaptation · Inflammatory bowel disease · Chronic disease · Paediatric · Children

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Introduction

Inflammatory bowel disease (IBD) is a group of chronic diseases that include Crohn's disease, ulcerative colitis, and indeterminate colitis. Approximately 25–30% of patients with Crohn's disease and 20% of patients with ulcerative

or indeterminate colitis have their disease diagnosed before the age of 20 years [1]. The recurrent unpredictable phases of remission and exacerbation of IBD symptoms, its treatment using multiple medications, infusions, nutritional therapy and surgical interventions, and concerns about long-term consequences, such as increased risk for colorectal cancer [2], can be very stressful and might negatively impact the health-related quality of life (HRQoL) of the children with IBD to a considerable degree.

HRQoL has become an important outcome measure to evaluate an individual's adaptation to a chronic medical condition [3]. It is an essential complement to the examination of clinical symptoms and functional limitations, and involves assessing each individual's perception of the impact of the disease on a broad range of health outcomes, including the physical, emotional, social, and cognitive functioning [4]. The previous studies that used a disease-specific HRQoL instrument among paediatric patients with IBD (i.e., the IMPACT questionnaire) revealed that higher physician-assessed disease activity was associated with lower self- and proxy-reported HRQoL in the children [5–11]. To the best of our knowledge, only one previously published study has attempted to describe disease-specific HRQoL changes over time among paediatric IBD patients and analyse their association with the children's medical characteristics [10], while one more study was performed among children with Crohn's disease only [7]. These investigators found that the HRQoL was lowest at the time of diagnosis, but that it improved thereafter. Furthermore, they found that having more severe disease at baseline negatively affected a child's HRQoL at the time of the follow-up. Knowledge of such predictors allows identifying those patients which are at risk for HRQoL deterioration over time.

The primary aims of the present prospective study were to longitudinally examine self-reported disease-specific HRQoL in children with IBD over a 1-year follow-up period and to analyse whether the child's medical characteristics (i.e., type of IBD, time since diagnosis, disease activity at baseline, and disease activity changes from baseline to follow-up) were predictive of their HRQoL changes over time. Since all the children included in this study had one additional year to adapt to their chronic disease over the period of time from baseline to follow-up, and since they all were receiving medical treatment, we expected to observe significant HRQoL improvements over time. Furthermore, we hypothesized that baseline disease activity and disease activity changes over time would be associated with HRQoL changes over time; more specifically, we anticipated that children with more severe baseline disease activity would have greater HRQoL improvements over time than children with low baseline disease activity and that a decrease in disease activity would be associated with HRQoL improvements. In addition, we expected that baseline HRQoL would significantly predict HRQoL changes over time in the sense that HRQoL changes would be more pronounced in patients who started with a low HRQoL than with a high HRQoL.

Methods

Participants

This prospective study was part of a comprehensive, multicentre study in Switzerland, called the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) [12]. The SIBDCS started in 2006 with the objective of following paediatric patients through yearly physician- and self-reported assessments of, among others, psychosomatic aspects, health resource consumptions, and psychosocial aspects related to the disease (e.g., disease-specific HRQoL). More information about the study can be found on http://www.ibdcohort.ch. The Swiss IBD paediatric cohort study includes children and adolescents up to 17 years of age diagnosed with IBD based on Lennard-Jones criteria [13], with diagnosis established at least 4 months prior to inclusion or associated with at least one relapse. The following six children's hospitals were involved in patient recruitment: Basel, Berne, Geneva, Lausanne, St. Gallen, and Zurich. All children and adolescents with IBD who came for regular check-ups with or without complaints in one of the six hospitals were asked to participate in the study. Exclusion criteria were permanent residency outside of Switzerland, refusal to sign the informed consent, and the presence of some other specific form of colitis (i.e., infectious colitis, microscopic colitis, ischemic colitis, eosinophilic enteritis, radiation colitis, or a urogenital ulcer). The Swiss IBD paediatric cohort study was approved by the review boards of all participating hospitals and was performed in full accordance with the Declaration of Helsinki. Ethical approval number for Basel was 274/08, for Berne 110/06, for Geneva 9-006, for Lausanne 212/08, for St. Gallen 09/050, and for Zurich StV-07/08.

In total, 187 paediatric patients with IBD within the age range of 7–16 years at baseline assessment (T0) were recruited between 2008 and 2013 and were all eligible for study participation. All parents signed the informed consent. Of the 187, 153 were included at T0 (response rate 81.8%). 37% were recruited by the hospital in Zurich, 3% in St. Gallen, 11% in Lausanne, 3% in Basel, 5% in Geneva, and 40% in Berne. Thirty-four children did not participate at T0 due to missing HRQoL data. Study participants did not significantly differ from the 34 non-participants in terms of their sex ($\chi^2 = 0.64$, $p = .43$), age at study inclusion ($U = -0.57$, $p = .57$), type of IBD diagnosis ($\chi^2 = 2.44$, $p = .12$), time since diagnosis ($U = -0.88$, $p = .38$), and

disease activity ($\chi^2 = 0.09$, $p = .76$). Of the 153, 90 children were analysed at a 1-year follow-up (T1, response rate 48.1%). These 90 children participating at both assessment points (T0 and T1) did not significantly differ from the 63 who participated at T0, but not at T1, in their sex ($\chi^2 = 0.87$, $p = .35$), age at study inclusion ($U = -0.46$, $p = .65$), type of IBD diagnosis ($\chi^2 = 0.10$, $p = .75$), time since IBD diagnosis ($U = -1.45$, $p = .15$), and disease activity ($\chi^2 = 2.98$, $p = .08$).

Methods of data collection

After parents provided written informed consent, the child's medical data were entered into a standardized form by the gastroenterologist at the hospital (i.e., child age at diagnosis and type of IBD diagnosis were collected retrospectively from medical records, while medical data at T0 and T1 were collected prospectively). HRQoL data at T0 and T1 were obtained by means of standardized questionnaires that were filled out by a study nurse in face-to-face interviews with patients. To ensure that the children could express their own views more openly, they were interviewed separately from their parents. HRQoL data were obtained on average 1.3 months after the assessment of the children's medical data at T0, with 67% of the questionnaires completed the same day. The mean interval between T0 and T1 was 1.02 years (SD = 0.22, range 0.52–1.44).

Measures

Child medical data

The time since diagnosis (years) was calculated by the difference between the child's age at HRQoL baseline assessment at T0 and the age at diagnosis. Type of IBD diagnosis was categorized into the two classes "Crohn's disease" (coded as 1) vs. "ulcerative/indeterminate colitis" (0). Previous intestinal surgery, surgery for a fistula or abscess, or other abdominal surgeries were further summarized into a dichotomous variable "previous surgery" vs. "no previous surgery". The following seven IBD complications were considered in a sum score representing the number of the previous complications (none, one, more than one): osteopaenia/osteoporosis, anaemia, malasorption syndrome, massive haemorrhage, perforation/peritonitis, growth failure, and adverse effect of treatment. The current need for enteral nutrition was summarized into a dichotomous variable "yes" vs. "no". Furthermore, each patient's current IBD-specific medication was classified into five categories, which included the intake of biologics, immune suppressants, corticosteroids, 5-amino salicylic acid, and other IBD medication. These categories were further dichotomized into "any IBD medication" vs. "no medication". Current disease activity at T0 and T1 was classified into inactive, mild, or moderate/severe using cut-off scores based on the Pediatric Ulcerative Colitis Activity Index (range 0–85) [14] and the Short Pediatric Crohn's Disease Activity Index (range 0–90) [15]. In the multivariate regression analysis, both scales were linearly transformed into a 0–100 scale.

Health-related quality of life

HRQoL was assessed using the German version (Switzerland) of the IMPACT-III questionnaire [16, 17]. For our study, the original English version of the IMPACT-III questionnaire was forward- and backward-translated and culturally adapted according to the schema and the guidelines outlined by Beaton and colleagues [18]. For each step of the process, quality control and translation decisions were performed by the Swiss adaptation team in consultation with the instrument's developer, which finally approved the translation. The IMPACT-III is a widely used instrument that assesses self reports of disease-specific HRQoL in children and adolescents with IBD. The IMPACT-III consists of 35 items asking about the frequency and intensity of the effect of IBD on various aspects of health over the last 2 weeks using a 5-point Likert response scale. In our study, a validated shortened version with 22 items of the IMPACT-III questionnaire was used [19]. The following domain scales as well as a measure of overall HRQoL (total score, 22 items) were calculated by summing the underlying items: emotional functioning (8 items), IBD symptoms (7 items), body image (4 items), and social functioning (3 items). For the total score, missing values ≤ 3 were imputed from the average of the other items. If 4 or more answers were missing, then the individual questionnaire was considered as incomplete and discarded. Scales were linearly transformed into a 0–100 scale, with higher scores indicating better HRQoL. In this study, the internal consistency was good for the total score and acceptable to good for the subscales at both T0 and T1.

Statistical analysis

Data were analysed using the statistical package SPSS, release 20.0 for Windows (SPSS Inc., Chicago, IL, USA) and R 3.2.4 (R Core Team, 2016). All statistical tests were two-sided with a predefined significance level of $p < .05$. Chi-square tests and Mann–Whitney U tests were used, as appropriate, to compare child sex, age at study inclusion, type of IBD, time since diagnosis, and disease activity between study participants and non-participants. Cronbach's alpha was calculated to test for internal reliability of the HRQoL scale scores. HRQoL differences between T0 and T1 were assessed using Wilcoxon tests; changes with

respect to dichotomous medical variables using McNemar's tests. Given that five Wilcoxon tests were performed for the pairwise HRQoL comparisons (total and four domain scales), a Bonferroni correction was applied by multiplying the uncorrected p values by 5. For all comparisons, effect sizes were computed by Cohen's d (0.20, small effect; 0.50, medium effect; >0.80, large effect) [20]. Five multiple linear regression models were used to predict HRQoL changes (T1 − T0, with the overall HRQoL and the four HRQoL domain scales as dependent variables) [21]. Three blocks of predictors were entered into each regression model. Block 1 comprised HRQoL at T0 (baseline total score and the respective baseline domain scale scores). Block 2 (child socio-demographic characteristics) comprised sex and age at T0. Block 3 (child medical characteristics) comprised type of IBD diagnosis, time since IBD diagnosis at T0, disease activity indices at T0, and disease activity changes from T0 to T1 (T1 minus T0). Predictors were selected on a-priori hypotheses and the statistical significance of bivariate correlations with HRQoL changes. The presence of multi-collinearity was examined by looking at the correlation matrix (correlations >0.80) and the variance inflation factor (VIF): no indication of multi-collinearity was detected [21]. The percentage of missing values across the eight variables involved in the multiple linear regression varied between 0 and 23.3%. Regarding these variables, 21 out of the 90 participants (23.3%) had incomplete data. Due to this, we decided to impute missing data for the multiple linear regression analysis. We used multiple imputation [22] to create and analyse 50 multiply imputed data sets as implemented in the R-package mice (version 2.25 in R 3.2.4) [23]. Incomplete variables were imputed under fully conditional specification [24]. Model parameters were estimated with multiple regressions applied to each imputed data set separately. These estimates and their standard errors were combined using Rubin's rules [22].

Results

Sample characteristics

The IBD diagnosis of the 153 included children (45.8% females) was made an average of 2.0 years before the assessment performed at T0 (SD = 2.1, range 0.3–15.2). Almost 60% of the children had a CD, whereas 36.6% had colitis ulcerosa and 4.6% had colitis indeterminate (Table 1).

Changes in medical characteristics of the children at T0 and T1 are summarized in Table 2. At T0, 20 children (13.1%) had undergone surgery. By T1, three more children had undergone surgery. Surgery for fistula and abscesses was most frequently done at both T0 and T1. At T0, 54.2% of the children, and at T1, 65.6% of them had at least one previous complication. Anaemia and growth delay were the most frequent complications at both T0 and T1. At T1, significantly more children had the previous complications than at T0, with ten children (11.1%) having complications for the first time at T1. A few children had enteral nutrition at T0 and T1, while no child had enteral nutrition at both timepoints. The majority of the children had IBD-specific medication at T0 (94.8%) and T1 (86.7%). The number of children who needed medications did not significantly change from T0 to T1 (p value =0.065). However, fewer children took corticosteroids and 5-amino salicyclic acid at T1 than at T0, while no significant changes were found with respect to the use of biologic agents or immune suppressants. Both at T0 and T1, the majority of children had inactive or only mildly-active disease. At T1 (3.3%), significantly less children had moderate/severe disease activity than at T0 (11.8%).

HRQoL changes from baseline to follow-up

Mean values for the IMPACT-III scales at T0 and T1 and statistics for mean comparisons are presented in Table 3. Significant changes were evident between T0 and T1 with small-to-moderate effect sizes for overall HRQoL and the domain 'physical functioning' (subscale "IBD symptoms"). At T1, children reported significantly better overall HRQoL

Table 1 Demographic characteristics of the sample at baseline and follow-up

	Baseline (T0) $n = 153$	Follow-up (T1) $n = 90$
Female sex, n (%)	70 (45.8)	44 (48.9)
Age at assessment, years, mean (SD), range	13.3 (2.2), 8.2–16.2	14.3 (2.2), 9.1–17.1
Type of IBD diagnosis		
Crohn's disease	90 (58.8)	52 (57.8)
Ulcerative colitis/indeterminate colitis	63 (41.2)	38 (42.2)
Time since diagnosis, years, mean (SD), range	2.0 (2.1), 0.3–15.2	3.3 (2.4), 1.2–16.1

Table 2 Child medical characteristics at baseline and follow-up: change from T0 to T1

	Baseline (T0) $n=153$	Follow-up (T1) $n=90$	Change T1-T0 p value
Previous surgery, *n* (%)	20 (13.1)	14 (15.6)	0.25
Intestinal surgery, *n* (%)[a]	14 (9.2)	4 (4.4)	–
Surgery for fistula and abcsesses, *n* (%)[a]	22 (14.4)	9 (10.0)	–
Other abdominal surgery, *n* (%)[a]	6 (3.9)	3 (3.3)	–
Number of previous complications, *n* (%)			0.002
None	70 (45.8)	31 (34.4)	
One	55 (35.9)	36 (40.0)	
More than one	28 (18.3)	23 (25.6)	
Current enteral nutrition, *n* (%)[b]	6 (3.9)	3 (3.3)	–
Current IBD medication, *n* (%)	145 (94.8)	78 (86.7)	0.065
Biologics, *n* (%)[a]	28 (18.3)	18 (20.0)	0.11
Immune suppressants, *n* (%)[a]	103 (67.3)	61 (67.8)	0.38
Corticosteroids, *n* (%)[a]	40 (26.1)	7 (7.8)	<0.001
5-Amino salicylic acid, *n* (%)[a]	67 (43.8)	27 (30.0)	0.019
Other, *n* (%)[a]	5 (3.3)	13 (14.4)	0.002
Disease activity classifications, *n* (%)			0.022
Inactive	80 (52.3)	46 (51.1)	
Mild	39 (25.5)	25 (27.8)	
Moderate/severe	18 (11.8)	3 (3.3)	
Missings	16 (10.5)	16 (17.8)	

p values are derived based on 90 children with data on both T0 and T1

T0 baseline assessment, *T1* follow-up assessment, *IBD* inflammatory bowel disease

[a]Some children had more than one surgery, respectively more than one medication

[b]No child had enteral nutrition at both T0 and T1

Table 3 Descriptive statistics for self-reported disease-specific health-related quality of life (HRQoL) in pediatric patients with inflammatory bowel disease (IBD)

IMPACT-III (CH)	Baseline (T0) $n=153$			Follow up (T1) $n=90$			Change (T1-T0) $n=90$	
	Median	IQR	M (SD)	Median	IQR	M (SD)	p value[a]	Effect size[b]
Emotional functioning	81.3	68.8–90.6	76.8 (17.5)	84.4	75.0–89.6	80.2 (13.8)	0.09	0.22
IBD symptoms	87.5	75.0–96.1	83.9 (14.4)	89.3	82.1–96.4	87.4 (11.2)	**0.04**	0.27
Body image	75.0	62.5–81.3	73.4 (15.0)	81.3	68.8–87.5	78.0 (12.3)	0.14	0.34
Social functioning	100.0	91.7–100.0	94.1 (12.7)	100.0	91.7–100.0	94.5 (10.8)	0.60	0.03
Overall HRQoL, total score	79.5	68.8–85.2	77.0 (10.9)	81.8	73.9–85.2	79.9 (8.1)	**0.02**	0.30

Significant values are indicated in bold

HRQoL Health-related quality of life, *IBD* inflammatory bowel disease, *IQR* interquartile range

[a]Wilcoxon test was performed

[b]Effect size according to Cohen's *d* was calculated

and significantly better physical functioning than at T0. After Bonferroni correction, these effects did not remain significant. Nonetheless, there was a consistent increase from T0 to T1 in all HRQoL scales, which should not be ignored.

Multivariate prediction of HRQoL changes from baseline to follow-up

Table 4 summarizes the results of five multiple linear regression models predicting HRQoL changes from T0 to

Table 4 Predictors of changes in self-reported disease-specific health-related quality of life among children with inflammatory bowel disease ($n=90$)

Predictor	Emotional functioning					IBD symptoms					Body image				
	B	95% CI	β	*p*	ΔR^2	*B*	95% CI	β	*p*	ΔR^2	*B*	95% CI	β	*p*	ΔR^2
Block 1					0.408***					0.469***					0.367***
HRQoL at T0	−0.55	(−0.70, −0.40)	−0.69	**<0.001**		−0.62	(−0.78, −0.45)	−0.73	**<0.001**		−0.60	(−0.77, −0.43)	−0.66	**<0.001**	
Block 2					0.004					0.004					0.043*
Male sex	−1.41	(−6.23, 3.40)	−0.10	0.56		−0.65	(−4.65, 3.35)	−0.06	0.75		−0.85	(−5.47, 3.76)	−0.07	0.71	
Age at T0	−0.30	(−1.44, 0.84)	−0.05	0.60		−0.25	(−1.15, 0.65)	−0.04	0.58		−1.34	(−2.43, −0.25)	−0.22	0.17	
Block 3					0.029					0.079*					0.020
Crohn's disease	−1.67	(−6.67, 3.33)	−0.12	0.51		−2.34	(−6.50, 1.82)	−0.18	0.27		−0.08	(−4.89, 4.73)	−0.01	0.97	
Time since diagnosis at T0	−0.43	(−1.43, 0.57)	−0.08	0.40		−0.27	(−1.16, 0.62)	−0.06	0.55		0.30	(−0.66, 1.27)	0.06	0.53	
Disease activity at T0	−0.16	(−0.38, 0.07)	−0.18	0.17		−0.25*	(−0.46, −0.04)	−0.33	**0.02**		−0.04	(−0.26, 0.17)	−0.07	0.68	
Disease activity from T0 to T1	−0.05	(−0.29, 0.19)	−0.05	0.66		−0.32**	(−0.52, −0.12)	−0.38	**0.002**		−0.13	(−0.35, 0.10)	−0.16	0.27	
Total R^2					0.441***					0.552***					0.430***
Predictor	Social functioning					Overall HRQoL									
	B	95% CI	β	*p*	ΔR^2	*B*	95% CI	β	*p*	ΔR^2					
Block 1					0.513***					0.481***					
HRQoL at T0	−0.57	(−0.57, 0.07)	−0.71	**<0.001**		−0.55	(−0.69, −0.42)	−0.76	**<0.001**						
Block 2					0.001					0.012					
Male sex	1.36	(−2.55, 5.27)	0.11	0.49		−0.56	(−3.12, 2.00)	−0.08	0.67						
Age at T0	0.25	(−0.63, 1.12)	0.04	0.58		−0.41	(−1.01, 0.20)	−0.11	0.18						
Block 3					0.026					0.043					
Crohn's disease	−3.92	(−7.90, 0.06)	−0.32	0.54		−1.53	(−4.21, 1.16)	−0.19	0.62						
Time since diagnosis at T0	0.02	(−0.81, 0.84)	0.00	0.97		−0.16	(−0.71, 0.39)	−0.05	0.56						
Disease activity at T0	−0.06	(−0.25, 0.13)	−0.08	0.52		−0.13*	(−0.26, −0.01)	−0.27	**0.04**						
Disease activity from T0 to T1	−0.04	(−0.25, 0.17)	−0.05	0.72		−0.13*	(−0.26, −0.01)	−0.25	**0.03**						
Total R^2					0.540***					0.536***					

IBD inflammatory bowel disease, *HRQoL* health-related quality of life, *T0* baseline assessment, *T1* 1-year follow-up assessment, *B* regression coefficient; *95% CI* 95% confidence interval, β standardized regression coefficient, *p* *p* value, ΔR^2 change in multiple correlation coefficient

Block 1 comprises baseline HRQoL, Block 2 comprises child socio-demographic characteristics, Block 3 comprises child medical characteristics

Male sex was coded as 1, female sex as 0; type of IBD diagnosis was categorized into "Crohn's disease" (coded as 1) vs. "ulcerative/indeterminate colitis" (coded as 0)

Significant values are indicated in bold; with respect to the change in multiple correlation coefficient by ***$p \leq .001$, **$p < .01$, *$p < .05$

T1 (overall HRQoL and the four HRQoL domain scales). In each regression model, the baseline HRQoL score was a significant predictor of HRQoL changes, in the sense that children with low baseline HRQoL had greater improvements than children with high baseline HRQoL. Child sex and age did not predict HRQoL changes over time, while the prediction of HRQoL changes in the domain 'body image' by child socio-demographic characteristics (sex and age together) reached significance (producing a significant increase in ΔR^2 from 0.367 to 0.410). Among the child's medical characteristics, disease activity indices at T0 and activity changes from T0 to T1 were significant predictors of overall HRQoL changes and changes in the domain 'IBD symptoms'. Children with low physician-assessed disease activity (inactive or mildly-active disease) experienced greater HRQoL improvements than children with higher disease activity at baseline. In addition, HRQoL improvements were significantly associated with decreases in disease activity. Type of IBD diagnosis and time since diagnosis were no significant predictors for HRQoL changes.

Discussion

This study aimed to investigate both HRQoL changes within a 1-year follow-up period and whether HRQoL changes might be predicted by the child's sex, age at baseline (T0), type of IBD, time since diagnosis at T0, disease activity indices at T0, or disease activity changes from T0 to 1-year of follow-up (T1).

We identified significant HRQoL improvements from T0 to T1 with respect to overall HRQoL and the HRQoL domain 'physical functioning'. After Bonferroni correction, these effects failed to remain significant. However, there was a consistent increase in all HRQoL domain scales which leads us to believe that our results are relevant [25]. There are two possible explanations for this. First, there might have been a positive treatment effect on HRQoL changes over time. In our study, the majority of the children were receiving medical treatment, while a few children had also undergone surgery and received enteral nutrition. We detected no significant association between HRQoL changes over time and previous surgery, enteral nutrition, and need for medications (data not shown). However, we do know that treatment has an effect on child disease activity, which decreased significantly from T0 to T1 (there were especially less moderate/severe cases at T1 than at T0). This, in turn, was significantly associated with overall HRQoL changes and changes in the HRQoL domain 'physical functioning'. Nevertheless, in the absence of a control group of untreated children, it is difficult to draw any conclusions regarding a direct or indirect (via disease activity changes) treatment effect. Second, there might have been a time effect influencing HRQoL changes. At T1, the children with IBD were 1 year older than at T0 and, thus, had one additional year to adapt to their chronic disease, which might be reflected in increased HRQoL at T1. This hypothesis is supported by a phase model of adjustment to medical stress [26, 27] that suggests that an individual's stress is higher at the time of a diagnosis than later when the acute threat has resolved and treatment regimens have been successfully established. In the two previously published prospective studies, findings were similar [7, 10]. In our study, the time since children's IBD diagnosis varied between participants. While for some patients, the diagnosis was made just a few months before the HRQoL assessment (still in the phase of acute stress); for others, the diagnosis was made already several years before. In line with Kazak et al. (2006) and Price et al. (2016), we assume that individual's adaptation cannot steadily increase over time, but it might particularly improve within the first few months after diagnosis and then levelling off. Thus, we believe that this large variation might explain the lack of significance of time, since diagnosis on HRQoL changes in our study.

On multivariate analysis, overall HRQoL changes over time were significantly predicted by baseline HRQoL, baseline disease activity, and disease activity changes over time. In fact, the strong and negative association between baseline HRQoL and HRQoL changes over time was expected. This relationship between baseline status and subsequent changes has attracted great interest in clinical research [28, 29] and has been particularly discussed in the context of the well-known phenomenon of "regression to the mean" [30, 31]. Regression to the mean (i.e., the negative association between baseline and change) occurs with any variable that fluctuates within given individual when two measurements of the same variable are made over a short time period, whether due to measurement error, true variation or both [29]. In our study, this means that high baseline HRQoL scores tended to decrease over time, while low baseline scores tended to increase. However, in the absence of a control group, it is not possible to disentangle the effect of regression to the mean from treatment effects. Among the child's medical characteristics, significant effects of baseline disease activity and disease activity changes over time on HRQoL changes were found. Children with inactive or mildly-active disease activity at baseline experienced greater HRQoL improvements over time than children with moderate or severe disease activity at baseline. In addition, a decrease in disease activity over time was associated with HRQoL improvements. While the latter finding is in line with our hypothesis, the previous one is in contrast to it. Due to the fact that the medical treatment focus on the reduction of disease activity, we anticipated that the treatment might be most successful in those children with high disease activity and, therefore, would have

greater HRQoL improvements from baseline to follow-up than in children with low baseline disease activity. Our data suggest that children with moderate/severe baseline disease severity are at higher risk for HRQoL deterioration over a 1-year follow-up period compared to children with inactive or mildly-active disease activity at baseline. It can be assumed that high disease activity negatively impacts the child's rating of his/her HRQoL in the short term and long term. However, our regression analysis on HRQoL changes from T0 to T1 indicated that the change in multiple correlation coefficients by child medical characteristics was only significant for the overall HRQoL and the HRQoL domain 'physical functioning'. This result makes logical sense, as HRQoL is defined as a multidimensional concept in which the domain 'physical functioning' incorporates aspects of both clinical symptoms and disease activity. We identified no significant associations between child medical characteristics and HRQoL changes in the domain scales 'emotional functioning', 'body image', or 'social functioning'. As HRQoL has been increasingly integrated into clinical practice in recent years as an essential complement to the examination of clinical symptoms and functional limitations, this result should be of great interest to health care providers. In line with other studies from the literature [5–11], there is a relationship between disease activity and disease-specific HRQoL, but medical characteristics cannot solely explain HRQoL changes over time. In fact, medical characteristics explain only a small proportion of the total variance in HRQoL changes. Thus, due to the multidimensionality of HRQoL, it seems necessary in future work to integrate such predictors that are not incorporated within the HRQoL concept (i.e., family functioning).

The strengths of the current study include its multicentred and prospective study design, a rather large sample compared to the previous studies involving paediatric patients with IBD in the age range of 7–16 years at baseline assessment, and the use of a validated disease-specific HRQoL instrument. We used a 22-item version of the IMPACT-III questionnaire with four instead of the six originally proposed HRQoL domains [19]. We found that it is important to use scale scores, which are psychometrically valid and robust, even if a few items of the original questionnaire, all relevant for the patients, were deleted based on statistical reasons. However, in a parallel analysis (not shown) with the six original scales, results also showed HRQoL improvements from T0 to T1, and a significant prediction of HRQoL changes by baseline HRQoL, disease activity at T0 and disease activity changes. In terms of a post-hoc power analysis ($\alpha = 0.05$, two-tailed) using the G*power software [32], our sample size provided adequate power to detect moderate effect sizes within the multiple regression analysis. Nevertheless, several limitations merit note. First, we were unable to provide data with respect to both generic and disease-specific HRQoL, which are seen as essential complements to each other [4] and which would have allowed a comparison of the influence of medical characteristics on general and disease-specific HRQoL changes over time. In addition, we were unable to provide data on children's pubertal status and to define its proportion of variance on HRQoL changes. Future studies might address this. Second, the disease activity indices of patients with Crohn's disease were assessed using the Short Pediatric Crohn's Disease Activity Index [15], which differs slightly from the Paediatric Crohn's Disease Activity Index (PCDAI) [33], which was used in most previous studies on paediatric Crohn's disease patients. However, because the PCDAI requires the determination of height velocity, the analysis of laboratory tests, and components of the physical exam (perirectal examination), the feasibility of this index has been called into question [34]. Thus, as the Short PCDAI was found to be a practical and valid tool to measure paediatric Crohn's disease activity, we used it in our study [15]. Third, the children's medical and HRQoL data were not assessed simultaneously in all cases, which might have weakened the association between disease activity and HRQoL. However, we failed to identify any significant difference between participants with a shorter answer delay and those with a longer delay with respect to the correlation between child disease activity and HRQoL (data not shown). Therefore, inclusion of child disease activity in the multiple regression models seems appropriate. Fourth, our response rate was 81.8% at T0 and 48.1% at T1. While our response rate at T0 was comparable to other studies within the IBD literature [6], we believe that the rather low follow-up participation rate at T1 might have been primarily caused by the time expensive assessment of both medical data and self-reported questionnaires, and by working and other constraints in the hospital as well as in the families. However, our analyses revealed no significant differences between study participants and non-participants with respect to sex, age at study inclusion, type of IBD, time since diagnosis, and disease activity, but we cannot rule out the possibility that the patients who participated in our study differed with respect to other variables (e.g., HRQoL) than those who did not.

The main implications that can be drawn from our findings are that—even though that overall HRQoL improved over a 1-year follow-up period among paediatric patients with IBD—special attention should be addressed to children with more severe disease activity. These children are at greatest risk for HRQoL deterioration over time. Furthermore, since the children's medical characteristics only explain a small proportion of the overall change in HRQoL over time, we recommend that future focus in both clinical practice and research be on factors that are not incorporated within the multidimensional HRQoL concept, to

gain better insight into variables that influence a child with IBD's HRQoL over time.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all parents of the children included in this study.

References

1. Kelsen, J., & Baldassano, R. N. (2008). Inflammatory bowel disease: The difference between children and adults. *Inflammatory Bowel Diseases, 14*, 9–11. doi:10.1002/Ibd.20560.
2. Eaden, J. A., Abrams, K. R., & Mayberry, J. F. (2001). The risk of colorectal cancer in ulcerative colitis: A meta-analysis. *Gut, 48*(4), 526–535.
3. Mackner, L. M., Greenley, R. N., Szigethy, E., Herzer, M., Deer, K., & Hommel, K. A. (2013). Psychosocial issues in pediatric inflammatory bowel disease: Report of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition, 56*(4), 449–458. doi:10.1097/MPG.0b013e3182841263.
4. Matza, L. S., Swensen, A. R., Flood, E. M., Secnik, K., & Leidy, N. K. (2004). Assessment of health-related quality of life in children: A review of conceptual, methodological, and regulatory issues. *Value in Health, 7*(1), 79–92. doi:10.1111/j.1524-4733.2004.71273.x.
5. Gallo, J., Grant, A., Otley, A. R., Orsi, M., MacIntyre, B., Gauvry, S., et al. (2014). Do parents and children agree? Quality-of-life assessment of children with inflammatory bowel disease and their parents. *Journal of Pediatric Gastroenterology and Nutrition, 58*(4), 481–485. doi:10.1097/Mpg.0000000000000236.
6. Gray, W. N., Graef, D. M., Schuman, S. S., Janicke, D. M., & Hommel, K. A. (2013). Parenting stress in pediatric IBD: Relations with child psychopathology, family functioning, and disease severity. *Journal of Developmental and Behavioral Pediatrics, 34*(4), 237–244. doi:10.1097/Dbp.0b013e318290568a.
7. Hill, R. J., Lewindon, P. J., Muir, R., Grange, I., Connor, F. L., Ee, L. C., et al. (2010). Quality of life in children with Crohn disease. *Journal of Pediatric Gastroenterology and Nutrition, 51*(1), 35–40. doi:10.1097/MPG.0b013e3181c2c0ef.
8. Marcus, S. B., Strople, J. A., Neighbors, K., Weissberg-Benchell, J., Nelson, S. P., Limbers, C., et al. (2009). Fatigue and health-related quality of life in pediatric inflammatory bowel disease. *Clinical Gastroenterology and Hepatology, 7*(5), 554–561. doi:10.1016/j.cgh.2009.01.022.
9. Perrin, J. M., Kuhlthau, K., Chughtai, A., Romm, D., Kirschner, B. S., Ferry, G. D., et al. (2008). Measuring quality of life in pediatric patients with inflammatory bowel disease: Psychometric and clinical characteristics. *Journal of pediatric gastroenterology and nutrition, 46*(2), 164–171. doi:10.1097/MPG.0b013e31812f7f4e.
10. Otley, A. R., Griffiths, A. M., Hale, S., Kugathasan, S., Pfefferkorn, M., Mezoff, A., et al. (2006). Health-related quality of life in the first year after a diagnosis of pediatric inflammatory bowel disease. *Inflammatory Bowel Diseases, 12*(8), 684–691.
11. van der Zaag-Loonen, H. J., Grootenhuis, M. A., Last, B. F., & Derkx, H. H. (2004). Coping strategies and quality of life of adolescents with inflammatory bowel disease. *Quality of life research: An international journal of quality of life aspects of treatment, care and rehabilitation, 13*(5), 1011–1019.
12. Pittet, V., Juillerat, P., Mottet, C., Felley, C., Ballabeni, P., Burnand, B., et al. (2009). Cohort profile: The Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). *International Journal of Epidemiology, 38*(4), 922–931. doi:10.1093/ije/dyn180.
13. Lennard-Jones, J. E. (1989). Classification of inflammatory bowel disease. *Scandinavian Journal of Gastroenterology Supplement, 170*, 2–6. **(discussion 16–19)**.
14. Turner, D., Otley, A. R., Mack, D., Hyams, J., De Bruijne, J., Uusoue, K., et al (2007). Development, validation, and evaluation of a pediatric ulcerative colitis activity index: A prospective multicenter study. *Gastroenterology, 133*(2), 423–432. doi:10.1053/j.gastro.2007.05.029.
15. Kappelman, M. D., Crandall, W. V., Colletti, R. B., Goudie, A., Leibowitz, I. H., Duffy, L., et al. (2011). Short pediatric Crohn's disease activity index for quality improvement and observational research. *Inflammatory Bowel Diseases, 17*(1), 112–117. doi:10.1002/ibd.21452.
16. Griffiths, A. M., Nicholas, D., Smith, C., Munk, M., Stephens, D., Durno, C., et al. (1999). Development of a quality-of-life index for pediatric inflammatory bowel disease: Dealing with differences related to age and IBD type. *Journal of pediatric gastroenterology and nutrition, 28*(4), S46–S52.
17. Otley, A., Smith, C., Nicholas, D., Munk, M., Avolio, J., Sherman, P. M., et al. (2002). The IMPACT questionnaire: A valid measure of health-related quality of life in pediatric inflammatory bowel disease. *Journal of pediatric gastroenterology and nutrition, 35*(4), 557–563.
18. Beaton, D. E., Bombardier, C., Guillemin, F., & Ferraz, M. B. (2000). Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine, 25*(24), 3186–3191. doi:10.1097/00007632-200012150-00014.
19. Werner, H., Landolt, M. A., Buehr, P., Koller, R., Nydegger, A., Spalinger, J., et al. (2014). Validation of the IMPACT-III quality of life questionnaire in Swiss children with inflammatory bowel disease. *Journal of Crohn's & Colitis, 8*(7), 641–648. doi:10.1016/j.crohns.2013.11.025.
20. Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*(1), 155–159. doi:10.1037/0033-2909.112.1.155.
21. Field, A. (2009). *Discovering statistics using SPSS*. London: Sage Publications.
22. Rubin, D. B. (1987). *Multiple imputation for nonresponse in surveys*. New York: Wiley.
23. van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software, 45*(3), 1–67.
24. Van Buuren, S., Brand, J. P. L., Groothuis-Oudshoorn, C. G. M., & Rubin, D. B. (2006). Fully conditional specification in multivariate imputation. *Journal of Statistical Computation and Simulation, 76*(12), 1049–1064. doi:10.1080/10629360600810434.

25. Altman, D. G., & Bland, J. M. (1995). Statistics notes—absence of evidence is not evidence of absence. *British Medical Journal, 311*(7003), 485–485.
26. Kazak, A. E., Kassam-Adams, N., Schneider, S., Zelikovsky, N., Alderfer, M. A., & Rourke, M. (2006). An integrative model of pediatric medical traumatic stress. *Journal of Pediatric Psychology, 31*(4), 343–355. doi:10.1093/jpepsy/jsj054.
27. Price, J., Kassam-Adams, N., Alderfer, M. A., Christofferson, J., & Kazak, A. E. (2016). Systematic review: A reevaluation and update of the integrative (Trajectory) model of pediatric medical traumatic stress. *Journal of Pediatric Psychology, 41*(1), 86–97. doi:10.1093/jpepsy/jsv074.
28. Hayes, R. J. (1988). Methods for assessing whether change depends on initial value. *Statistics in Medicine, 7*(9), 915–927.
29. Tu, Y. K., & Gilthorpe, M. S. (2007). Revisiting the relation between change and initial value: A review and evaluation. *Statistics in Medicine, 26*(16), 3205–3206. doi:10.1002/sim.2538.
30. Bland, J. M., & Altman, D. G. (1994). Statistics notes. 2. Regression towards the mean. *British Medical Journal, 308*(6942), 1499–1499.
31. Bland, J. M., & Altman, D. G. (1994). Some examples of regression towards the mean. *BMJ (Clinical research ed.), 309*(6957), 780.
32. Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*(2), 175–191. doi:10.3758/Bf03193146.
33. Hyams, J. S., Ferry, G. D., Mandel, F. S., Gryboski, J. D., Kibort, P. M., Kirschner, B. S., et al. (1991). Development and validation of a pediatric Crohns-disease activity index. *Journal of Pediatric Gastroenterology and Nutrition, 12*(4), 439–447.
34. Turner, D., Hyams, J., Markowitz, J., Lerer, T., Mack, D. R., Evans, J., et al. (2009). Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflammatory Bowel Diseases, 15*(8), 1218–1223. doi:10.1002/ibd.20867.