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Health-related quality of life improves during one year of medical and surgical treatment in a European population-based inception cohort of patients with Inflammatory Bowel Disease — An ECCO-EpiCom study☆

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Abbreviations: CD, Crohn's disease; ECCO, European Crohn's and Colitis Organization; EpiCom, Epidemiological Committee; GCS, Glucocorticosteroids; IBD, Inflammatory Bowel Disease; IBDU, Inflammatory Bowel Disease Unclassified; HRQoL, Health-related quality of life; OR, Odds ratio; SF-12, Short Form 12; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; UC, Ulcerative colitis

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Abstract

Background & Aims: Health-related quality of life (HRQoL) is impaired in patients with Inflammatory Bowel Disease (IBD). The aim was prospectively to assess and validate the pattern of HRQoL in an unselected, population-based inception cohort of IBD patients from Eastern and Western Europe.
Methods: The EpiCom inception cohort consists of 1560 IBD patients from 31 European centres covering a background population of approximately 10.1 million. Patients answered the disease specific Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and generic Short Form 12 (SF-12) questionnaire at diagnosis and after one year of follow-up.
Results: In total, 1079 patients were included in this study. Crohn's disease (CD) patients mean SIBDQ scores improved from 45.3 to 55.3 in Eastern Europe and from 44.9 to 53.6 in Western Europe. SIBDQ scores for ulcerative colitis (UC) patients improved from 44.9 to 57.4 and from 48.8 to 55.7, respectively. UC patients needing surgery or biologicals had lower SIBDQ scores before and after compared to the rest, while biological therapy improved SIBDQ scores in CD. CD and UC patients in both regions improved all SF-12 scores. Only Eastern European UC patients achieved SF-12 summary scores equal to or above the normal population.

Conclusion: Medical and surgical treatment improved HRQoL during the first year of disease. The majority of IBD patients in both Eastern and Western Europe reported a positive perception of disease-specific but not generic HRQoL. Biological therapy improved HRQoL in CD patients, while UC patients in need of surgery or biological therapy experienced lower perceptions of HRQoL than the rest.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) affect patients not only physically but also through limitations on social, educational, professional, and emotional activities due to chronicity, unpredictable disease course, young age of onset and their medical and surgical therapies. Patients with Inflammatory Bowel Disease (IBD) experience an impaired perception of health-related quality of life (HRQoL) compared with a healthy background population,[1–4] with disease course and disease activity,[5,6] the perceived quality of care delivered, and the individual's psychological status and social support[7,8] as important factors affecting HRQoL. Data on HRQoL from unselected population-based cohorts are limited as most studies are based on selected cohorts or phase III trials[9,10] of varying design, prohibiting generalisations about the IBD patient population.[11] However, population-based unselected cohorts including mild-to-severe cases offer the most accurate picture of community effectiveness regarding therapeutic approaches for IBD patients and the impact of these approaches on HRQoL.

The European Crohn's and Colitis Organization's (ECCO) Epidemiological Committee (EpiCom) study is a prospectively collected unselected population-based inception cohort of 1560 IBD patients, recruited from 31 medical centres from Eastern and Western Europe. Previously, the group demonstrated a two-to-one West–East incidence gradient in Europe with incidences correlating with the GDP of each country.[12] IBD patients in Eastern and Western Europe were not different regarding socio-demographic and disease related characteristics as well as disease course but regional differences in treatment choices during the initial year of disease were found i.e. in the use of biological agents and 5-ASA for CD and UC patients.[13,14] The aim of this study was therefore to investigate the differences in HRQoL at diagnosis and after the initial year of disease, across Eastern and Western Europe and, to assess the impact of treatment choices on HRQoL.

2. Materials and methods

2.1. Study population

The EpiCom-cohort is a population-based prospective inception cohort of incident IBD patients established through collaboration amongst 31 medical centres from 8 Eastern and 14 Western European countries covering a total background population of 10.1 million inhabitants (3.3 million in Eastern and 6.8 million in Western Europe). A total of 1560 incident IBD patients (550 with CD, 840 with UC and 170 with Inflammatory Bowel Disease Unclassified (IBDU)) diagnosed between 1 January and 31 December 2010, and living in the predefined catchment areas at the time of diagnosis, were prospectively included in the EpiCom cohort and followed up annually starting in 2010. Standardised methods for case ascertainment, diagnostic criteria for case definition, time period of inclusion and recorded patient data were used. One centre from Eastern Europe included only patients aged <15 years at diagnosis and did not take part in the HRQoL assessment of patients as only adult patients were included in the present study.

2.2. Classifications and definitions

The diagnosis of CD, UC or IBDU was based on the *Copenhagen Diagnostic Criteria*.[15–17] Disease extent for UC, as well as disease location and behaviour for CD, were defined according to the *Montreal Classification*.[18] Medical treatment was grouped into five treatment groups in ascending potency of treatment: 5-aminosalicylates (5-ASA) (oral and/or topical 5-ASA treatment ± topical steroids), glucocorticosteroids (GCS) (oral steroids ± 5-ASA or topical steroids), immunomodulators (azathioprine, mercaptopurine, cyclosporine or methotrexate ± steroids), biologicals (infliximab or adalimumab in combination with any of the above), and surgery (major abdominal surgery due to IBD regardless of medical treatment prior to surgery). Immunomodulators were combined in one category due to the fact that 94% of patients received treatment with thiopurines. A severe disease course in UC was defined as any disease extent and a need for high dose GCS (0.5–1 mg/kg), and/or immunomodulators, and/or biologicals, and/or surgery. Severe CD was defined as the need for immunomodulators, and/or biologicals, and/or surgery within the first year after diagnosis.

2.3. Questionnaires

Patient-reported HRQoL was assessed using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and the Short Form 12 (SF-12). Validated translations of the questionnaires were used if available. The SIBDQ is a disease-specific questionnaire consisting of ten questions covering four dimensions: bowel, systemic, emotional and social,[19] which has been shown to correlate well with the longer IBDQ questionnaire.[20] The questionnaire is scored on a seven-point scale with higher scores indicating a better HRQoL. The total score ranges from 10 (worst health) to 70 (best health). The SF-12 is a generic HRQoL questionnaire of twelve questions taken from the *Short Form 36* questionnaire,[21] which are grouped into a physical and a mental component summary

score (PCS and MCS) and eight multi-item scales: Physical functioning (PF), Role limitation due to physical health (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). The SF-12 scores were transformed to achieve a mean score of 50 and a standard deviation of 10 in the 1998 general U.S-population,[22] which has been shown to have a good equivalence with country-specific scores in ten Western European countries.[23,24]

2.4. Data collection and assessment of HRQoL

Patients were included in the cohort at diagnosis and followed prospectively every third month throughout the follow-up period. Data regarding demographics, disease activity, medical therapy, surgery, blood samples, cancers and deaths was regularly collected. Data validity was secured by a variety of measures which have been thoroughly described elsewhere.[12] Patient-reported questionnaires were administered twice during the follow-up period: a) at time of diagnosis or within a 90-day period, and b) at nine to twenty-four months of follow-up. This interval was chosen in order to compensate for variations in follow-up visits due to holidays, weekends and personal reasons of the patients, and since centres chose to follow-up patients for either twelve months or until the end of the year 2011 for local practical reasons. Questionnaires were administered to participating patients by one of the following methods: 1) interview conducted by the physician at an outpatient visit, or 2) self-administrated. All data were entered by physicians and/or IBD specialist trained nurses in the web-based inception cohort EpiCom database.[25] Validated translated versions of the questionnaires were available for all centres except for Greenland, the Faroe Islands and Chisinau, Moldova where a Danish and Romanian translation, respectively, was used instead.

2.5. Statistical analysis

Statistical analyses were performed using SAS software v. 9.2. Demographics and disease classification between groups were compared with a Chi-square test. Standard parametric methods were used to analyse differences in HRQoL scores between groups. Results for continuous variables are expressed as median (range) unless otherwise stated, while scores for questionnaires are expressed as mean (standard deviation, SD). If more than two questions in the SIBDQ were missing no total SIBDQ score was calculated; if one or two questions were missing the total SIBDQ score was rescaled with 10/9 or 10/8. Dimensions containing missing data were not calculated. Good HRQoL was defined as a score above 50 points based on results from the IBDQ.[26] Responders were defined as patients experiencing an improved SIBDQ score from ≤ 50 at diagnosis to >50 at follow-up. Only completed SF-12 questionnaires were calculated and included in the analysis. Changes in mean SIBDQ and SF-12 (PCS and MCS) scores from diagnosis until the end of follow-up were analysed using linear normal analysis of covariance (ANCOVA) while controlling for the effects of gender, type of diagnosis, geographical region, age at diagnosis, smoking status, treatment with steroids, employment status, level of education, extra-intestinal manifestations, disease extent, disease behaviour, severe disease course, as well as surgery, biological therapy or hospitalization during follow-up. SIBDQ responders were analysed by logistic regression using the same set of covariates with backward elimination of insignificant factors. A p-value of <0.05 was considered statistically significant.

2.6. Ethical considerations

The study was approved by the relevant ethical committees according to local regulations. All patients gave informed consent prior to answering the questionnaires.

3. Results

In total, 1079 (69% of the total cohort) IBD patients aged 15 years or older at diagnosis from 30 study centres answered the questionnaires, 402 (37%) with CD, 575 (53%) with UC, and 102 (10%) with IBDU. The majority of patients, 838 (78%), were diagnosed in Western Europe. A subset of 436 (31%) patients from the original cohort did not give consent to answer the questionnaires (288, 64%) or were lost during follow-up (148, 34%) and thus were excluded. In terms of socio-demographic characteristics and disease course, patients included in the study only differed in the distribution of diagnosis from the excluded patients, as the fraction of CD patients was larger and the fraction of IBDU patients was smaller in the former group. Patients' demographic characteristics are shown in Table 1. No difference between the two geographic regions was seen, with the exception of the highest treatment step reached during follow-up for CD patients and the educational status in CD and UC patients.

3.1. SIBDQ

A total of 1071 patients filled out at least one SIBDQ. Of those, 825 (77%) patients answered a SIBDQ at diagnosis and 837 (78%) at follow-up; 591 (55%) patients answered a questionnaire both at diagnosis and at follow-up. The median time to answering SIBDQ was 0.6 months (range: 0–3) and 14.6 months (range: 9–24) at diagnosis and follow-up, respectively. The mean scores for the SIBDQ in Western and Eastern Europe are shown in Table 2. For CD patients disease-specific HRQoL improved significantly from 44.9 to 53.6 ($p < 0.01$) in Western Europe and from 45.3 to 55.3 ($p < 0.01$) in Eastern Europe during follow-up. Likewise, SIBDQ scores for UC patients improved from 48.8 in Western Europe and 44.9 in Eastern Europe at diagnosis to 55.7 and 57.4, respectively ($p < 0.01$). Of the IBDU patients, only those in Western Europe experienced a significantly more positive perception of HRQoL, rising from 49.9 to 54.9 ($p = 0.01$).

In Western Europe, the mean SIBDQ total score was significantly lower for CD than for UC patients at both diagnosis (44.9 vs. 48.8, $p < 0.01$) and at follow-up (53.6 vs. 55.7, $p = 0.03$). Furthermore, Western European UC patients had a significantly higher mean SIBDQ score at diagnosis compared to UC patients in Eastern Europe (48.8 vs. 44.9, $p < 0.01$). The proportion of patients with good HRQoL (SIBDQ total score over 50) improved during follow-up with the exception of Eastern European IBDU patients (Fig. 1).

Overall, the mean SIBDQ scores for all IBD patients improved in the majority of centres ($p < 0.01$) (Fig. 2).

During follow-up and prior to completing the last SIBDQ, 36 (9%) CD patients (median time to surgery: 4.9 months, range: 0–15) and 11 (2%) UC patients (median time to surgery: 7.7 months, range: 1–13) from Eastern and Western Europe underwent surgery, while 46 (11%) CD patients (median time to biologicals: 4.7 months, range: 0–23) and 14 (2%) UC patients (median time to biologicals: 5.5 months, range: 0–16) received biological therapy and no surgery. UC patients undergoing surgery or receiving biological therapy during follow-up had significantly lower mean SIBDQ scores at both diagnosis and at follow-up compared to UC patients not undergoing surgery or receiving biological therapy during follow-up (Fig. 3). For CD patients this was only the case for patients needing biological therapy during follow-up. The mean SIBDQ scores significantly improved during follow-up for both CD (41.6 to 54.4, $p < 0.01$) and UC patients (37.9 to 49.2, $p < 0.01$) needing surgery. CD patients treated with biologicals clinically significantly improved their SIBDQ scores (40.9 to 52.1, $p < 0.01$) while the improvement in UC did not reach significance (37.4 to 45.2, $p = 0.22$).

A total of 591 (55%) patients were included in the ANCOVA analysis and responder analysis for SIBDQ. These patients only differed in terms of smoking status (more patients included in the analysis where former smokers) from the rest of the study population. For IBD patients overall (335, 57%) with low HRQoL at diagnosis, only baseline SIBDQ score (odds ratio (OR) 1.1 CI 95% 1.02–1.08, $p < 0.01$) predicted achieving good HRQoL (SIBDQ score >50) at follow-up (Fig. 4). For UC patients this was the case for baseline SIBDQ score (OR 1.1 CI 95% 1.02–1.11, $p < 0.01$), limited disease extent (E1 vs. E2: OR 5.3 CI95% 2.0–14.1; E1 vs. E3: OR 4.9 CI95% 1.8–13.8; $p < 0.01$), not receiving biological therapy (no biologicals vs. biologicals: OR 25.2 CI95% 2.4–259.8, $p < 0.01$), and not undergoing surgery during follow-up (no surgery vs. surgery: OR 4.4 CI95% 1.1–18.7, $p = 0.03$). No significant predicting factors for CD patients were found. The results of the ANCOVA analysis are shown in Table 3.

3.2. SF-12

In total, 1074 patients answered a SF-12 questionnaire, 830 (77%) at diagnosis and 833 (78%) at follow-up. 589 (55%) patients answered a questionnaire at both diagnosis and follow-up. Median time to answering the SF-12 was 0.6 months (range: 0–3) and 14.7 months (range: 9–24) at diagnosis and follow-up, respectively. The mean scores for the SF-12 survey are shown in Table 4. CD patients in both Western and Eastern Europe improved their generic HRQoL in all eight multi-item scales and both summary scores from diagnosis to follow-up. In the same way UC patients improved in both summary scores and all multi-item scales (Western European UC patients however in all but "general health"). Only Western European IBDU patients improved in terms of the vitality item and MCS (Fig. 5). However, only Eastern European UC and IBDU patients achieved a generic HRQoL in terms of the two SF-12 summary scores equal to or higher than the healthy background population (Table 4). A subset of 589 (55%) patients was included in the ANCOVA analysis for SF-12; results are shown in Table 3.

During follow-up and prior to filling out the last SF-12, a total number of 36 (9%) CD patients (median time to surgery: 4.9 months, range: 0–15) and 12 (2%) UC patients (median time to surgery: 8.3 months, range: 1–22) from Eastern and Western Europe underwent surgery, while 47 (12%) CD patients (median time to biologicals: 4.4 months, range: 0–23) and 14 UC (2%) patients (median time to biologicals: 5.5 months, range: 0–16) received biological therapy. The mean summary scores and multi-item scores at follow-up for those patients compared to the rest are shown in Fig. 6. UC patients receiving biological therapy scored lower for MCS and the following items: VT, SF, RE, and MH, while UC patients undergoing surgery scored lower for PCS and the following items: RP, GH, VT, SF and MH ($p < 0.01$). UC patients undergoing surgery did not improve in any summary or multi-item score during follow-up, while patients treated with biological therapy improved in RP, BP, GH, and PCS (data not shown). CD patients needing surgery improved all scores with the exception of PF and RE, while CD patients treated with biologicals improved all scores but MH and PCS (data not shown).

4. Discussion

We have endeavoured to show that thorough medical and surgical treatment in a population-based inception cohort of unselected IBD cases in a community setting improved both generic and disease-specific HRQoL significantly during the first year of disease. The majority of CD and UC patients in both Eastern and Western Europe experienced a more positive perception of disease-specific HRQoL, though not of the generic HRQoL. Overall, no differences in generic and disease-specific HRQoL were found between patients from Eastern and Western Europe. Patients with UC who had a worst case scenario and were receiving biological therapy or undergoing surgery during follow-up had significantly worse disease-specific and generic QoL at follow-up, when compared to other UC patients.

Up to now only a few studies[6,27–29] have assessed the HRQoL of IBD patients using population-based, unselected cohorts. Furthermore, in these cohorts HRQoL was assessed several years after diagnosis. Thus, little is known about the HRQoL in IBD patients during the initial onset of disease. In this study we were able to assess HRQoL at diagnosis and after approximately one year of disease. In terms of generic HRQoL, both UC and CD patients significantly improved their SF-12 scores for all items and summary scores, although only Eastern European UC patients achieved a SF-12 score similar to or higher than the healthy background population at follow-up. Previous studies have similarly shown that the generic HRQoL of CD and UC patients is reduced when compared to the healthy background population.[1,3,30]

Conversely, regarding disease-specific HRQoL, the majority of CD and UC patients experienced a more positive perception of HRQoL at follow-up. Both surgery[31] and medical treatment[32–34] has been shown to improve both generic and disease-specific HRQoL if disease activity is reduced. Patients in the EpiCom cohort received early and aggressive treatment with immunomodulators and reduced their disease activity during the initial year of disease[13]; however, a severe disease course was not associated with a

decrease in SIBDQ score during follow-up nor influenced changes in HRQoL scores. As degree of disease activity is an important contributor to patients' perceived HRQoL,[35] and since mucosal healing in IBD patients is associated with achieving a good HRQoL independently of the type of medical treatment,[36] it is possible that treatment choices

Table 1 Patient characteristics of 1079 incident IBD patients from the EpiCom-cohort.

	Western European centres			Eastern European centres		
	CD	UC	IBDU	CD	UC	IBDU
No. of patients	305 (36%)	437 (52%)	96 (11%)	97 (40%)	138 (57%)	6 (2%)
Male	160 (52%)	240 (55%)	47 (49%)	56 (58%)	77 (56%)	4 (67%)
Female	145 (48%)	197 (45%)	49 (51%)	41 (42%)	61 (44%)	2 (33%)
Age at diagnosis, years	35 (16–89)	39 (15–89)	39 (17–77)	31 (15–78)	36 (18–81)	30 (20–34)
Time to diagnosis, months	4.6 (0–374)	2.4 (0–255)	2.4 (0–362)	3.4 (0–125)	2.2 (0–240)	2.7 (0–38)
Smoking status at diagnosis						
Never	122 (41%)	233 (55%)	45 (49%)	35 (36%)	76 (55%)	4 (67%)
Currently	107 (36%)	35 (8%)	14 (15%)	36 (38%)	14 (10%)	2 (33%)
Former smoker	71 (24%)	155 (37%)	33 (36%)	25 (26%)	48 (35%)	0 (0%)
Level of education at diagnosis						
Academic education	65 (22%) *	81 (20%) *	16 (18%)	14 (15%)	38 (28%)	0 (0%)
Non-academic education	159 (53%) *	235 (57%) *	48 (53%)	51 (53%)	66 (48%)	6 (100%)
Currently attending education	46 (15%) *	48 (12%) *	7 (8%)	26 (27%)	27 (20%)	0 (0%)
No education	28 (9%) *	46 (11%) *	20 (22%)	5 (5%)	7 (5%)	0 (0%)
Employment status at diagnosis						
Employed	155 (52%)	225 (54%)	51 (55%)	47 (49%)	76 (55%)	5 (83%)
Self-employed	17 (6%)	29 (7%)	6 (6%)	6 (6%)	5 (4%)	0 (0%)
Unemployed	45 (15%)	42 (10%)	11 (12%)	14 (15%)	9 (7%)	1 (17%)
Student	47 (16%)	54 (13%)	10 (11%)	20 (21%)	22 (16%)	0 (0%)
Retired	35 (12%)	68 (16%)	15 (16%)	9 (9%)	26 (19%)	0 (0%)
Extra-intestinal manifestations at diagnosis						
None	266 (86%)	391 (89%)	82 (84%)	82 (82%)	120 (86%)	5 (83%)
Skin	6 (2%)	8 (2%)	4 (4%)	2 (2%)	1 (1%)	0 (0%)
Eyes	4 (1%)	6 (1%)	3 (3%)	2 (2%)	1 (1%)	0 (0%)
Joints	28 (9%)	31 (7%)	7 (7%)	12 (12%)	13 (9%)	1 (17%)
Primary sclerosing Cholangitis (PSC)	1 (0%)	1 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Pancreatitis	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Other	4 (1%)	4 (1%)	2 (2%)	2 (2%)	1 (1%)	0 (0%)
Disease extent at diagnosis						
E1: Proctitis		85 (19%)			26 (19%)	
E2: Left-sided		185 (42%)			64 (46%)	
E3: Extensive colitis		167 (38%)			48 (35%)	
Disease location at diagnosis						
L1: Terminal ileum	87 (29%)		37 (39%)			
L2: Colon	83 (28%)		19 (20%)			
L3: Terminal ileum + colon	70 (23%)		23 (24%)			
L4: Upper GI	22 (7%)		2 (2%)			
L1 + L4	19 (6%)		5 (5%)			
L2 + L4	7 (2%)		3 (3%)			
L3 + L4	13 (4%)		7 (7%)			
Disease behaviour at diagnosis						
B1: non-stricturing, non-penetrating	184 (60%)		66 (68%)			
B2: stricturing	60 (20%)		18 (19%)			
B3: penetrating	28 (9%)		5 (5%)			
B1p: B1 + perianal	14 (5%)		1 (1%)			
B2p: B2 + perianal	3 (1%)		0 (0%)			

(continued on next page)

Table 1 (*continued*)

	Western European centres			Eastern European centres		
	CD	UC	IBDU	CD	UC	IBDU
B3p: B3 + perianal	16 (5%)		7 (7%)			
Highest treatment step reached during follow-up						
0: No treatment	7 (2%) *	3 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
1: 5-ASA	37 (12%) *	214 (49%)	45 (47%)	27 (28%)	85 (62%)	4 (67%)
2: GCS	48 (16%) *	117 (27%)	27 (28%)	24 (25%)	33 (24%)	1 (17%)
3: Immunomodulators	104 (34%) *	69 (16%)	11 (11%)	31 (32%)	16 (12%)	1 (17%)
4: Biological therapy	63 (21%) *	21 (5%)	10 (10%)	5 (5%)	1 (1%)	0 (0%)
5: Surgery	46 (15%) *	13 (3%)	3 (3%)	10 (10%)	2 (1%)	0 (0%)

* Difference between geographic regions, $p < 0.05$.

made in this cohort were appropriate in terms of reducing disease activity and achieving mucosal healing.

Given the short observation period of the first 12 months of disease, it is not surprising that only disease-specific HRQoL normalized during follow-up whereas generic HRQoL, with the exception of Eastern European UC patients, remained below the healthy background population. Generic HRQoL measurements capture the full impact of an individual's disease and allow for comparisons across patients, diseases and different ages, however often do not necessarily include items of particular relevance for a given disease and lack of sensitivity to detect change over time in groups of patients with specific diseases.[1,37] Disease-specific HRQoL measurements on the other hand assess specific issues impairing patients' health status and reflect treatment effects better and are more responsive to treatment interventions, such as those experienced by patients in the EpiCom cohort. The IBD diagnosis is still new for these patients and while HRQoL may seem improved when only asked about a single group of dimensions, e.g. disease specific items, when asked to consider their state of health from a more general point of view it may need more time for these patients to normalize their HRQoL perception.

In this study neither treatment with glucocorticosteroids (alone or in combination) nor treatment with thiopurines was associated with a worse disease-specific HRQoL for CD or UC patients. HRQoL has in previous studies been negatively associated with corticosteroid treatment[6,27,28,30] reflecting either a continued or worsening disease activity or corticosteroid-related side effects. Furthermore, in population-based inception cohorts the use of thiopurines was associated with a deterioration of disease-specific HRQoL in CD patients[6] at five years of follow-up. Due to the short disease duration the impact of an underlying more severe disease course may need a longer follow-up to be proven.

More Western European patients received a biological therapy during follow-up without any regional differences in perceived HRQoL. Improvement of disease-specific HRQoL by biological therapy has been demonstrated in several placebo-controlled trials with highly selected IBD patients with long disease duration.[33,34] In this unselected cohort disease-specific and generic HRQoL of CD patients receiving biological therapy improved significantly during follow-up and reached normal SIBDQ scores. In contrast, UC patients receiving biological agents did not significantly improve HRQoL scores and had, in fact, worse HRQoL scores when compared to the rest. The same findings were made in terms of surgery (resections and colectomies) as UC patients undergoing surgery at this early stage of disease despite significant improvement had significantly lower disease-specific and generic HRQoL scores at follow-up when compared to UC patients not undergoing surgery. However, the median time to

Table 2 Mean scores (SD) for the Short Inflammatory Bowel Disease Questionnaire.

	Diagnosis			Follow-up		
	CD	UC	IBDU	CD	UC	IBDU
Western Europe						
D1: Bowel	13.6 (4.3)	14.7 (4.2) [b]	14.9 (4.4)	16.3 (3.6) [a]	16.9 (3.5) [a]	16.6 (3.4) [a]
D2: Emotional	13.3 (4.6)	14.4 (4.3) [b]	14.0 (4.8)	15.5 (4.0) [a]	15.9 (4.0) [a]	16.1 (3.9) [a]
D3: Systemic	8.6 (3.2)	9.5 (3.0)	9.9 (2.7)	10.3 (2.7) [a,b]	10.7 (2.8) [a,b]	10.2 (3.2) [b]
D4: Social	8.9 (4.1)	10.1 (3.9) [b]	10.6 (3.6)	11.1 (3.4) [a]	11.9 (3.0) [a]	11.7 (2.9) [a]
Total score	44.9 (13.6)	48.8 (12.9) [b]	49.9 (12.3)	53.6 (11.3) [a]	55.7 (11.0) [a]	54.9 (11.0) [a]
Eastern Europe						
D1: Bowel	14.4 (4.4)	13.6 (3.9)	18.0 (1.7)	17.1 (3.3) [a]	17.5 (3.4) [a]	17.7 (2.9)
D2: Emotional	12.9 (4.0)	12.8 (4.4)	14.0 (1.0)	15.2 (3.3) [a]	16.1 (3.2) [a]	16.2 (1.8)
D3: Systemic	8.7 (2.9)	9.1 (2.9)	11.0 (2.6)	11.2 (2.2) [a]	11.5 (2.3) [a]	12.3 (1.0)
D4: Social	8.8 (4.2)	8.9 (4.1)	12.7 (2.3)	11.5 (3.3) [a]	11.9 (2.6) [a]	12.7 (1.6)
Total score	45.3 (12.7)	44.9 (12.8)	55.7 (4.5)	55.3 (10.5) [a]	57.4 (9.6) [a]	58.8 (6.4)

[a] Difference in the mean score between time of diagnosis and follow-up, $p < 0.05$.
[b] Difference in the mean score between regions, $p < 0.05$.

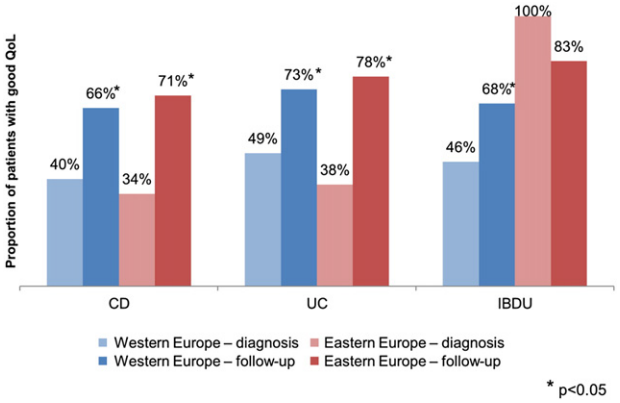

Figure 1 Proportion of patients with good (SIBDQ score >50) disease-specific health-related quality of life at diagnosis and follow-up in an unselected IBD cohort.

surgery and rescue therapy with biological agents was short and close to the follow-up assessment. Thus the impact of the intervention on patients' HRQoL might not have had enough time to become evident in UC patients.

Disease phenotype for CD patients did not have an impact on whether patients achieved a good disease-specific HRQoL or not. A possible reason for this could be the low proportion of patients with stricturing or penetrating disease, however this finding is in line with other studies.[29,38] In UC more severe disease extent was associated with not achieving a good HRQoL at follow-up. One could speculate that more extensive UC led to more aggressive therapy, such as immunosuppressives, which in this subgroup of patients led to a poorer HRQoL.

While most patients experienced significant improvements in HRQoL during the follow-up period, the question about the degree of change required to be clinically significant has to our knowledge only been addressed for the SIBDQ, where a change in SIBDQ score of ≥ 9.3 points has been suggested to be clinically significant.[19] On this premise only Eastern European patients exhibited a clinically relevant improvement in disease specific HRQoL over time as well as CD patients undergoing surgery or receiving biologicals as well as UC patients colectomised during follow-up. Further studies investigating the correlation of changes in HRQoL scores and e.g. disease activity are warranted, and whether this regional difference in time will disappear with longer follow-up or will in fact persist, the five and ten year follow-up of the EpiCom cohort will hopefully answer.

Some limitations in this study need to be taken into consideration. First, a subset of patients did not give consent to fill out the questionnaires. These patients, however, did not differ from those giving consent in terms of socio-demographic characteristics. Furthermore, not all patients filled out questionnaires at both the time of diagnosis and follow-up and unfortunately it was not possible to resend the questionnaire in order to secure full data inclusion. Also, the large margin regarding time of completion of the questionnaires might influence the results since some patients will have had longer and/or different treatment than others. In addition, the method of administering the questionnaires was not entirely consistent. Depending on the patients' educational level, whether local translations of the questionnaires were available, and according to local logistical factors, the questionnaires were either interview-administered by the physician or self-administered by the patients. But all data was completed by trained personnel. Results could be biased according to how the questionnaire was administered, since patients might not have given sincere answers on a face-to-face. However, for IBDQ at least, this has been shown not to affect the scores significantly.[39] Also, comparing SF-12 scores against the same healthy population (general U.S. population), rather than to country-specific norms, has only been shown to be a valid method in Western European countries.[23,24] The distribution of patients is skewed as the majority of patients were diagnosed in Western European centres. This is to be expected from this inception cohort since most participating Eastern European centres are low-incidence areas.[40] As the patient populations from Eastern and Western Europe were similar in terms

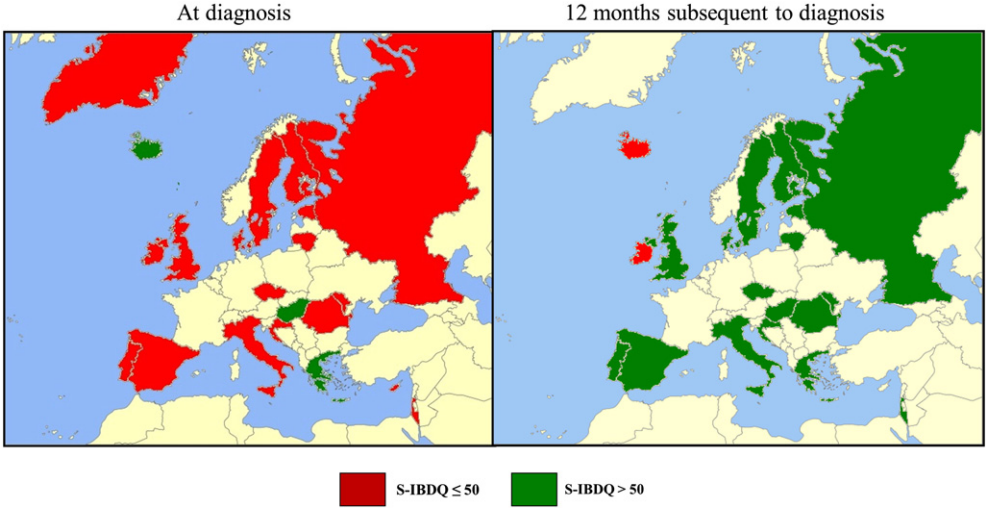

Figure 2 Mean Short Inflammatory Bowel Disease Questionnaire (SIBDQ) scores in the 2010 IBD inception cohort at diagnosis and 1 year FU in Eastern and Western Europe.

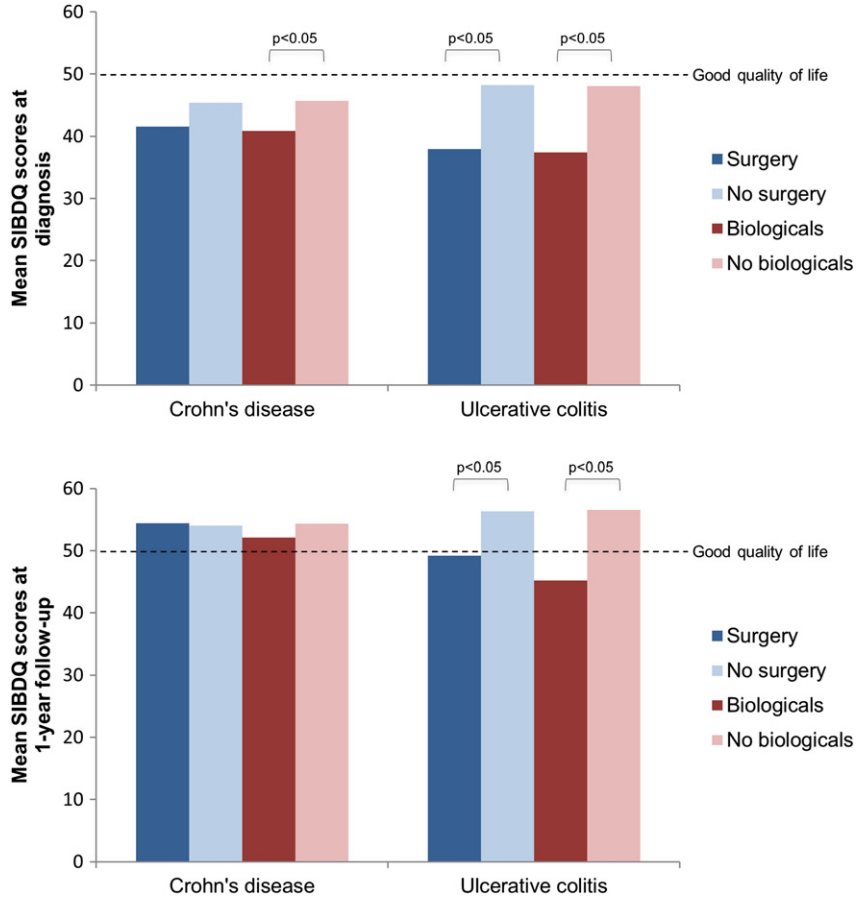

Figure 3 Short Inflammatory Bowel Disease Questionnaire (SIBDQ) scores in patients undergoing surgery or receiving biological therapy during follow-up.

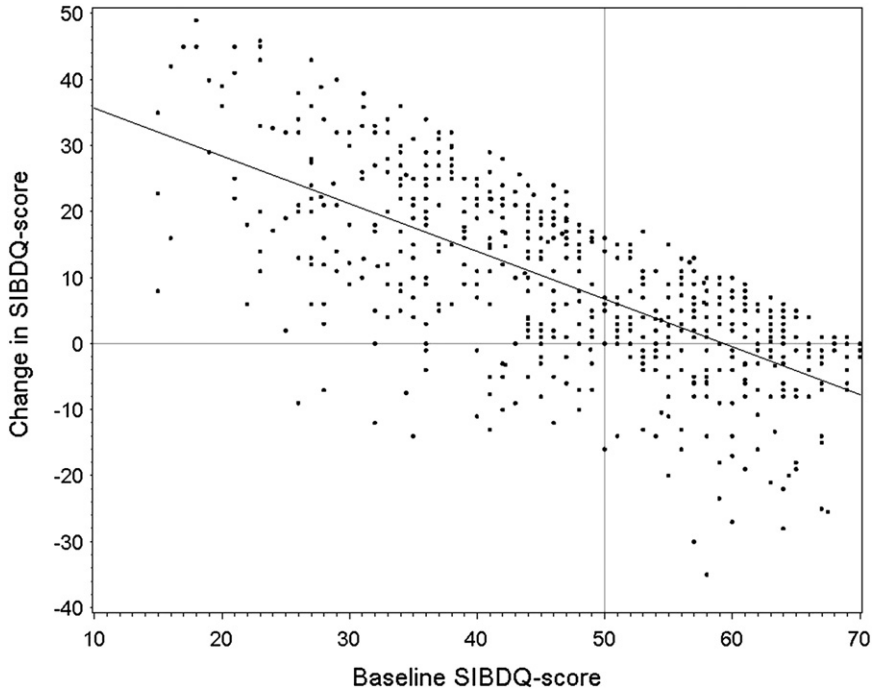

Figure 4 Change in SIBDQ score during follow-up depending on baseline SIBDQ score in a European inception cohort of IBD patients.

Table 3 Factors influencing positive changes in health-related quality of life at follow-up.

	SIBDQ		SF-12, MCS		SF-12, PCS	
	CD	UC	CD	UC	CD	UC
Coming from Eastern Europe	–	–	P = 0.049	–	–	–
Age <40 years at diagnosis	–	–	–	–	–	p = 0.032
Being a non-smoker	–	p < 0.001	–	–	–	–
Having an education	–	–	–	–	p < 0.001	–
No extra-intestinal manifestations	–	–	–	–	p = 0.045	–
No biological therapy during follow-up	–	p < 0.001	p = 0.037	p < 0.001	–	–
No surgery during follow-up	–	p < 0.05	–	–	–	–
Shorter disease extent in UC	–	P = 0.025	–	–	–	–

PCS, physical component summary score; MCS, mental component summary score.

of socio-economic characteristics, diagnostic procedures used and time to diagnosis and disease classification,[12] we do not think the disease course being influenced by the region of origin. Lastly, HRQoL cross-cultural differences and geographical variations in the perception of health status, the impact of disease on HRQoL, as well as differences in healthcare delivery across Eastern and Western Europe may have influenced the way patients responded to HRQoL questionnaires.[41–43]

The strengths of the study are its prospective design and that the cohort is a population-based inception cohort of incident IBD patients diagnosed within well-defined geographic areas and with standardised diagnostic criteria, case ascertainment methods, and intervals of follow-up visits and recorded data. As such, the patients are unselected and represent the broad spectrum of disease severity from mild, indolent to severe cases. Treatment choices and their potential impact on HRQoL are the results of community effectiveness of treatment guidelines amongst physicians.

In conclusion, based on a European prospective population-based inception cohort of unselected IBD patients, generic and disease-specific HRQoL tends to improve during the first year of disease subsequent to diagnosis. The majority of CD and UC patients in both Eastern and Western Europe experienced a more positive perception of disease-specific HRQoL; however this was not the case for generic HRQoL.

Table 4 Mean scores (SD) for the Short Form 12 questionnaire.

	Diagnosis			Follow-up		
	CD	UC	IBDU	CD	UC	IBDU
Western Europe						
PF	47.2 (11.8)	49.2 (10.5)[b]	50.1 (10.0)[b]	50.0 (10.6)[a]	51.1 (9.6)[a]	49.5 (10.0)[b]
RP	40.9 (13.2)	44.7 (12.0)	44.9 (12.4)	46.8 (10.6)[a,b]	48.9 (9.4)[a]	47.6 (9.8)
BP	39.0 (14.1)	46.1 (12.4)[b]	45.3 (11.6)	47.1 (11.4)[a]	50.0 (10.5)[a,b]	47.4 (11.1)
GH	38.7 (13.0)	42.5 (12.1)[b]	40.7 (11.0)[b]	42.7 (11.2)[a,b]	44.0 (11.6)	43.8 (11.0)
VT	43.6 (12.6)	45.2 (11.7)	45.3 (11.1)	49.1 (12.0)[a,b]	49.9 (11.3)[a,b]	49.5 (10.5)[a]
SF	41.4 (12.6)	44.5 (11.6)	45.8 (10.8)	47.4 (10.6)[a]	48.1 (10.3)[a]	49.0 (9.5)
RE	40.8 (15.0)	43.4 (13.7)	43.4 (13.8)	45.4 (12.1)[a]	46.8 (11.2)[a]	46.6 (11.2)
MH	45.8 (11.5)	45.6 (11.4)	46.5 (11.0)	48.4 (11.3)[a]	48.5 (11.4)[a,b]	49.5 (10.6)
PCS	42.3 (11.3)	46.9 (9.9)[b]	46.1 (9.7)	47.6 (9.7)[a]	49.3 (9.0)[a]	47.5 (10.1)
MCS	43.1 (12.0)	43.7 (11.6)	43.8 (11.9)	47.1 (11.7)[a]	47.5 (11.3)[a]	48.7 (10.8)[a]
Eastern Europe						
PF	48.2 (11.4)	46.4 (11.1)	56.5 (0.0)	51.7 (8.3)[a]	51.3 (8.3)[a]	55.0 (3.5)
RP	42.5 (12.1)	43.6 (11.3)	49.5 (13.3)	49.7 (8.7)[a]	49.4 (9.5)[a]	51.8 (8.5)
BP	41.6 (11.7)	42.6 (12.0)	50.6 (5.9)	48.4 (11.7)[a]	52.1 (8.9)[a]	50.6 (10.5)
GH	40.1 (12.3)	39.3 (11.6)	54.1 (8.7)	45.5 (10.2)[a]	44.9 (10.3)[a]	47.6 (7.0)
VT	46.5 (11.8)	47.3 (11.5)	54.5 (11.6)	52.4 (11.3)[a]	52.3 (10.8)[a]	56.1 (9.9)
SF	43.1 (13.3)	43.4 (12.3)	46.5 (10.1)	49.9 (8.9)[a]	49.5 (9.3)[a]	53.2 (5.2)
RE	41.0 (12.9)	42.1 (12.0)	37.4 (17.1)	47.4 (11.9)[a]	46.9 (11.1)[a]	45.8 (9.0)
MH	43.1 (12.6)	43.2 (11.6)	50.3 (12.7)	49.7 (11.5)[a]	51.3 (9.6)[a]	53.4 (9.8)
PCS	44.7 (10.2)	44.3 (10.3)	56.3 (7.0)	49.4 (7.0)[a]	50.2 (7.3)[a]	52.6 (6.0)
MCS	42.2 (12.7)	43.5 (11.0)	43.3 (17.4)	49.5 (11.3)[a]	50.2 (9.7)[a]	50.7 (6.4)

PF, physical functioning; VT, vitality; RP, role-physical; SF, social functioning; BP, bodily pain; RE, role-emotional; GH, general health; MH, mental health; PCS, physical component summary score; MCS, mental component summary score.

[a] Difference in the mean score between time of diagnosis and follow-up, $p < 0.05$.

[b] Difference in the mean score between regions, $p < 0.05$.

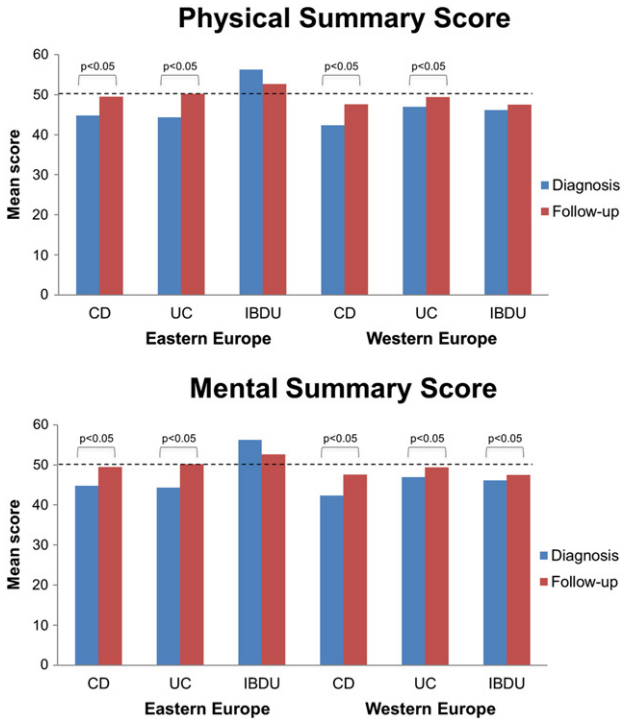

Figure 5 Mean summary scores for the Short Form 12 questionnaire at diagnosis and follow-up in Crohn's disease (CD) and ulcerative colitis (UC) patients.

While biological therapy significantly improved and normalized HRQoL in CD patients, UC patients in need of aggressive therapy with surgery or biological agents had a significantly lower HRQoL at follow-up than other patients in this study.

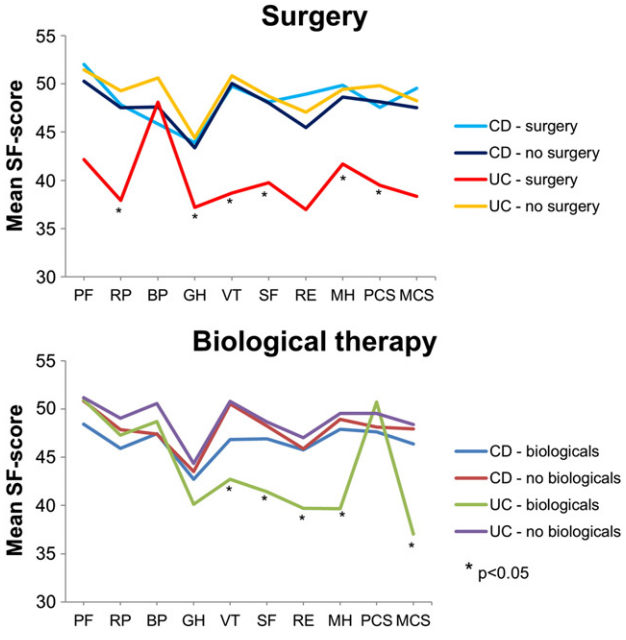

Figure 6 Short Form 12 questionnaire scores in patients undergoing surgery or receiving biological therapy during follow-up.

Conflict of interest

The authors have no conflicts of interest to disclose.

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All authors have made significant contributions to the research described in this manuscript. JB carried out the study, collected and analysed data and drafted the manuscript. All authors collected and entered data and revised the draft of the manuscript. PM took part in the planning and designing of the study and revised the draft of the manuscript. All authors have read and approved the final manuscript.

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