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Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses—Part II

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Background: There has been burgeoning interest in quality of life (QoL) in inflammatory bowel disease (IBD) in recent decades, with hundreds of studies each year now assessing this outcome. This paper is part 2 of a systematic review evaluating 5 key QoL comparisons within IBD states and relative to others without IBD. Part 1 examined QoL comparing IBD and a healthy/general population and other medically ill groups. Part 2, presented here, examines within-disease comparisons of active/inactive disease, Ulcerative colitis (UC) / Crohn's disease (CD), and change in QoL over time. Outcomes using generic versus IBD-specific QoL measures were also examined.

Methods: Adult and pediatric studies were identified through systematic searches of 7 databases from the 1940s (where available) to October 2015.

Results: Of 6173 abstracts identified, 466 were selected for final review based on controlled design and validated measurement, of which 83 unique studies (75 adult, 8 pediatric) addressed the within-disease comparisons. The pooled mean QoL scores were significantly lower in active versus inactive IBD (n = 26) and for those with CD versus UC (n = 37), consistent across IBD-specific and generic QoL measures, for almost all comparisons. There was significant improvement in QoL over time (n = 37). Study quality was generally low to moderate. The most common measures of QoL were the disease-specific Inflammatory Bowel Disease Questionnaire and generic 36-Item Short Form Survey (SF-36) (adults) and the IBD-specific IMPACT (children).

Conclusions: For adults in particular, there was strong confirmation that QoL is poorer during active disease and may be poorer for those with CD. The finding that QoL can improve over time may be encouraging for individuals with this chronic disease.

Key Words: inflammatory bowel disease, meta-analysis, quality of life, systematic review

INTRODUCTION

Patients suffering from inflammatory bowel disease (IBD) often report impaired quality of life (QoL), reflected in higher rates of comorbid anxiety and depression when compared with healthy controls.[1] QoL in IBD cohorts is measured in a wide range of IBD research, including clinical trials of new anti-inflammatory medication, surgery, dietetics, and psychology. While systematic reviews have examined measures and determinants of QoL in IBD,[2,3] there have been no systematic reviews using standardized, rigorous methodology focused on a priori planned comparisons to address more specific questions about QoL in IBD, such as the variation seen among disease types (CD versus UC), disease status (active versus inactive), and the temporal trajectory. The present paper is the second of a 2-part review documenting QoL in IBD. In part 1 of this systematic review, 2 questions were examined: (1) is QoL in IBD similar or different to that reported for the healthy/general population controls? and (2) is QoL in IBD similar or different to that reported in other groups of medically ill patients? It was confirmed that QoL for children and adults with IBD is poorer relative to healthy individuals, but not significantly different for adults with IBD when compared with individuals with chronic medical conditions.

The present review aims to systematically and comprehensively address QoL in IBD subtypes and during active versus inactive phase of the disease, as well as changes in QoL over time. Previous nonsystematic reviews have documented differences in QoL between CD and UC[4] and between active versus inactive phases of the disease,[5] while the temporal changes in QoL have not been systematically evaluated before.

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Further, no meta-analysis was conducted to date to summarise and compare the levels of QoL in the subpopulations of IBD. Therefore, the present paper presents the most up-to-date and critical evaluation of currently available data on QoL by IBD activity, subtype, and over time. Extending part 1 of this systematic review, part 2 reviewed the following specific questions:

Question 3: Is QoL similar or different during active versus inactive IBD?

Question 4: Is QoL similar or different in UC (active/inactive) versus CD (active/inactive)?

Question 5: Does QoL change over time in IBD (i.e., any evidence of disease adaptation)?

MATERIALS AND METHODS

This systematic review was registered in the International Prospective Register of systematic reviews PROSPERO (CRD42015026139). The full details relating to the inclusion/exclusion criteria, search methodology, data collection, and analysis procedures and quality and risk of bias assessment are outlined in part 1 of this systematic review.[6] (See supplementary materials for the completed PRISMA checklist.)

RESULTS

Of the 6173 studies identified during the database searches, 2344 were removed as duplicates. Titles and abstracts were screened for the remaining 3829 papers, and 3363 did not meet the inclusion criteria (see Fig. 1), leaving 466 included for full review. A total of 83 unique studies (75 adult, 8 pediatric) were included in the final review, with 26 studies for question 3 and 37 studies for both questions 4 and 5.

Study Characteristics

Question 3: QoL in IBD when disease is active versus inactive

As shown in supplementary Table 1, 26 studies (N = 5777; 58% CD, mean age = 39.4 years, 52% female) examined differences in QoL between active (N = 2290) and inactive (N = 2743) IBD; 1 study did not report the number of participants by disease status. Seventeen studies were from Europe (including the United Kingdom), 6 were from North America, 2 from Australia, and 1 from Africa (Tunisia). Twenty studies used cross-sectional designs, and 6 were cohort designs. Total sample size ranged from 38 to 1156. Twenty of 26 studies reported percentage of patients with inactive versus active disease, and 14 (54%) studies used one of several well-validated disease activity indices (HBI, CDAI, Seo, Powell Tuck, True-Love Witt). Twenty-four of the studies were conducted in adults (mean age = 41.6, 52% female). Of the 24 adult-focused QoL studies, 16 (67%) used the Inflammatory Bowel Disease Questionnaire (IBDQ)[7]as the primary measure of QoL, and 4 (17%) used the Medical Outcomes Study Questionnaire Short Form.[8] Additional measures of QoL were the Rating Form of IBD Patient Concerns (RFIPC) (N = 4), EuroQoL-5 (EQ-5D) (N = 2), and Psychological General Well-Being Index (PGWBI) (N = 3), and each used the Assessment of Quality of Life (AQoL) and the Questions on Life Satisfaction (FLZ). Two of the 26 studies (N = 251, mean age 14.5, 47% female)[9, 10] examined quality of life scores in pediatric/adolescent populations. Both pediatric studies measured QoL with IMPACT.[11]

Question 4: QoL in CD versus UC

As shown in supplementary Table 2, 37 studies (N = 15,246, 44% CD, mean age = 39.3, 59% female) examined potential differences in QoL between CD (N = 6645) and UC (N = 7788). Twenty-eight studies came from Europe (including the United Kingdom), and 9 were from North America. Thirty-one studies had a cross-sectional design, 4 were cohort studies, 1 was prospective, and 1 was a case control design. Total sample size ranged from 28 to 2931, with sample size for CD ranging from 13 to 1082 and UC ranging from 14 to 1661. QoL was compared between CD and UC with the generic measures (e.g., 12-Item Short Form Survey (SF-12), 36-Item Short Form Survey (SF-36), EQ-5D) in 8 studies exclusively, and 12 studies used a combination of generic and disease-specific IBDQ/Short Inflammatory Bowel Disease Questionnaire (SIBDQ); 5 of the 28 studies using the IBDQ or SIBDQ also included the SF-36 or SF-12. EQ-5D was measured in 5 studies, 4 of those used the IBDQ or SIBDQ, as well. Other measures included: PGWBI (N = 3), World Health Organization (WHO) QoL (N = 1), the 15D instrument of health-related quality of life (N = 2), Questions on Life Satisfaction (FLZ) (N = 1), Grogono-Woodgate Index (GWI) (N = 1), and Duke-UNC Health Profile (DUHP) (N = 1). One of the studies was done in a pediatric population (N = 110; 58% CD, median age = 13.8, 58% female) using the KidsScreen-27 as its QoL measure.[36]

Question 5: Changes in QoL over time

As shown in Supplementary Table 3, 37 studies (IBD: N = 19,194; 58.6% CD, mean age = 36.2, 54% female) had applicable data exploring changes in QoL over time. Twenty-five studies came from Europe, 8 from North America, 3 from Australia/New Zealand and one from Latin America (Brazil). Twenty-two of the studies were cross-sectional, 14 were cohort-based, and one was a case control design. The sample size ranged from 18 to 7819, with 4 studies having > 1000 IBD participants. Six of the 37 studies were focused on children/adolescents (IBD: N = 859; 59% CD, mean age = 13.8, 50% female). QoL measures were quite variable in both the adult and pediatric studies. For adult studies, some version of the disease-specific IBDQ was used most frequently (IBDQ-32 or translated versions, n = 11; SIBDQ-10, n = 4; mIBDQ-36, n = 3). The

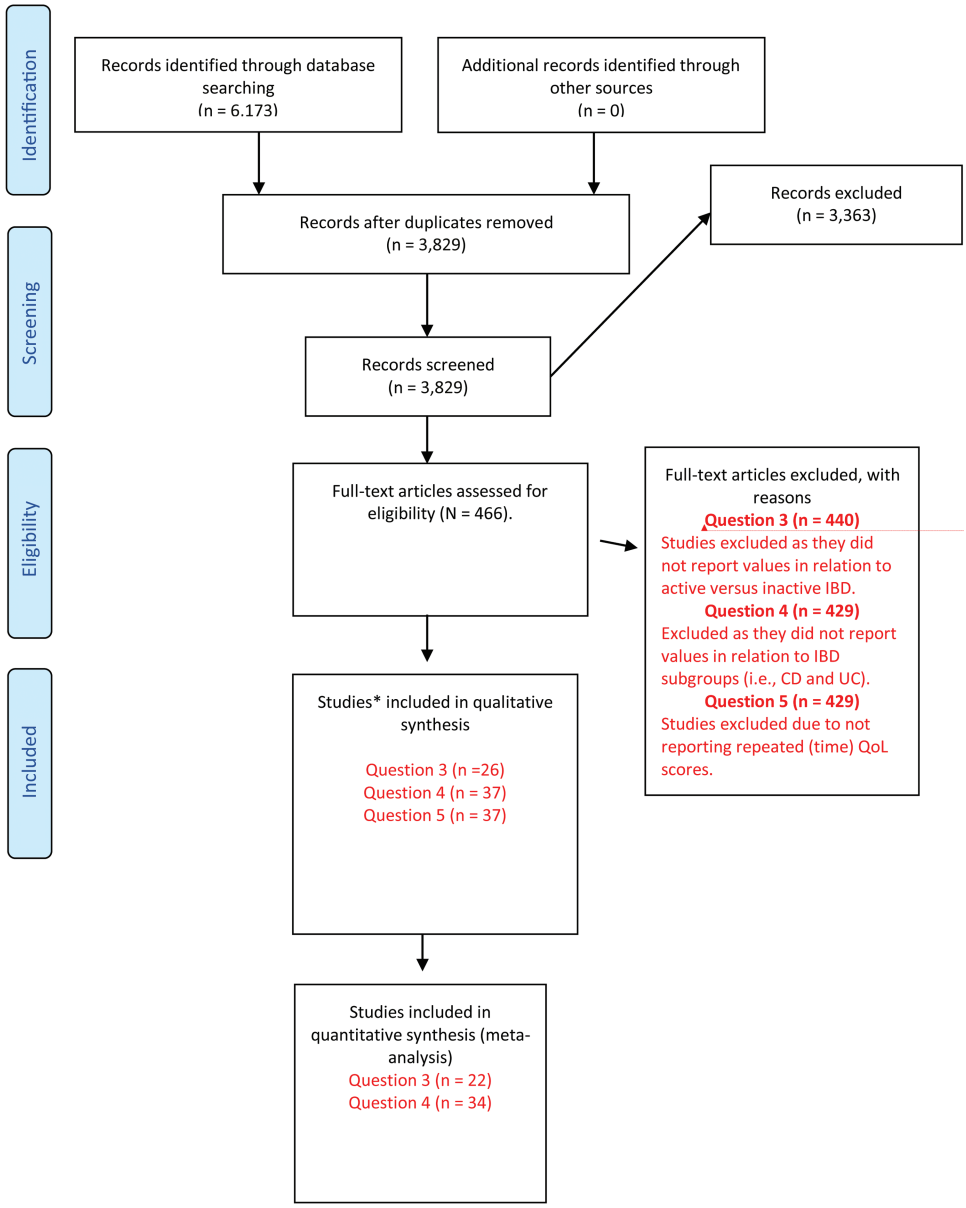

FIGURE 1. PRISMA flow diagram.

generic MOS quality of life measure, the SF-36 or variant, was also commonly used (SF-36, n = 5; SF-12, n = 2), and the worries rating scale, the RFIPC, was included in six studies. Other measures were used in 1 to 3 studies (i.e., 15D, AQoL, Cleveland Global Quality of Life (CGQL), EQ5, Italian Questionnaire on Quality of Life (IQQoL), PGWBI, Paediatric Inflammatory Bowel Disease Questionnaire (PIBDQ), The World Health Organization Quality of Life-Bref (WHOQoL-Bref); total exceeds 31 as some studies used > 1 scale). In the pediatric studies, 3 used a version of the IMPACT measure (IMPACT III, n = 2; IMPACT II, n = 1), and each used the PedsQL 4.0, KIDSSCREEN-27 and 15D/16D/17D.

Quality of Life Study Outcomes

Question 3: QoL in IBD when disease is active versus inactive

Of the 26 adult studies that evaluated quality of life comparisons among IBD-active and IBD-inactive patients, 22 were able to be combined in at least one of the meta-analyses undertaken to answer this question. There were only 2 studies that presented data for QoL for active versus inactive IBD in pediatric samples. Both studies demonstrated significantly lower (i.e., worse) QoL for those with active compared with inactive disease.[9, 10] Given the low number of studies, we did not formally

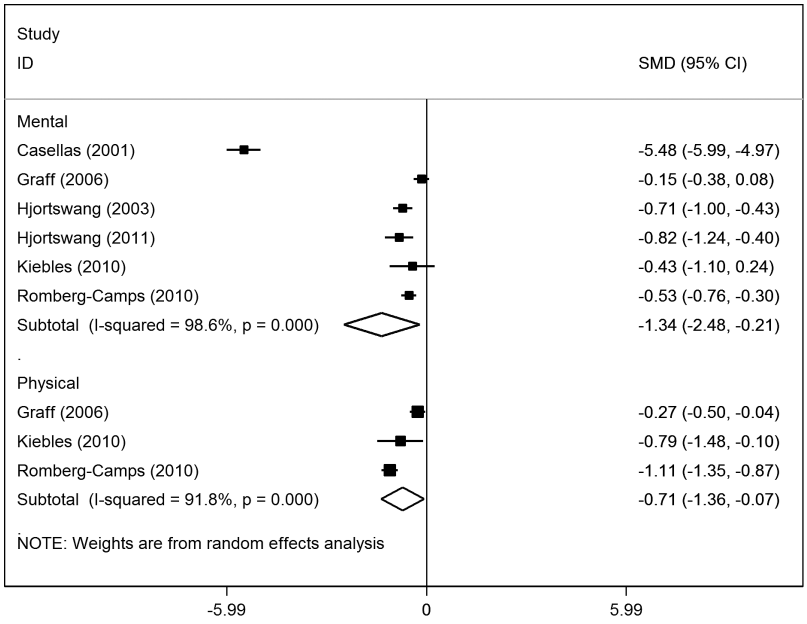

FIGURE 2. Physical and mental QoL component scores for active versus inactive IBD.

pool these results. The other 2 excluded studies did not provide sufficient data to be included in any of the meta-analyses.[12, 16] For adult samples, studies reporting physical and mental QoL scores were combined (Fig. 2).

The pooled estimate for physical QoL scores (n = 3 studies and 689 participants) was −0.71 (95% CI, −1.36 to −0.07) and for mental QoL scores (n = 6 studies and 1350 participants) was −1.34 (95% CI, −2.48 to −0.21), demonstrating that the pooled mean QoL scores were lower in active compared with inactive IBD samples, with larger impact for mental QoL scores compared with physical QoL scores. There were also sufficient numbers of studies for adult populations to pool the total scores for both generic and IBD specific QoL scores comparing active and inactive IBD (Fig. 3).

The pooled estimate for the generic total QoL scores (n = 6 studies and 1891 participants) was −1.19 (95% CI, −1.68 to −0.70) and for IBD specific QoL scores (n = 16 studies and 3395 participants) was −1.29 (95% CI, −1.52 to −1.05). Both types of measures highlighted poorer QoL in active compared with inactive IBD patients, with a slightly greater difference in QoL between active and inactive IBD, demonstrated with IBD-specific QoL measures compared with generic QoL measures. Note that all analyses undertaken within question 3 had high levels of heterogeneity (I^2 values all over 85%), so these results should be interpreted with caution.

Question 4: QoL comparing disease subtypes and disease activity state

Thirty-seven studies evaluated quality of life among IBD subtypes and/or disease activity states; 36 were in adult populations, and 1 in pediatric sample. Overall, 34 of the 37 studies were included in at least 1 of the meta-analyses undertaken to answer this question.

CD versus UC. The one pediatric study did not observe a statistically significant difference between patients with CD and UC in physical (47.3 versus 48.5, $P = 0.59$) or mental (52.7 versus 54.4, $P = 0.42$) QoL scores.[36] In total, 28 of the 36 studies in adult populations presented sufficient data on the comparison of QoL between CD and UC to be included in at least 1 of the meta-analyses undertaken to answer this specific question. Eight studies did not provide sufficient data to be included in any of the meta-analyses related to the CD versus UC comparison.[30, 34, 44, 48, 57, 61, 64] The pooled estimate for the physical (−0.12, 95% CI, −0.26 to 0.02, n = 7 studies and 2375 participants) and mental (−0.09, 95% CI, −0.19 to 0.00, n = 8 studies and 2664 participants) QoL scores demonstrated lower (i.e., worse) QoL in those with CD compared with those with UC, but these differences were borderline significant. Interestingly, the generic total QoL scores (−0.12, 95% CI, −0.21 to −0.04, n = 6 studies and 4350 participants) and IBD-specific QoL (−0.08, 95% CI, −0.14. to −0.03, n = 22 studies and 9010 participants) measures both demonstrated significant differences between those with CD compared with UC. The magnitude of the effect was the same for generic physical QoL as to that observed in the generic total QoL scores. Very similar effects were also seen for generic mental QoL with that observed for specific total QoL scores. It is also worth noting that the heterogeneity (I^2 values—low to moderate) was lower for these studies than those observed for other meta-analyses presented here (see Fig. 4).

CD versus UC based on active versus inactive disease. In total, 10 of the 37 studies in adult populations presented sufficient

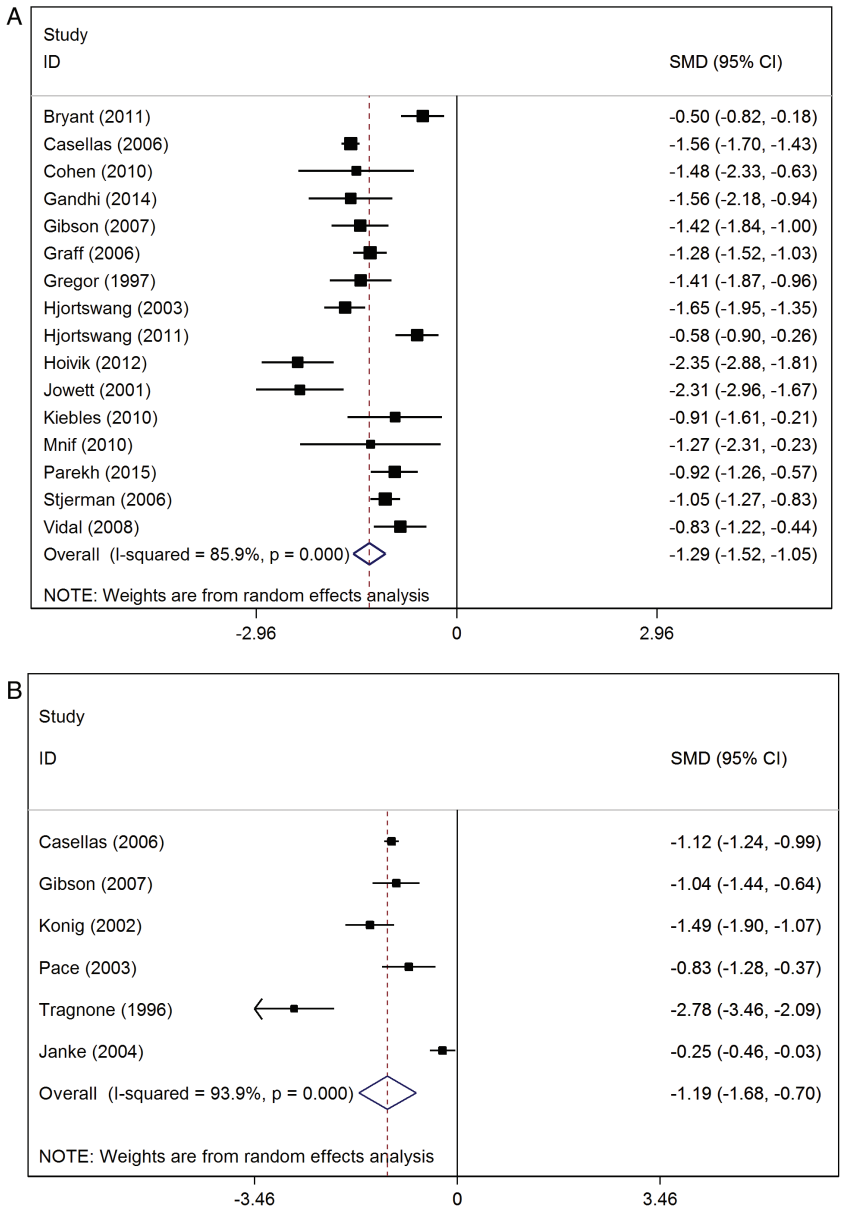

FIGURE 3. Specific (A) and generic (B) QoL scores for adult populations comparing active and inactive IBD.

data on the comparison of QoL between CD in remission and UC in remission[15, 20, 34, 44, 45, 48, 61, 62, 64, 65] and 4 studies between active CD and active UC[20, 45, 46, 65] are included in at least 1 of the meta-analyses undertaken to answer this specific question.

For the remission question, there were 6 studies that provided data on specific IBD QoL measures, 3 that reported mental QoL scores, and 2 that reported generic QoL total scores (Fig. 5). The pooled estimate for the mental (−0.38, 95% CI, −0.70 to −0.05, n = 3 studies and 373 participants) QoL scores demonstrated lower (i.e., worse) scores with CD in remission compared with UC in remission. A similar pattern, although not statistically significant, was also seen for IBD specific QoL total scores (−0.64, 95% CI, −1.58 to 0.31, n = 6 studies and 732 participants). A different pattern was seen for the generic QoL total scores with no difference demonstrated between the 2 groups (0.05, 95% CI, −0.36 to 0.46, n = 3 studies and 417 participants). Note that analyses had moderate to high levels of heterogeneity (I^2 values all over 58%).

There were 4 studies (557 participants) included in the active disease comparison of IBD specific total QoL scores between CD and UC (Fig. 5: B). The pooled estimate was −0.05 (95% CI, −0.22 to −0.12). This demonstrated little difference in QoL scores with active CD compared with active UC. The I^2 value indicates no heterogeneity amongst these studies.

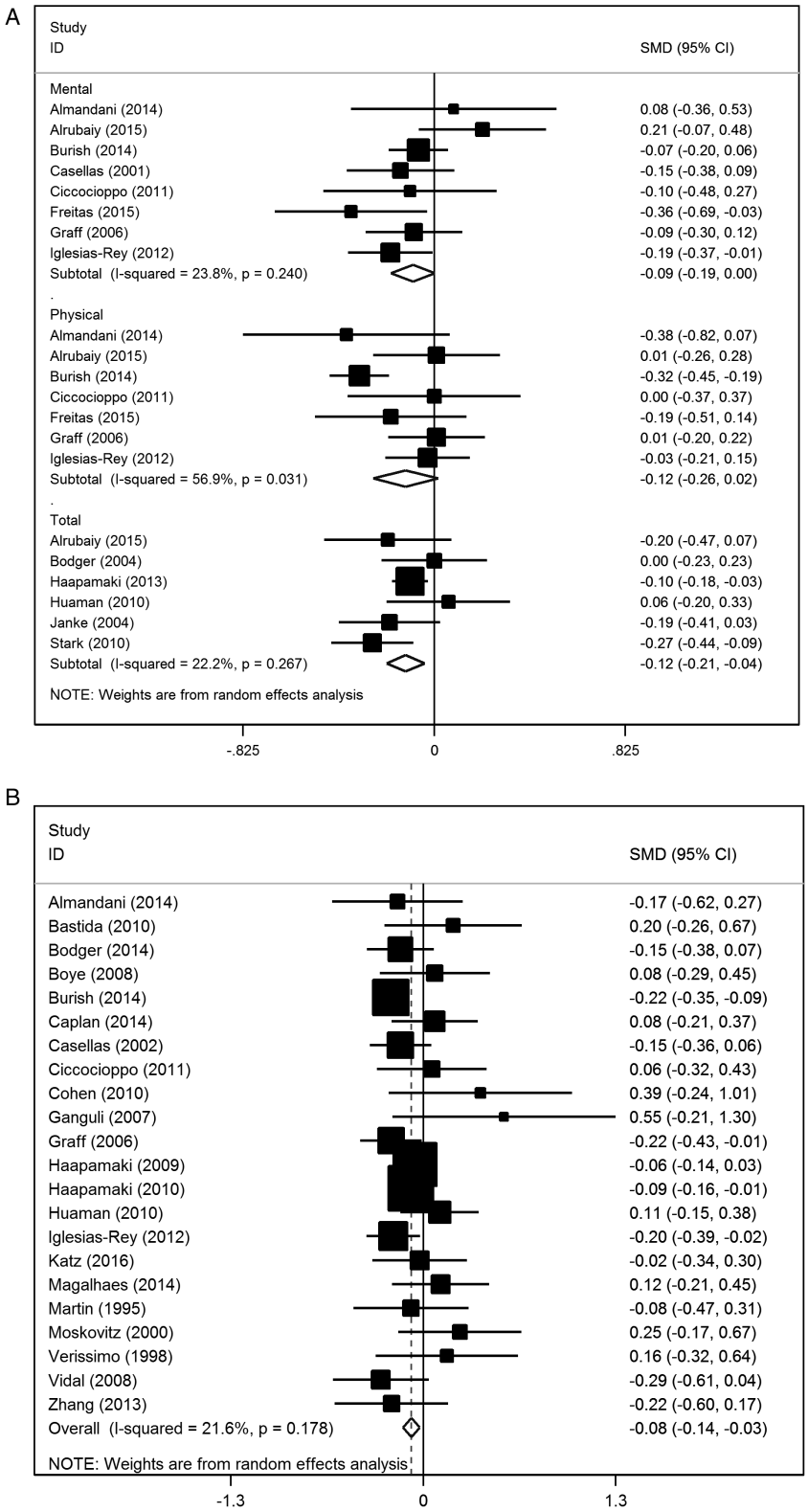

FIGURE 4. Generic (A) and specific (B) QoL scores for adult populations comparing CD and UC.

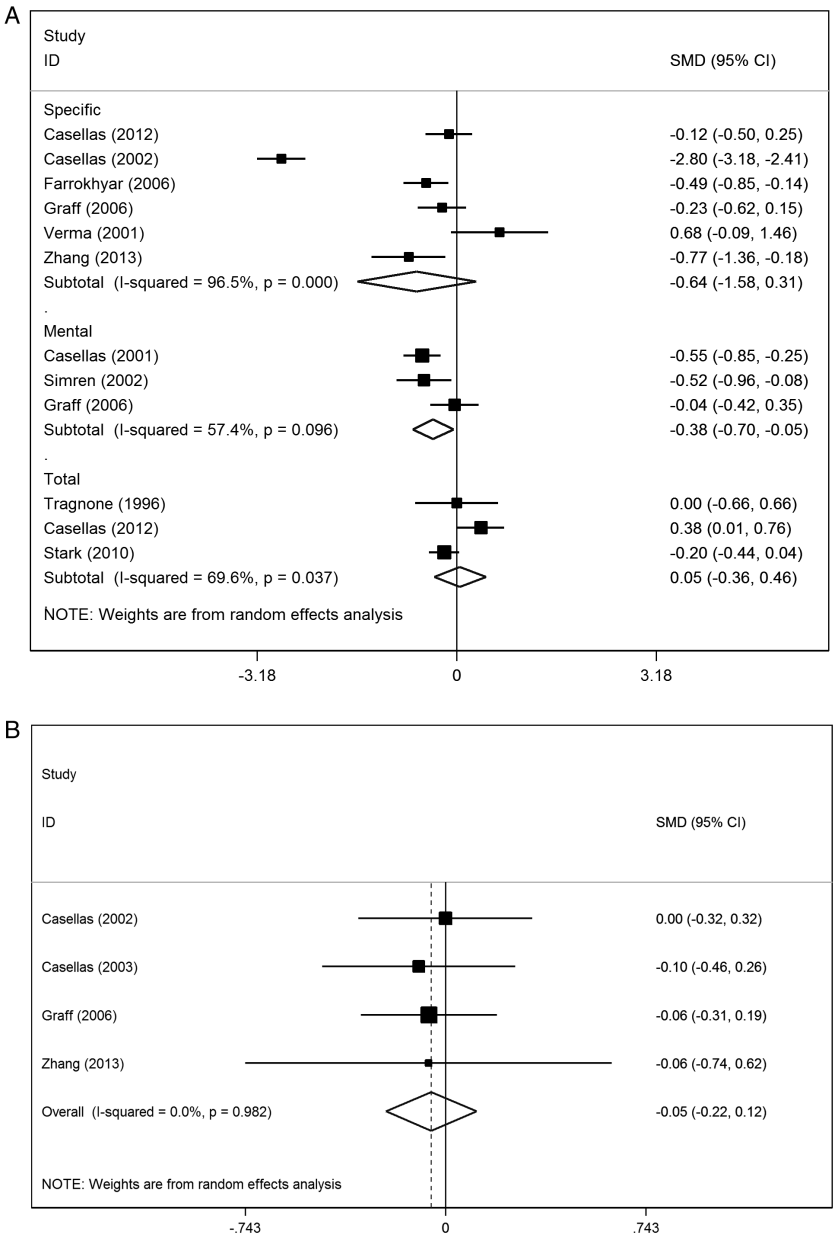

FIGURE 5. Generic, specific and mental QoL scores for adult populations comparing CD and UC by disease activity. A, CD remission and UC remission. B, CD active versus UC active.

Question 5: Changes in QoL over time

Of the 37 studies contributing to this question, 14 were cohort studies, 22 were cross-sectional, and 1 was a case-control study. Twenty-eight of the 37 studies considered the association between disease duration and QoL based on cross-sectional data, and 10 examined longitudinal data.[89] While the most optimal design to examine changes over time is longitudinal, we present both cross-sectional and longitudinal designs with the caveat that cross-sectional data is associated with a greater bias than longitudinal designs. Formal pooling of studies was considered, but due to different ways in which this was statistically explored, differences in the timing of the outcome assessment, different outcome measures used, inconsistent categorization of duration of disease (where it was undertaken), and insufficient data presented, it was deemed not appropriate to undertake a meta-analysis for this question. Hence a narrative synthesis was performed and is outlined.

Twenty-two studies explored whether disease duration predicted QoL; some explored duration as a continuous measure (n = 10), while others categorized duration (n = 10). One study used both methods. Nearly every study that categorized duration did the categorization in a different way (e.g.,

above or below 4.5 years, above or below 20 years; first versus recurrent; 1 year previous versus longer; short versus long; quartiles or quintiles of disease duration).

Twenty-five of the 28 studies reporting cross-sectional data used adult samples. Of these 25 studies, 10 explored whether duration (continuous measure) predicted QoL, 9 explored whether duration (categorized) predicted QoL, 2 looked at both continuous and categorized duration, and 3 looked at the correlation between duration and QoL. Irrespective of the type of analysis, of these 27 analyses (25 studies), 8 reported significant associations of QoL with disease duration, indicating better QoL with greater duration of IBD. Sixteen analyses did not find a significant relationship (i.e., reported that disease duration did not predict QoL or that duration was not associated with QoL). For 1 study, there was insufficient data presented to indicate whether the result was statistically significant or not. Two of the 3 pediatric studies found no evidence of an association between disease duration and QoL[36, 79]; 1 did find that duration was correlated with QoL.[83]

The longitudinal studies ranged from a 6- to 24-month time frame. Seven of the 10 studies used adult samples, and of those, 4 described significant improvement in quality of life over time,[42, 69, 84, 85] and 3 reported improved scores, although these latter comparisons either were not evaluated or were nonsignificant.[67, 68, 89] Two of the 3 pediatric studies found that quality of life significantly improved over time[73, 88]; 1 did not find a significant improvement over time.[74]

Quality Appraisal

Quality scores for each study are presented in Supplementary Tables 1–3.

Question 3: IBD active versus IBD inactive

Quality ranged from 1 to 7 of a maximum 10 points, with a mean quality rating of 3.5, indicating a moderate quality. Overall, 4 out of 26 studies (15.39%) scored 6 or more on the quality scale.

Question 4: CD versus UC

Quality ranged from 1 to 8 of a maximum 10 points, with a mean of 3.95, indicating a moderate quality. Overall, 6 out of 37 studies (16.22%) scored 6 or more on the quality scale.

Question 5: Change over time in quality of life

Quality ranged from 1 to 7 of a maximum 7 points, with a mean of 3.03, indicating moderate quality. Overall, 11 of 37 studies (29.73%) scored 4 or more on the quality appraisal scale.

DISCUSSION

QoL is an important indicator of patient outcomes in both observational and interventional studies in the IBD literature. Given the importance of assessing QoL *within* IBD cohorts to understand impact relative to disease state, this comprehensive review relates to multiple comparisons of QoL in IBD across adult and pediatric populations. We also explored potential differences in the use of generic versus IBD-specific QoL measures for IBD participants in this paper.

In this part 2 of the systematic review, the findings clearly supported that QoL is significantly poorer for individuals when their disease is active relative to when it is quiescent and that QoL, in relation to mental functioning, is particularly impacted. While overall, those with CD had lower QoL scores than UC participants, the difference was not significant. However, when the disease state was also considered, those with CD in remission had significantly lower mental QoL than those with UC in remission; there was no difference between the two disease subtypes when the disease was active. Approximately one-third of the cross-sectional studies evaluating disease duration and QoL reported significant results, all of which supported a positive relationship between disease duration and QoL, such that QoL was higher with longer disease duration. The longitudinal studies provided more definitive support for an improvement in QoL over time.

The finding that QoL scores were numerically lower (i.e., worse) in those with CD compared with UC, although not statistically different, has been previously reported[4]; however, considering the intrusive and sometimes disabling symptoms of UC, including diarrhoea, urgency, and bowel incontinence, it is possible that QOL concerns in UC and CD are more similar than different. Future studies should evaluate QOL with this in mind. Consistent with past UC[5] and CD reviews[2] was the finding that active disease is associated with poorer QoL than inactive disaese. Although based on small sample sizes, differences between CD versus UC and active versus inactive disease states across QoL in paediatic cohorts were consistent with that found in the adult cohorts.

The findings from this review also suggests that QoL in IBD may improve over time. The majority of cross-sectional studies found no relationship between IBD duration and QoL, likely because these studies focused on 1 point in time and thus were blinded to temporal changes. However, those that did find a significant association all identified the positive direction of the relationship. The longitudinal studies, which are more appropriately designed to evaluate changes in QoL over time, did observe a significant temporal improvement in QoL in 4 of the 7 adult studies and 2 of the 3 pediatric studies. The improvement over time may reflect an adjustment process to the self-management demands of chronic illness,[93] at least among resilient individuals without evidence of psychiatric comorbidity. The concept of reprioritization has been proposed as a marker of an adaptive shift to illness. Reprioritization reflects that, despite the ongoing symptoms (e.g., chronic diarrhoea), patients no longer react to them as negatively, viewing them as the "new normal," with a resulting changed meaning of various dimensions of QoL, and thus improved QoL over time.[94]

Current thinking on the concept of QoL confirms this observation by demonstrating that QoL is not constant and changes over time between and within individuals.[95] This reinforces the need for longitudinal designs in studying QoL in IBD and other chronic illnesses.

It was difficult to directly compare IBD specific and generic QoL measures. When reviewing across the pooled estimates from each meta-analysis and comparing the results for generic and disease specific measures, slightly higher estimates were seen for generic QoL measures in relation to question 4 (i.e., comparing CD and UC); these differences were not found across other questions in this systematic review. Other meta-analyses demonstrated little difference between the 2 measures. It is also worth noting that generally, slightly higher estimates were seen for mental compared to physical component scores across meta-analyses for generic QoL measures. Due to inconsistent results and as outlined in part 1, generic QoL measures may be most practical to use in cross-disease comparisons, but could underestimate IBD impact. However, where possible, especially in IBD-focused investigations, a disease-specific measure would be most appropriate.

Limitations and Suggestions for Future Research

Consistent with a systematic review on IBD and psychological comorbidity done by our group,[1] the publications utilized in the current review were predominantly from Western Europe and North America, with few to no studies from areas such as Eastern Europe, South America, Asia, and Africa.

There were several challenges in evaluating the studies related to data gaps. We were unable to examine sex differences in QoL across the key review questions, as studies often did not report sufficient detail to permit data extraction directly for pooling in the meta-analysis. Frequently, standard deviations were not reported. Other data was occasionally available, which permitted standard deviations to be imputed, but there are limitations to using such approximations. These methods involve making assumptions about unknown statistics, and as such, the imputations could be incorrect. For example, when *P* values were used to calculate standard deviations, there were difficulties encountered, with significance levels reported as $P < 0.01$ (or similar), rather than the exact *P* value itself. We addressed this problem by using a conservative approach and assuming the *P* value at the upper limit, but this would have an impact on how accurate the imputation of the standard deviation would be.

Another issue encountered was that data on some outcomes was only partially reported or not specified when the comparison was not statistically significant. Primary studies provided sufficient data for pooling when results were statistically significant, but for those outcomes that were not, insufficient data was presented to allow pooling. That introduces a potential for outcome reporting bias, potentially overestimating effects.

Despite a large number of studies meeting the overall inclusion criteria for the review, often only a small subset of the studies provided sufficient data to be included in each individual meta-analysis. I^2 values were predominantly high, suggesting significant heterogeneity across the studies. Given the clinical and methodological diversity in the included studies, we anticipated that there would be heterogeneity and planned to incorporate the heterogeneity into each meta-analysis by using a random-effect model. It would have been useful to explore possible causes of heterogeneity, but there were too few studies to permit this. Finally, the current systematic review was not focused on exploring the many factors that may influence QoL (e.g., psychological and physiological comorbidities, malnourishment, poor coping, anaemia, fatigue, disease activity, and surgery), and these could be targeted by future research.

RECOMMENDATIONS

QoL measures are and will continue to be an essential outcome measure in IBD research. This review suggests that IBD-specific measures demonstrated slightly larger differences across groups (e.g., active versus inactive IBD) compared with generic measures, suggesting they may be somewhat more sensitive. It is suggested that if comparisons between IBD and non-IBD groups are involved, a generic QoL measure may be optimal; however, when IBD cohorts are the focus of the research, a disease-specific measure would be most appropriate. Researchers could also consider pairing QoL evaluation with a valid assessment of health economic outcomes; therefore, a combination of specific and nonspecific QoL measures (e.g., EQ-5D) that also assess the related economic outcome data would add a valuable dimension to QoL knowledge.

FUTURE DIRECTIONS

Based on the extensive screening and review process completed for this project, and consistent with observations from other critiques and reviews,[1, 96] we would recommend applying the following design and reporting elements to improve QoL-related IBD research: (1) cohort, case-control designs rather than cross-sectional designs; (2) population-based, or at a minimum, consecutively recruited participants; (3) comparison groups, including both healthy and chronically ill controls; (4) justification for the sample size and attrition; (5) control for confounders (e.g., psychiatric history); (6) presentation of data separately for IBD subtypes, disease activity, gender, and provide means (SD) and proportions with confidence intervals where appropriate; (7) pairing with IBD outcomes such as time to relapse, as well as inclusion of objective measures such as fecal calprotectin or optimally endoscopy; and finally, (8) continuing to explore the role of psychosocial and physiological factors (e.g., psychological and physiological comorbidities, malnourishment, illness

perceptions, poor coping, anaemia, fatigue, disease activity, and surgery) and their influence on QoL.

SUPPLEMENTARY DATA

Supplementary data is available at *Inflammatory Bowel Diseases* online.

REFERENCES

1. Mikocka-Walus, A., Knowles SR, Keefer L, et al. Controversies revisited: a systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. *Inflamm Bowel Dis*. 2016. 22: 752–62.
2. van der Have M, van der Aalst KS, Kaptein AA, et al. Determinants of health-related quality of life in Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2014;8:93–106.
3. Alrubaiy L, Rikaby I, Dodds P, et al. Systematic review of health-related quality of life measures for inflammatory bowel disease. *J Crohns Colitis*. 2015;9:284–92.
4. Casellas, F., Lopez-Vivancos J, Malagelada JR, Health related quality of life in inflammatory bowel disease. *Gastroenterol.* 1996. 9: 53–61.
5. Irvine EJ. Quality of life of patients with ulcerative colitis: past, present, and future. *Inflamm Bowel Dis*. 2008;14:554–65.
6. Knowles, SR, Graff, LA, Wilding, H, et al. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses – part I. *Inflamm Bowel Dis*. 2018;24:742–51.
7. Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's relapse prevention trial study group. *Gastroenterology*. 1994;106:287–96.
8. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30:473–83.
9. Abdovic S, Mocic Pavic A, Milosevic M, et al. The IMPACT-III (HR) questionnaire: a valid measure of health-related quality of life in Croatian children with inflammatory bowel disease. *J Crohns Colitis*. 2013;7:908–15.
10. Otley A, Smith C, Nicholas D, et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2002;35:557–63.
11. Otley A, Smith C, Nicholas D, et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2002;35:557–63.
12. Andrzejewska, J., et al., Quality of life in patients with Crohn's disease and ulcerative colitis. Comparative analysis. *Prz Gastroenterol*. 2009. 4: 251–5.
13. Bryant RV, van Langenberg DR, Holtmann GJ, et al. Functional gastrointestinal disorders in inflammatory bowel disease: impact on quality of life and psychological status. *J Gastroenterol Hepatol*. 2011;26:916–23.
14. Casellas F, Arenas JI, Baudet JS, et al. Impairment of health-related quality of life in patients with inflammatory bowel disease: a Spanish multicenter study. *Inflamm Bowel Dis*. 2005;11:488–96.
15. Casellas F, López-Vivancos J, Badia X, et al. Influence of inflammatory bowel disease on different dimensions of quality of life. *Eur J Gastroenterol Hepatol*. 2001;13:567–72.
16. Cheung WY, Garratt AM, Russell IT, et al. The UK IBDQ-a British version of the inflammatory bowel disease questionnaire. Development and validation. *J Clin Epidemiol*. 2000;53:297–306.
17. Cohen D, Bin CM, Fayh AP. Assessment of quality of life of patients with inflammatory bowel disease residing in southern Brazil. *Arq Gastroenterol*. 2010;47:285–9.
18. Gandhi S, Jedel S, Hood MM, et al. The relationship between coping, health competence and patient participation among patients with inactive inflammatory bowel disease. *J Crohns Colitis*. 2014;8:401–8.
19. Gibson PR, Weston AR, Shann A, et al. Relationship between disease severity, quality of life and health-care resource use in a cross-section of Australian patients with Crohn's disease. *J Gastroenterol Hepatol*. 2007;22:1306–12.
20. Graff LA, Walker JR, Lix L, et al. The relationship of inflammatory bowel disease type and activity to psychological functioning and quality of life. *Clin Gastroenterol Hepatol*. 2006;4:1491–101.
21. Gregor JC, McDonald JW, Klar N, et al. An evaluation of utility measurement in Crohn's disease. *Inflamm Bowel Dis*. 1997;3:265–76.
22. Hjortswang H, Järnerot G, Curman B, et al. The influence of demographic and disease-related factors on health-related quality of life in patients with ulcerative colitis. *Eur J Gastroenterol Hepatol*. 2003;15:1011–20.
23. Hjortswang H, Tysk C, Bohr J, et al. Health-related quality of life is impaired in active collagenous colitis. *Dig Liver Dis*. 2011;43:102–9.
24. Høivik ML, Bernklev T, Solberg IC, et al.; IBSEN Study Group. Patients with Crohn's disease experience reduced general health and vitality in the chronic stage: ten-year results from the IBSEN study. *J Crohns Colitis*. 2012;6:441–53.
25. Janke KH, Raible A, Bauer M, et al. Questions on life satisfaction (FLZM) in inflammatory bowel disease. *Int J Colorectal Dis*. 2004;19:343–53.
26. Jowett SL, Seal CJ, Barton JR, et al. The short inflammatory bowel disease questionnaire is reliable and responsive to clinically important change in ulcerative colitis. *Am J Gastroenterol*. 2001;96:2921–8.
27. Kiebles JL, Doerfler B, Keefer L. Preliminary evidence supporting a framework of psychological adjustment to IBD: results from a pilot study. *Gastroenterol*, 2010. 138: S322.
28. König HH, Ulshöfer A, Gregor M, et al. Validation of the euroqol questionnaire in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2002;14:1205–15.
29. Mnif L, Mzid A, Amouri A, et al. Health-related quality of life in patients with inflammatory bowel disease: a Tunisian study. *Tunis Med*. 2010;88:933–6.
30. Pace F, Molteni P, Bollani S, et al. Inflammatory bowel disease versus irritable bowel syndrome: a hospital-based, case-control study of disease impact on quality of life. *Scand J Gastroenterol*. 2003;38:1031–8.
31. Parekh NK, McMaster K, Nguyen DL, et al. Coping strategies used by adult patients with inflammatory bowel disease. *South Med J*. 2015;108:337–42.
32. Romberg-Camps MJ, Bol Y, Dagnelie PC, et al. Fatigue and health-related quality of life in inflammatory bowel disease: results from a population-based study in the Netherlands: the IBD-south limburg cohort. *Inflamm Bowel Dis*. 2010;16:2137–47.
33. Stjernman H, Grännö C, Bodemar G, et al. Evaluation of the inflammatory bowel disease questionnaire in Swedish patients with Crohn's disease. *Scand J Gastroenterol*. 2006;41:934–43.
34. Tragnone A, et al. Quality of life and inflammatory bowel disease. *Gastroenterol*. 1996;9:47–52.
35. Vidal A, Gómez-Gil E, Sans M, et al. Health-related quality of life in inflammatory bowel disease patients: the role of psychopathology and personality. *Inflamm Bowel Dis*. 2008;14:977–83.
36. Rogler D, Fournier N, Pittet V, et al.; Swiss IBD Cohort Study Group. Coping is excellent in Swiss children with inflammatory bowel disease: results from the Swiss IBD cohort study. *J Crohns Colitis*. 2014;8:409–20.
37. Almadani SB, Adler J, Browning J, et al. Effects of inflammatory bowel disease on students' adjustment to college. *Clin Gastroenterol Hepatol*. 2014;12:2055–62.e1.
38. Alrubaiy L, Cheung WY, Dodds P, et al. Development of a short questionnaire to assess the quality of life in Crohn's disease and ulcerative colitis. *J Crohns Colitis*. 2015;9:66–76.
39. Bastida G, Nos P, Aguas M, et al. The effects of thiopurine therapy on health-related quality of life in inflammatory bowel disease patients. *BMC Gastroenterol*. 2010;10:26.
40. Bodger K, Ormerod C, Shackcloth D, et al. Development and validation of a rapid, generic measure of disease control from the patient's perspective: the IBD-control questionnaire. *Gut*. 2014;63:1092–02.
41. Boye B, Jahnsen J, Mokleby K, et al. The INSPIRE study: are different personality traits related to disease-specific quality of life (IBDQ) in distressed patients with ulcerative colitis and Crohn's disease? *Inflamm Bowel Dis*. 2008;14:680–6.
42. Burisch J, Weimers P, Pedersen N, et al.; EpiCom-group. 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. *J Crohns Colitis*. 2014;8:1030–42.
43. Caplan RA, Maunder RG, Stempak JM, et al. Attachment, childhood abuse, and IBD-related quality of life and disease activity outcomes. *Inflamm Bowel Dis*. 2014;20:909–15.
44. Casellas F, Barreiro de Acosta M, Iglesias M, et al. Mucosal healing restores normal health and quality of life in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2012;24:762–9.
45. Casellas F, López-Vivancos J, Casado A, et al. Factors affecting health related quality of life of patients with inflammatory bowel disease. *Qual Life Res*. 2002;11:775–81.
46. Casellas F, López Vivancos J, Malagela JR. Previous experience and quiality of life in patients with inflammatory bowel disease during relapse. *Rev Esp Enferm Dig*. 2003;95:476–9, 471.
47. Ciccocioppo R, Klersy C, Russo ML, et al. Validation of the Italian translation of the inflammatory bowel disease questionnaire. *Dig Liver Dis*. 2011;43:535–41.
48. Farrokhyar F, Marshall JK, Easterbrook B, et al. Functional gastrointestinal disorders and mood disorders in patients with inactive inflammatory bowel disease: prevalence and impact on health. *Inflamm Bowel Dis*. 2006;12:38–46.
49. Freitas TH, Andreoulakis E, Alves GS, et al. Associations of sense of coherence with psychological distress and quality of life in inflammatory bowel disease. *World J Gastroenterol*. 2015;21:6713–27.
50. Ganguli SC, Kamath MV, Redmond K, et al. A comparison of autonomic function in patients with inflammatory bowel disease and in healthy controls. *Neurogastroenterol Motil*. 2007;19:961–7.
51. Haapamäki J, Tanskanen A, Roine RP, et al. Medication use among inflammatory bowel disease patients: excessive consumption of antidepressants and analgesics. *Scand J Gastroenterol*. 2013;48:42–50.

52. Haapamäki J, Roine RP, Sintonen H, et al. Health-related quality of life in inflammatory bowel disease measured with the generic 15D instrument. *Qual Life Res*. 2010;19:919–28.
53. Haapamäki J, Turunen U, Roine RP, et al. Impact of demographic factors, medication and symptoms on disease-specific quality of life in inflammatory bowel disease. *Qual Life Res*. 2009;18:961–9.
54. Huamán JW, Casellas F, Borruel N, et al. Cutoff values of the inflammatory bowel disease questionnaire to predict a normal health related quality of life. *J Crohns Colitis*. 2010;4:637–41.
55. Iglesias-Rey M, Barreiro-de Acosta M, Caamaño-Isorna F, et al. Influence of alexithymia on health-related quality of life in inflammatory bowel disease: are there any related factors? *Scand J Gastroenterol*. 2012;47:445–53.
56. Katz L, Tripp DA, Ropeleski M, et al. Mechanisms of quality of life and social support in inflammatory bowel disease. *J Clin Psychol Med Settings*. 2016;23:88–98.
57. Lam MY, Lee H, Bright R, et al. Validation of interactive voice response system administration of the short inflammatory bowel disease questionnaire. *Inflamm Bowel Dis*. 2009;15:599–607.
58. Magalhães J, Castro FD, Carvalho PB, et al. Quality of life in patients with inflammatory bowel disease: importance of clinical, demographic and psychosocial factors. *Arq Gastroenterol*. 2014;51:192–7.
59. Martin A, Leone L, Fries W, et al. Quality of life in inflammatory bowel disease. *Ital J Gastroenterol*. 1995;27:450–4.
60. Moskovitz DN, Maunder RG, Cohen Z, et al. Use of community resources before inflammatory bowel disease surgery is associated with postsurgical quality of life. *Can J Gastroenterol*. 2000;14:95–8.
61. Simrén M, Axelsson J, Gillberg R, et al. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol*. 2002;97:389–96.
62. Stark RG, Reitmeir P, Leidl R, et al. Validity, reliability, and responsiveness of the EQ-5D in inflammatory bowel disease in Germany. *Inflamm Bowel Dis*. 2010;16:42–51.
63. Verissimo R, Mota-Cardoso R, Taylor G. Relationships between alexithymia, emotional control, and quality of life in patients with inflammatory bowel disease. *Psychother Psychosom*. 1998;67:75–80.
64. Verma S, Tsai HH, Giaffer MH. Does better disease-related education improve quality of life? A survey of IBD patients. *Dig Dis Sci*. 2001;46:865–9.
65. Zhang CK, Hewett J, Hemming J, et al. The influence of depression on quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2013;19:1732–9.
66. Ananthakrishnan AN, Beaulieu DB, Ulitsky A, et al. Does primary sclerosing cholangitis impact quality of life in patients with inflammatory bowel disease? *Inflamm Bowel Dis*. 2010;16:494–500.
67. Banovic I, Gilibert D, Cosnes J. Crohn's disease and fatigue: constancy and co-variations of activity of the disease, depression, anxiety and subjective quality of life. *Psychol Health Med*. 2010;15:394–405.
68. Benedini V, Caporaso N, Corazza GR, et al. Burden of Crohn's disease: economics and quality of life aspects in Italy. *Clinicoecon Outcomes Res*. 2012;4:209–18.
69. Blondel-Kucharski F, Chircop C, Marquis P, et al.; Groupe d'Etudes Thérapeutique des Affections Inflammatoires Digestives (GETAID). Health-related quality of life in Crohn's disease: a prospective longitudinal study in 231 patients. *Am J Gastroenterol*. 2001;96:2915–20.
70. Canavan C, Abrams KR, Hawthorne B, et al. Long-term prognosis in Crohn's disease: factors that affect quality of life. *Aliment Pharmacol Ther*. 2006;23:377–85.
71. Casellas F, Vivancos JL, Sampedro M, et al. Relevance of the phenotypic characteristics of Crohn's disease in patient perception of health-related quality of life. *Am J Gastroenterol*. 2005;100:2737–42.
72. Freitas TH, Hyphantis TN, Andreoulakis E, et al. Religious coping and its influence on psychological distress, medication adherence, and quality of life in inflammatory bowel disease. *Rev Bras Psiquiatr*. 2015;37:219–27.
73. Greenley RN, Kunz JH, Schurman JV, et al. Abdominal pain and health related quality of life in pediatric inflammatory bowel disease. *J Pediatr Psychol*. 2013;38:63–71.
74. Haapamäki J, Roine RP, Sintonen H, et al. Health-related quality of life in pediatric patients with inflammatory bowel disease related to disease activity. *J Paediatr Child Health*. 2011;47:832–7.
75. Hjortswang H, Ström M, Almer S. Health-related quality of life in Swedish patients with ulcerative colitis. *Am J Gastroenterol*. 1998;93:2203–11.
76. Hjortswang H, Ström M, Almeida RT, et al. Evaluation of the RFIPC, a disease-specific health-related quality of life questionnaire, in Swedish patients with ulcerative colitis. *Scand J Gastroenterol*. 1997;32:1235–40.
77. Iglesias M, Vázquez I, Barreiro-de Acosta M, et al. Health related quality of life in patients with Crohn's disease in remission. *Rev Esp Enferm Dig*. 2010;102:624–30.
78. Jäghult S, Saboonchi F, Johansson UB, et al. Identifying predictors of low health-related quality of life among patients with inflammatory bowel disease: comparison between Crohn's disease and ulcerative colitis with disease duration. *J Clin Nurs*. 2011;20:1578–87.
79. Kilroy S, Nolan E, Sarma KM. Quality of life and level of anxiety in youths with inflammatory bowel disease in Ireland. *J Pediatr Gastroenterol Nutr*. 2011;53:275–9.
80. Kiran RP, Delaney CP, Senagore AJ, et al. Prospective assessment of cleveland global quality of life (CGQL) as a novel marker of quality of life and disease activity in Crohn's disease. *Am J Gastroenterol*. 2003;98:1783–9.
81. Lix LM, Graff LA, Walker JR, et al. Longitudinal study of quality of life and psychological functioning for active, fluctuating, and inactive disease patterns in inflammatory bowel disease. *Inflamm Bowel Dis*. 2008;14:1575–84.
82. Long MD, Kappelman MD, Martin CF, et al. Development of an internet-based cohort of patients with inflammatory bowel diseases (CCFA partners): methodology and initial results. *Inflamm Bowel Dis*. 2012;18:2099–106.
83. Lowe W, Kenwright D, Wyeth J, et al. Crohn disease: effect on children's lifestyles. *J Pediatr Gastroenterol Nutr*. 2012;54:397–400.
84. McCombie AM, Mulder RT, Gearry RB. Coping strategies and psychological outcomes of patients with inflammatory bowel disease in the first 6 months after diagnosis. *Inflamm Bowel Dis*. 2015;21:2272–80.
85. Meder A, Świâtkowski M, Meder G, et al. Quality of life and coexisting anxiety-depressive disorders in patients with inflammatory bowel disease during relapse and a further 11 months observation. *Gastroenterologia Polska*, 2010. 17: 273–9.
86. Moradkhani A, Beckman LJ, Tabibian JH. Health-related quality of life in inflammatory bowel disease: psychosocial, clinical, socioeconomic, and demographic predictors. *J Crohns Colitis*. 2013;7:467–73.
87. Mussell M, Böcker U, Nagel N, et al. Predictors of disease-related concerns and other aspects of health-related quality of life in outpatients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2004;16:1273–80.
88. Otley AR, Griffiths AM, Hale S, et al.; Pediatric IBD Collaborative Research Group. Health-related quality of life in the first year after a diagnosis of pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2006;12:684–91.
89. Saibeni S, Cortinovis I, Beretta L, et al.; Gruppo di Studio per le Malattie Infiammatorie Intestinali. Gender and disease activity influence health-related quality of life in inflammatory bowel diseases. *Hepatogastroenterology*. 2005;52:509–15.
90. Scarpa M, Ruffolo C, D'Incà R, et al. Health-related quality of life after ileocolonic resection for Crohn's disease: long-term results. *Inflamm Bowel Dis*. 2007;13:462–9.
91. Tabibian A, Tabibian JH, Beckman LJ, et al. Predictors of health-related quality of life and adherence in Crohn's disease and ulcerative colitis: implications for clinical management. *Dig Dis Sci*. 2015;60:1366–74.
92. Zahn A, Hinz U, Karner M, et al. Health-related quality of life correlates with clinical and endoscopic activity indexes but not with demographic features in patients with ulcerative colitis. *Inflamm Bowel Dis*. 2006;12:1058–67.
93. Stanton AL, Revenson TA, Tennen H, Health psychology: psychological adjustment to chronic disease. *Annu Rev Psychol*. 2007;58:565–92.
94. Lix LM, Sajobi TT, Sawatzky R, et al. Relative importance measures for reprioritization response shift. *Qual Life Res*. 2013;22:695–703.
95. Carr AJ, Gibson B, Robinson PG. Measuring quality of life: is quality of life determined by expectations or experience? *BMJ*. 2001;322:1240–3.
96. Knowles SR, Monshat K, Castle DJ. The efficacy and methodological challenges of psychotherapy for adults with inflammatory bowel disease: a review. *Inflamm Bowel Dis*. 2013;19:2704–15.