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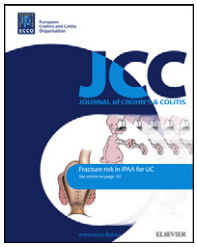

REVIEW ARTICLE

Determinants of health-related quality of life in Crohn's disease: A systematic review and meta-analysis

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Crohn's disease;
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Abstract

Background and aims: Understanding the determinants of Crohn's disease (CD) patients' health-related quality of life (HRQOL) may facilitate interventions that improve HRQOL. Therefore, we systematically assessed determinants of HRQOL in adult CD patients.
Methods: The databases PubMed, EMBASE, the Cochrane Library, PsycINFO and CINAHL were searched for English abstracts, related to socio-demographic, psychological, clinical and treatment-related determinants of HRQOL in CD disease. Two independent reviewers extracted study characteristics and assessed the methodological quality according the criteria of Hayden et al. The main outcome was the number of studies showing a statistically significant association between the above-mentioned determinants and HRQOL. A meta-analysis was performed to quantify the relationship between disease activity and HRQOL.
Results: Of the 2060 articles identified, 29 eligible studies were included. The majority of studies were cross-sectional and had a moderate to high quality. Data on psychological determinants were scarce. Work disability, increased disease activity, number of relapses, corticosteroid treatment and hospitalization rate were significantly associated with a lower HRQOL in the majority of included studies. Biological treatment positively influenced HRQOL. The pooled data on the association between disease activity and HRQOL resulted in a weighed mean correlation coefficient of −0.61 (CI −0.65 to −0.57).
Conclusions: HRQOL of adult CD patients is consistently determined by markers of active disease, including work disability, increased disease activity, number of relapses, biological treatment and hospitalization rate. As disease activity contributed to only 37% of HRQOL, there remains a need for additional, possibly modifiable, determinants. These determinants may refine possibilities to improve HRQOL.
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Contents

1. Introduction

Crohn's disease (CD) is a chronic, progressive and potentially disabling disease. CD patients often deal with unpredictable and potentially debilitating symptoms, including diarrhoea, fatigue and urgency. In addition, they require long-term treatment with frequent adverse effects, the need of surgery and hospitalizations.[1] Therefore, CD patients report a lower HRQOL compared with healthy individuals.[2]

HRQOL represents the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient. It encompasses several dimensions of life, including physical functioning, psychosocial functioning, role functioning, mental health and general health perceptions.[3] HRQOL is determined by socio-demographic, clinical and psychological and treatment-related determinants.[4,5] Although disease activity is an important determinant of HRQOL in CD, even asymptomatic patients report a lower HRQOL, suggesting a role for other determinants.[6,7]

A comprehensive understanding of the above-mentioned determinants of CD patients' HRQOL may facilitate clinicians in clinical decision making, defining risk groups and allowing more accurate prediction of HRQOL.[8] This latter is especially relevant when choosing between two interventions with an equal clinical efficacy or when treating asymptomatic patients.[9]

In two previous reviews, clinical determinants (mainly disease activity) and psychosocial determinants of HRQOL in CD have been meticulously described — however none have performed a systematic search strategy.[4,5] This may have resulted in an incomplete retrieval of articles, thereby biasing results. In addition, the methodological quality of included studies has not been ascertained, making it difficult to interpret and compare results.

Therefore, we conducted a systematic review to assess and critically appraise the socio-demographic, clinical, psychological and treatment-related factors determining HRQOL in adult CD patients.

2. Material & methods

This systematic review was conducted in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[10]

2.1. Search strategy (Supplementary; Table 1)

In collaboration with a librarian a search strategy was designed to identify articles concerning determinants of HRQOL in adult CD. PubMed (since 1966), EMBASE (since 1966), Cochrane Library (since 1996), PsycInfo (since 1960) and CINAHL (since 1982) were systematically searched for titles and abstracts published between inception date of the database and July 9th, 2012. The search strategy contained a combination of keywords (and their synonyms) and Medical Subject Headings (MESH)/EMTREES (in the case of EMBASE), including "Crohn's disease", "determinant", and "health-related quality of life". Both search strategy and search filter were modified for each database. The search strategy was supplemented with reference tracking from all included studies, relevant reviews and by using Web of Science.

2.2. Study selection

Titles and abstracts were identified as potentially eligible by two independent reviewers [KA, MH]. Titles and abstracts

meeting the following inclusion criteria were selected for full-article review:

1. English language article
2. Population: adult Crohn's disease patients (≥18 years)
3. Outcome: health-related quality of life measured with a validated instrument (Table 1)
4. Determinant: any reported determinant related with HRQOL
5. Article published in a peer reviewed journal.

Case reports, case series (<50 patients), editorials, commentaries, economic evaluation studies, diagnostic studies, experimental studies, validation studies, induction trials, trials not correcting for relevant covariates, and qualitative studies were excluded. Review articles were excluded as well – however – their reference lists were searched for eligible articles. All retrieved full-text articles were again independently reviewed by the reviewers [KA, MH], according to the same predefined inclusion and exclusion criteria. When consensus regarding the eligibility could not be accomplished, agreement was obtained through discussions with a third arbiter [HF].

2.3. Quality appraisal

A quality appraisal was performed in order to minimize bias and improve the reliability of our findings. Two reviewers [KA, MH] independently assessed the quality of each study by scoring 33 items divided into six sources of bias: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and analysis (Supplementary; Table 2).[11] Bias was considered present if the majority of items within a potential source of bias pointed in this direction. The quality of the study was rated "high" if there was low or moderate risk of bias in all sources of bias. The quality of a study was rated "moderate" if there was a high risk of bias in one source. The quality of a study was rated "low" if there was a high risk of bias in at least two sources. Differences in quality appraisal between the reviewers were evaluated. When consensus could not be accomplished, agreement was obtained through discussions with a third arbiter [HF].

Table 1 Disease-specific and generic health-related quality of life instruments used in patients with Crohn's disease.

Disease-specific HRQOL questionnaire
Cleveland Clinic Questionnaire Inflammatory bowel
Inflammatory Bowel Disease Questionnaire 32 (IBDQ-32, -36, -9)
McMaster IBDQ
Rating Form of Inflammatory bowel disease Pattern Concerns (RFIPC)
Short IBDQ (SIBDQ)
Ulcerative Colitis and Crohn's Disease Health Status Scales
Generic HRQOL questionnaire
Euroqol-5D (EQ-5D)
Nottingham Health Profile (NHP)
Psychological General Well Being Scale (PGWB)
Quality of Well-Being Index (QWB)
Short form 36, -12, -20 (SF-36, -12 or -20)
Sickness Impact Profile (SIP)
Time trade-off

2.4. Data synthesis and analysis

Of all studies both reviewers extracted data concerning study characteristics and associations between determinants and HRQOL. All studies were reviewed for information about any reported socio-demographic, clinical, psychological and treatment-related determinants of both generic and disease-specific HRQOL. When possible, determinants that seemed to describe similar characteristics were merged into one factor (e.g. disease duration and time since diagnosis). The main outcome was the frequency of studies showing a significant association between these determinants and total HRQOL. Determinants that were measured, but not included in the univariate or multivariate analysis, were classified as "not assessed". Disparities in results between the reviewers were discussed and if necessary, discussed with the arbiter.

Given the heterogeneity in the study design we stratified for cross-sectional studies and prospective studies (including randomized controlled trials) and separately assessed the associations within these strata. Given the relatively high number of cross-sectional studies, we further stratified for cross-sectional studies with either a low or moderate to high risk of bias.

Data on the association between disease activity and HRQOL were pooled by using R statistical software version 2.13.2. Heterogeneity of the studies was evaluated by using the Cochrane Q-test.[12]

3. Results

3.1. Search strategy and selection criteria (Fig. 1)

The search strategy yielded 2060 published articles. Removal of all duplicates resulted in 1610 articles that were screened on title and abstract following the predefined inclusion and exclusion criteria. Incorrect study design and mixed IBD population were the main reasons for exclusion. In total, 1339 articles were excluded, leaving 217 for full-text screening. After full-text review, 27 studies were included in the systematic review.[13–39] Consensus between the two independent reviewers [KA, MH] was reached in 83% of cases. Reference tracking retrieved two additional articles.[40,41]

3.2. Baseline characteristics (Table 2)

Of the 29 studies, nine studies utilized data from three study populations. Four studies, of which three were published by Bernklev et al.[16–18] and one by Høivik et al.[29], utilized data from the Inflammatory Bowel South-Eastern Norway (IBSEN) cohort. Høivik et al.'s study was considered as an original study as they analysed a subgroup of CD patients after ten years of follow-up, whereas the remaining three studies analysed data from IBD patients after five years of follow-up.[29] In addition, Casellas et al. published three studies utilizing data from the

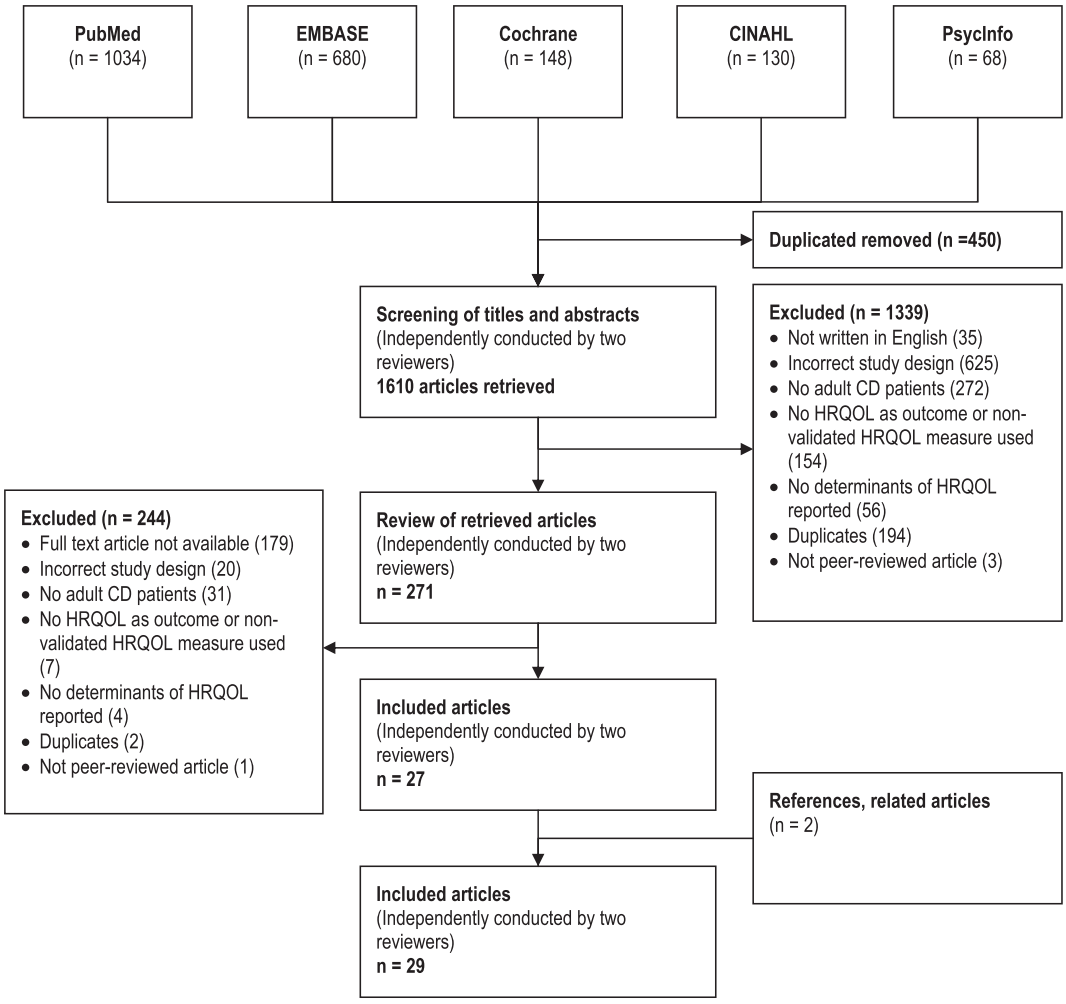

Figure 1 Flowchart showing the search strategy (July 9th 2012).

same Spanish cohort.[22–24] Two Dutch studies utilized data from the same South-Limburg Cohort.[34,35] Therefore, 24 original studies remained, which were suitable for extracting study characteristics.[13–16,19–22,25–33,35–41]

Most studies originated from Europe (15/24; 63%),[14–16,19–22,28–31,35–37,39] others were performed in the USA,[13,25,38] Canada,[33] Australia,[27] or in multiple nations worldwide.[26,32,40,41] Most studies had a cross-sectional design (11/24; 46%).[20,22,25,27,30,31,33,36–39] Other types of study design were: cohort studies (5/24; 21%),[15,16,19,29,34] case–control studies (4/24; 17%)[13,14,21,28] and randomized controlled trials (4/24; 17%).[26,32,40,41] Seventeen out of 24 studies (67%) were multicentre studies,[14,16,19–22,26,27,29,32,35–41] and all studies recruited outpatients, of which nine studies (38%) also recruited inpatients.[19,20,22,25,26,32,33,40,41] Sample sizes varied between 52 and 628 patients, with a majority of females (3,576/5,735; 62%) and with mean/median ages ranging from 29 to 45 years.[13–16,19,20,22,25–33,35–41] Disease duration varied from six months to twenty years.[13,14,16,19,21,22,25–31,36,37,39–41]

With regard to the HRQOL measures, most studies employed both generic and disease-specific HRQOL measures (13/24; 54%).[14,16,19,22,25–27,29,30,32,37,40,41] The most frequently used disease-specific and generic measures were the IBDQ (15/24; 61%)[16,20–22,26–32,35,37,40,41] and the Short Form-36 (13/24; 54%),[14–16,19,22,26,29,30,32,37,38,40,41] respectively (Table 2).

Associations between determinants and HRQOL were mainly analysed using multivariate statistics (16/24; 75%)[14,16,19–22,25,27,29–31,35–39] of which multiple linear or logistic regression analysis was the most frequently used statistical method (9/16; 56%).[16,19–22,29,30,37,39]

3.3. Critical appraisal (Table 3, Supplementary; Table 2)

Although some studies utilized data from the same study population,[16–18,22–24,34,35] studies differed regarding reporting and presentation of the results. Therefore, each of the 29 studies was assessed separately.

The overall interobserver agreement regarding quality assessment (risk of bias) was 90%. Twelve studies were considered to be of high quality ("low risk of bias"),[13,16–18,20–23,29,34,37,38] 15 studies were considered to be of moderate quality,[14,19,24–28,30–32,35,36,39–41] and two studies were considered to be of low quality ("high risk of bias).[15,33]

With regard to each of the six sources of bias, methodological shortcomings most frequently observed were: no

clear description of recruitment methods (item 1c, Supplementary; Table 2), no information about dropouts (item 2b), no information about missing data for prognostic factors (item 3d), no information about standardized methods and outcome measurement for all participants (item 4c), incomplete data for potential confounders (item 5a), and no description of a conceptual model, supporting the analytic strategy (item 6b).

3.4. Determinants of HRQOL

Instead of overall HRQOL, one study used different domains of HRQOL as outcome measures.[33] Therefore this study was excluded, leaving 23 studies for further analysis.[13–16,19–22,25–32,35–41]

3.4.1. Socio-demographic determinants (Fig. 2)

For all studies reporting a significant association between any one socio-demographic determinant (except work disability) and HRQOL there were at least as many studies reporting no significant association between that determinant and HRQOL. As reported by four articles, female gender was found to be significantly associated with a lower HRQOL.[16,19,22,37] Work disability was reported twice,[13,16] smoking status (smoking versus non-smoking) was reported twice,[19,35] and age once,[21] as having a significant impact on total HRQOL. Being female, of older age, being a smoker and reporting IBD-related work disability adversely affected HRQOL.

3.4.2. Psychological determinants

Two studies examined the association between psychological distress, personality traits and disease-specific HRQOL. Boye et al. found that "social conformity" (decent, keeping order, doing things right and keeping social norms at a high level) was significantly associated with HRQOL.[20] Van der Eijk et al. showed that psychological distress, including anxiety and depression, and the occurrence of stressful life events all had a significant negative impact on HRQOL.[39]

3.4.3. Clinical determinants (Fig. 3)

With regard to disease activity and the number of relapses, there were more studies reporting a significant than a non-significant association with HRQOL. HRQOL was negatively influenced by an increased disease activity in ten studies[16,19,21,22,27,29,34,36,37,39] and by an increased relapse rate in two studies.[18,22] Other clinical determinants found to be significantly associated with HRQOL were extra-intestinal manifestations[36] and shorter disease duration.[31]

3.4.4. Treatment-related determinants (Fig. 4)

With regard to biological treatment and CD-related hospitalizations, there were more studies reporting a significant than a non-significant association with HRQOL. HRQOL was negatively influenced by CD-related hospitalizations in two studies,[19,22] whereas HRQOL was positively influenced by biological treatment, including infliximab, adalimumab, natalizumab and certolizumab in four studies.[26,32,40,41] In four out of nine studies HRQOL was negatively associated with corticosteroid treatment.[18,19,34,37]

When stratifying for cross-sectional studies[20,22,25,27,30,31,33,36–39] and prospective studies[15,16,19,26,29,32,34,40,41], it was found that female gender, work disability and increased disease activity were consistently associated with a lower HRQOL in both strata. Only prospective studies reported a significant association between disability and HRQOL[16] and between biological treatment and HRQOL.[26,32,40,41] When stratifying for cross-sectional studies with either a low[20,22,37,38] or moderate to high risk of bias,[25,27,30,31,33,36,39] no discrepancies were found regarding determinant-HRQOL associations between these strata.

3.5. Meta-analysis

Six studies reported a correlation coefficient for the association between disease activity and overall HRQOL and were included for meta-analysis.[17,24,27,28,31,36] Although there was a slight difference in the instruments used to assess disease activity and HRQOL, data seemed comparable and thus eligible for pooling of results. In a random-effects model, the weighted mean correlation found was of −0.61 (95% CI −0.654 to −0.5684). The total variability due to heterogeneity was 75.27% (p = 0.0016).

4. Discussion

This systematic review of 29 studies, including 24 original studies with a total of 5735 participants, is the first systematic review assessing the determinants of HRQOL in adult patients with CD. Overall, the methodological quality of these studies was moderate to high, indicating that there was a low to moderate risk of biased results. HRQOL was consistently impaired by work disability, increased disease activity, number of relapses and hospitalization rate. Biological treatment was significantly associated with an improved HRQOL. Disease activity contributed to 37% of patients' HRQOL. There was a paucity of psychological data, which precluded us from identifying consistent associations between psychological factors and generic or disease-specific HRQOL.

To date, two iterative reviews have carefully summarized data on determinants of HRQOL in the mixed IBD population.[4,5] One review particularly assessed the influence of disease activity on HRQOL,[4] whereas the other assessed the influence of psychosocial factors on HRQOL.[5]

In line with our results, Cohen et al. found that HRQOL was impaired in CD patients with clinically active disease, and that disease activity was negatively correlated with HRQOL. Contrary to our results, Cohen et al. also found a negative association between surgery and the HRQOL of CD patients.[4] This negative association was only reported in one study, assessing the long-term prognosis of CD patients.[21] Other included studies did not report this negative association. Possibly, in these studies the post-operative follow-up period was too short to reveal a decreased HRQOL. In addition, HRQOL appeared to improve shortly after surgery, but not in the long term.[42] This is consistent with the fact that in most studies disease activity eventually recurs after surgery.[43–45]

Sainsbury et al. conducted a search for studies which evaluated psychological, social and demographic

Table 2 Characteristics of included studies (n = 29).

Article	Study characteristics			Characteristics CD participants					Determinant		HRQOL
First author Year of Publication Country Reference	Design	Setting	Follow-up, years	Sample size IBD	Sample size CD	Mean/ median age, years (SD, IQR)	Sex Ratio, M/F	Mean/median disease duration, years (SD, IQR)	Determinant	Measure	Questionnaire
Ananthakrishnan 2008 USA [13]	CCS	Tertiary hospital	–	185	185	42.8 ± 14.1	82/103	13.7 ± 10.9	Demographics Clinical data Psychiatric comorbidity Work disability	NS HBI DSM-IV	SIBDQ
Andersson P. 2003 SE [14]	CCS	Multicentre Outpatients	–	383	127	44 (18–78)	56/71	16 (8–25)	Socio-demographics Disease activity Self-perceived general health	Interview CDAI VAS	SF-36 PGWB
Banovic I. 2010 FR [15]	PC	Outpatients	1	52	52	41.1 ± 12.5	23/29	NS	Socio-demographics Disease activity Fatigue Sleep disturbances Anxiety, depression	NS CDAI MFI ISI, PSQI HADS	SF-36
Bernklev T. 2006 NO [16]	PC	Multicentre Outpatients IBSEN Cohort	–	495	161	38.6 ± 15.5	49% female[a]	5	Socio-demographics Sick leave, unemployment, disability Clinical data	Interview Interview Interview	SF IBDQ
Bernklev T. 2004 NO [17]	PC	Multicentre Outpatients IBSEN Cohort	–	497	169	38.6 ± 15.5	83/86	5	Socio-demographics Clinical data	Interview Interview, Vienna	IBDQ-32
Bernklev T. 2005 NO [18]	PC	Multicentre Outpatients IBSEN Cohort	–	497	169	38.6 ± 15.5	83/86	5	Socio-demographics Medication Extra intestinal manifestations Disease course	Interview Hospital records Interview and physical examination Interview	IBDQ-32
Blondel-Kucharski F. 2001 FR [19]	PC	Multicentre Inpatients/ outpatients	1	231	231	29 (17–78)	99/132	6.3 (0.3–41.8)	Socio-demographics Clinical data Global disease course	NS Predefined definition GDCS, VAS	SF-36 RFIPC
Boye B. 2008	CS	Multicentre Inpatients/	–	110	54	38.1 (18–60)	14/40	NS	Socio-demographics Personality	NS	IBDQ-32

[20]		organizations							Clinical data	LOC, TAS HBI	
Canavan C. 2006 UK [21]	CCS	Multicentre Outpatients	–	221	221	NS	90/131	>20 years <10 years	Socio-demographics Clinical data	CDISR Self-reported	IBDQ-32 RFIPC
Casellas F. 2005 ES [22]	CS	Multicentre Primary and tertiary hospitals Inpatients/ outpatients	–	1156	628	34 (26–44)	274/354	5 (1.8–13.4)	Socio-demographics Clinical data	NS HBI	EQ-5D IBDQ-36
Casellas F. 2005 ES [23]	CS	Multicentre Primary and tertiary hospitals Inpatients/ outpatients	–	198	198	30 (23–38)	76/122	3 (0.4–6.8)	Socio-demographics Clinical data	NS HBI, Vienna	IBDQ-36 EQ-5D PGWB
Casellas F. 2001 ES [24]	CS	Inpatients/ outpatients	–	289	129	33 (24–40)	44/85	4.1 (1.2–8.3)	Socio-demographics Clinical data	HBI NS	PGWB IBDQ-36
Drossman D. 1989 USA [25]	CS	Inpatients/ outpatients	–	150	87	35.0 ± 12.2	33/54	11.6 ± 9.1	Socio-demographics Clinical data	Self-reported questionnaire Self-reported questionnaire, physician rating	SIP RFIPC
Feagan F.G. 2003 Multinational [40]	RCT IFX single dose IFX 5 mg IFX 10 mg	Multicentre Inpatients/ outpatients	1	110 113 112	110 113 112	37 ± 12	205/130	9.6 ± 7.5	Socio-demographics Clinical data	NS CDAI, Montréal	SF-36 IBDQ-32
Feagan F.G. 2007 Multinational [41]	RCT NAT vs. placebo	Multicentre Inpatients/ outpatients	1.2	168 171	168 171	37 ± 13 37 ± 12	77/91 59/112	10 ± 9 10 ± 7.3	Socio-demographics Clinical data	NS CDAI, Montréal	EQ SF IBDQ
Feagan F.G. 2009 Multinational [26]	RCT CER vs. placebo	Multicentre Inpatients/ outpatients	0.5	215 210	215 210	37.6 ± 12.1 37.5 ± 11.3	92/123 109/101	8.6 ± 7.1 7.3 ± 7.8	Socio-demographics Clinical data	NS CDAI, Montréal	EQ-5D SF-36 IBDQ-32 WPAI
Gibson P.R. 2007	CS	Multicentre Tertiary	–	143	143	38.4 ± 12.2	60/83	9.4 ± 7.4	Socio-demographics	Self-reported questionnaire	AQoL IBDQ-32

(continued on next page)

Table 2 (*continued*)

Article	Study characteristics			Characteristics CD participants					Determinant		HRQOL
First author Year of Publication Country Reference	Design	Setting	Follow-up, years	Sample size IBD	Sample size CD	Mean/ median age, years (SD, IQR)	Sex Ratio, M/F	Mean/median disease duration, years (SD, IQR)	Determinant	Measure	Questionnaire
AUS [27]		hospitals Outpatients							Clinical data	CDAI	
Guassora A.D. 2000 DK [28]	CCS	Outpatients	–	94	94	38 (18–65)	39/55	7(0–29)	Socio-demographics Disease activity	NS CDAI	McMaster IBDQ
Høivik M.L. 2011 NOR [29]	PC IBSEN Cohort	Multicentre Outpatients	–	98	98	42 ± 13.7	57/41	10	Socio-demographics Clinical data	Interview/ self-reported questionnaire Interview, Vienna	SF-36 IBDQ-32
Iglesias M. 2010 ES [30]	CS	Outpatients	–	92	92	37.6 ± 11.4	48/44	9.2 ± 8.1	Socio-demographics Clinical data	Patient records Montréal	SF-36 IBDQ-36
Jaghult S. 2011 SE [31]	CS	Outpatients	–	197	83	43.7 ± 13.6	36/47	7.6 ± 2.6	Socio-demographics Clinical data Coping	NS HBI SOC (short form)	IBDQ-32 RFIPC
Loftus EV et al. 2008 Multinational [32]	RCT ADA induction ADA 40 mg eow ADA 40 mg weekly	Multicentre Inpatients/ outpatients	1	170 172 157	170 172 157	36.9 ± 11.9 36.4 ± 11.1 36.9 ± 11.8	65/105 61/111 62/95	NS	Socio-demographics Depression Fatigue Disease activity	NS Zung Depression Scale FACIT-Fatigue Scale CDAI	SF-36 IBDQ-32
Maunder R et al. 1999 CAN [33]	CS	Tertiary hospital Inpatients/ outpatients	–	343	157	36.7	149/194[a]	NS	Socio-demographics Symptom severity	NS Self-reported	RFIPC
Romberg-Camps M.J.L. 2010 NL [34]	PC IBD-South-Limburg cohort	Multicentre Outpatients Inpatients, outpatients	–	707	304	40 (21–89)	104/200	8.1 (0.7–15.4)	Socio-demographics Fatigue Anxiety, depression Clinical data	NS MFI-20 HADS HBI, Vienna, medication	SF-36 IBDQ-32
			–	1105	545		218/327	NS	Socio-demographics	NS	IBDQ-32

Russel M.G. 1996 NL [35]	CS IBD-South-Limburg cohort	Multicentre Outpatients				37 (13–90)			Smoking habits	Self-reported questionnaire	
Schirbel A. 2010 DE [36]	CS	Multicentre Outpatients	–	334	179	38.9 ± 11.6	71/108	9.2 (2.8–15.6)	Socio-demographics Clinical data Pain	Questionnaire CDAI GPQ, VAS	SIBDQ
Stjernman H. 2010 SE [37]	CS	Multicentre Outpatients	–	447	447	45 (33–55)	188/259	14 (6–25)	Socio-demographic Clinical data	NS CDAI, PGA	SF-36 IBDQ-32 RFIPC PGWB SHS
Straus W.L. 2000 USA [38]	CS	Multicentre Tertiary and private hospitals Outpatients	–	442	442	42.7 ± 14.6	193/249	NS	Socio-demographics Clinical data Race	Self-reported questionnaire CDAI Black/white	SF36
Eijk I. van der 2004 European [39]	CS EC-IBD cohort	Multicentre Outpatients	–	517	195	42 (34–56)	247/270[a]	6–8	Socio-demographics Psychological distress Coping Social support Stressful life events Clinical data Quality of care Disease activity	NS MHI-5 CISS MOSSSS SRRQ HBI QUOTE-IBD	SIBDQ

Abbreviations: ADA = adalimumab, AQoL = Assessment of Quality of Life, BPA = Buss–Perry Aggression Questionnaire, CCS = case–control study, CDISR = Crohn's disease Index for Survey Research, CER = certolizumab, CISS = Coping Inventory of Stressful Situations, CS = cross-sectional study, EC-IBD = European Collaborative study group on Inflammatory Bowel Disease, eow = every other week, EPQ = Eysenck Personality Questionnaire, EQ-5D = EuroQol 5 Dimensions, GDCS = Global Disease Course Score, GPQ = German Pain Questionnaire, HADS = Hospital Anxiety Depression Scale, HBI = Harvey–Bradshaw Index, ISI = Insomnia Severity Index, LOC = Multidimensional Health Locus of Control Scale, MFI = Multidimensional Fatigue Inventory, MHI-5 = Mental Health Inventory-5, MOSSSS = Medical Outcomes Study Social Support Survey, NAT = natalizumab, NS = not specified, PC = prospective cohort study, PGA = Physicians Global Assessment, PGWB = Psychological General Well Being Index, PSQI = Pittsburgh Sleep Quality Index, QUOTE-IBD = Quality of Care Through the IBD patients eyes, RCS = retrospective cohort study, SHS = Short Health Scale, SIP = Sickness Impact Profile, SRRQ = Social Readjustment Rating Questionnaire, TAS = Toronto Alexithymia Scale.

a: Data from the whole study sample, including patients without Crohn's disease.

b: Repeat assessment sample.

Table 3 Overview of results from the critical appraisal.

First author	Study participation	Study attrition	Prognostic factor	Outcome	Confounding	Analysis	Overall quality
Ananthakrishnan	1	x	1	1	2	2	1
Andersson	1	x	2	1	3	2	2
Banovic	3	2	1	1	3	2	3
Bernklev 2006	1	2	1	1	2	1	1
Bernklev 2005	1	2	2	1	1	1	1
Bernklev 2004	1	2	2	1	2	1	1
Blondel–Kucharski	2	2	2	1	1	2	2
Boye	1	x	1	1	2	2	1
Canavan	1	x	1	1	2	2	1
Casellas 2005	2	x	1	1	2	1	1
Casellas 2005	2	x	1	1	2	1	1
Casellas 2001	1	x	1	1	2	2	2
Drossman	2	x	2	1	3	2	2
Feagan 2009	1	2	2	1	2	2	2
Feagan 2007	1	2	2	1	2	2	2
Feagan 2003	1	2	2	1	2	2	2
Gibson	1	x	2	1	2	2	2
Guassora	1	x	1	1	3	2	2
Høivik	1	2	1	1	2	1	1
Iglesias	1	x	1	1	2	3	2
Jaghult	2	x	1	1	2	2	2
Loftus	1	2	2	1	2	2	2
Maunder	2	x	3	1	3	2	3
Romberg	1	2	1	1	2	1	1
Russel	1	x	1	1	3	2	2
Schirbel	1	x	1	1	3	2	2
Stjernman	2	x	1	1	2	1	1
Straus	2	x	1	1	1	1	1
Van der Eijk	3	x	2	1	1	1	2

1 = low risk for bias, 2 = moderate risk for bias, 3 = high risk for bias, x = not applicable.

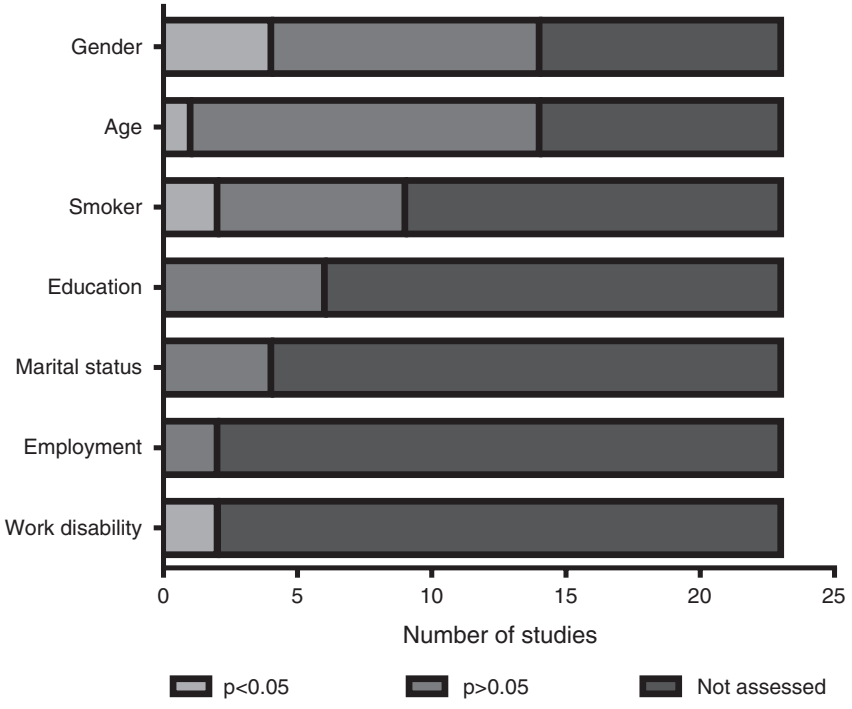

Figure 2 Socio-demographic determinants of disease-related HRQOL: frequency of findings.

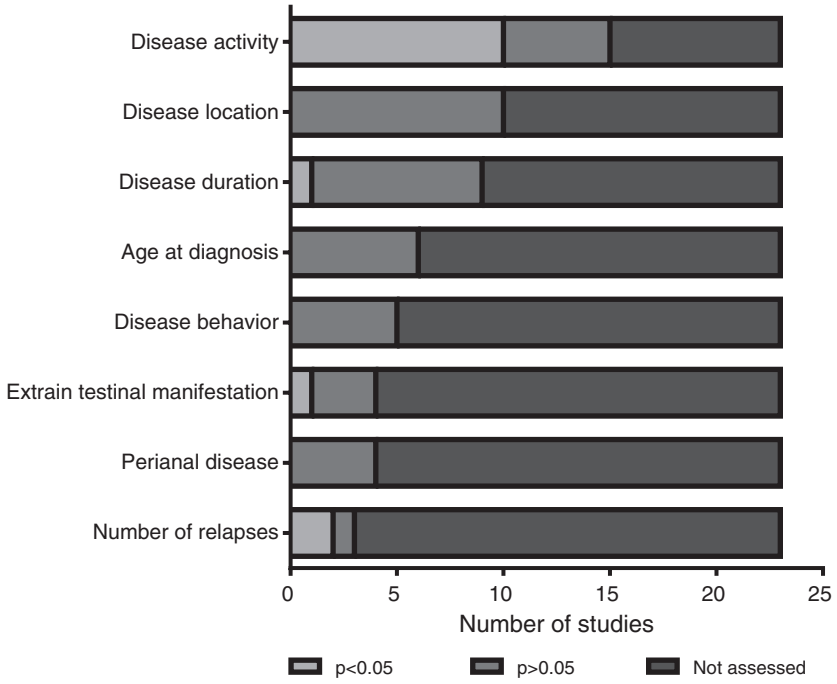

Figure 3 Clinical determinants of disease-related HRQOL: frequency of findings.

characteristics of adult IBD patients, yielding 107 relevant studies.[5] This remarkably high number of included studies is mainly attributable to including studies of mixed IBD populations and studies with small sample sizes (<50 patients), which were excluded in our study. In their review, Sainsbury et al. found a number of psychological and social factors to be related with a lower HRQOL in IBD patients, including female gender, lower socioeconomic status, ethnicity and perceived stress.[5] In line with our results, female gender was associated with a lower HRQOL. Several hypotheses for this finding exist. Psychosocial factors may play a greater role in females than in males.[19] Others state that females have greater disease-related concerns and worries about being a burden of being treated differently as a result of their illness.[46] Furthermore, females are also more likely to report concerns related to attractiveness, body image and feeling alone.[33] Noteworthy, females also report poorer HRQOL than males across various chronic illnesses — including asthma,[47] rheumatoid arthritis[48] and diabetes[49] and even in the general healthy population.[50]

The negative influence of low socioeconomic status, ethnicity and higher perceived stress on HRQOL in CD patients could not be corroborated in our study, as these factors were reported by any of the included studies.

Psychological factors, such as illness perceptions and psychological distress (anxiety and depression), were

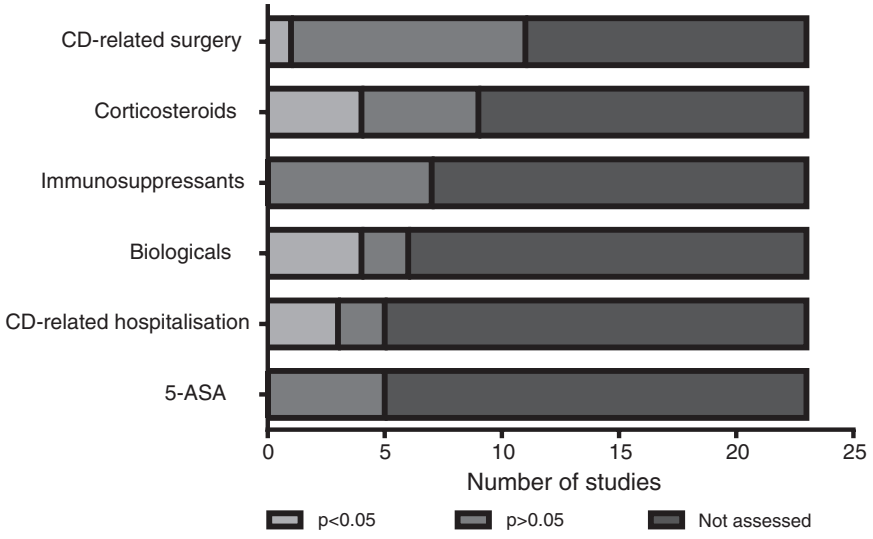

Figure 4 Treatment-related determinants of disease-related HRQOL: frequency of findings.

underrepresented in the included articles, but warrant further research. Previous studies in IBD have found that illness perceptions contributed to 4–21% of patients' HRQOL, in addition to socio-demographic and clinical determinants.[51–53] More importantly, as these illness perceptions are modifiable, they provide potential targets for HRQOL enhancing interventions. In addition, anxiety and depression are highly prevalent in IBD patients, and have been found to be related with HRQOL.[39,54–56]

HRQOL was significantly impaired by work disability in two out of three studies. Noteworthy, work disability rates of IBD patients range between 1.3 and 34%,[13,16,57–63] with even higher rates in CD patients under 40 years of age.[63] As work disability leads to a heavy psychosocial and financial burden for patients, all efforts should be made to prevent work disability and to help work disabled patients back into the labour market.

Although we found a negative association between corticosteroid treatment and HRQOL in four out of nine studies, this finding should be interpreted with caution. First of all, this negative association was mainly based on cross-sectional studies, thereby, a potential positive or negative influence of corticosteroid treatment on HRQOL over time could not be determined.[20,35,38] Furthermore, not all studies appropriately corrected for disease activity, making it impossible to determine an independent association between corticosteroid treatment and HRQOL.[19,38] It is known that corticosteroids are frequently associated with specific side effects, including cosmetic side effects and sleep and mood disturbances, with a possible negative effect on HRQOL.[64] However, whether these corticosteroid-specific side effects are responsible for the negative association between corticosteroid use and HRQOL remains a matter of debate. As HRQOL measures have been available in IBD management since the early 1980s, appropriate studies assessing the influence of conventional immunosuppressants, such as thiopurines and methotrexate, on CD patients' HRQOL were lacking. The available evidence from our analyses that HRQOL is positively influenced by biological treatment is relatively strong, as this evidence was mainly based on prospective randomized studies.[26,32,40,41] Further non-randomized prospective studies are warranted to validate the positive impact of biological treatment on HRQOL in daily clinical practice.

Our study has several important strengths. The strength of the association between any of the determinants and HRQOL was assessed, indicating which of the variables significantly contributed to the HRQOL of CD patients. In addition, evidence on the determinants of HRQOL in CD is systematically summarized and critically appraised, showing all evidence available and revealing areas in which further research is required. As stated in the Introduction, a comprehensive understanding of the determinants of HRQOL may guide clinical decision making. Important clinical decision, such as top-down versus step-up therapy, ileocolonic resection versus anti-TNF therapy and anti-TNF mono-therapy versus combination anti-TNF plus thiopurine therapy, should ideally be based on this kind of evidence, as these decisions may have significant consequences to patients' daily lives.

Our study has some limitations as well. As we included studies with heterogeneous sample sizes, study designs, determinant and outcome measures, we were unable to quantify the relationships between other determinants, besides disease activity, and HRQOL. Although the pooled association between disease activity and HRQOL was relatively strong, this finding should be interpreted with caution as the meta-analysis indicated significant heterogeneity across the included studies. Furthermore, as we excluded abstracts and unpublished studies, publication bias cannot be completely ruled out. However, as most of the available and reviewed studies had a moderate to high quality, we feel that the contribution of unpublished studies would be minimal. Of note, all randomized controlled trials received financial support by a pharmaceutical company, which might suggest publication bias. However, none these companies were involved in the data analysis.

In conclusion, determinants that were found to consistently impact the HRQOL of adult CD patients, included markers of active disease such as work disability, clinical disease activity, increased relapse rate, biological treatment and hospitalization. Unfortunately, these determinants are not very helpful for clinicians when dealing with asymptomatic CD patients or when choosing between treatments with a comparable clinical efficacy (for example clinical remission). As disease activity contributed to only 37% of HRQOL, there remains a need for additional, possibly modifiable, determinants. Therefore, in order to improve our understanding of HRQOL and to facilitate clinical decision making, more long-term prospective data on, preferably, modifiable determinants of HRQOL are highly needed. Ultimately, this will improve HRQOL in an important subset of patients, leading to a decrease in health care and society costs.[65]

Contributors

MH and KA contributed to study concept and design, acquisition, analysis and interpretation of data. HF, AK and BO contributed to interpretation of data. MH, KA and ML contributed to statistical analysis. All authors contributed to drafting of the manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2013.04.007.

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