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

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

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Background: Quality of life (QoL) is commonly assessed in inflammatory bowel disease (IBD); the relationship of QoL within IBD states and relative to others has not been comprehensively evaluated. This systematic review, published across 2 papers, evaluates 5 key QoL comparisons. Part I, presented here, examines between-disease comparisons: (1) IBD/healthy(general) population and (2) IBD/other medically ill groups. Part II examines within-disease comparisons: (3) active/inactive disease, (4) ulcerative colitis/Crohn's disease, and (5) change over time. Outcomes using generic vs 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; 30 unique studies (23 adult, 7 pediatric) addressed the between-disease comparisons. The pooled mean QoL scores were (1) lower in adult and pediatric IBD samples compared with healthy controls (n = 19), and for both mental and physical QoL, where measured; and (2) higher but not significant for those with IBD compared with various medically ill controls (n = 15). Findings were consistent across IBD-specific and generic QoL measures. Study quality was generally low to moderate. The most common measures of QoL were the disease-specific Inflammatory Bowel Disease Questionnaire and generic SF-36 (adults), and the generic PedsQL (children).

Conclusions: There was robust confirmation that QoL for individuals with IBD was poorer than for healthy individuals, for both adults and children. QoL in IBD may be better relative to some other gastrointestinal (GI) and non-GI medical conditions for children.

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

INTRODUCTION

Inflammatory bowel diseases (IBDs), of which Crohn's disease (CD) and ulcerative colitis (UC) are subtypes, are chronic relapsing inflammatory conditions of the gastrointestinal tract with unclear etiology and unpredictable course. In a review of the IBD prevalence literature, Molodecky et al.[1] reported that in Europe, 322 per 100,000 people are diagnosed with CD and up to 505 per 100,000 people are affected by UC. Symptoms can include diarrhea, abdominal pain, weight loss, anemia, and arthralgia. Treatment commonly involves medications such as corticosteroids and biologics. Surgery is often needed at some point in the disease course, particularly for those with CD.

IBD is associated with significant psychosocial burden. The course of IBD can be chronic and unpredictable, with embarrassing and painful symptoms that can leave individuals worried about many aspects of life, such as bowel control, fatigue, social isolation, and a fear of developing cancer or needing surgery.[2] In a systematic review of comorbid depression and anxiety in IBD, Mikocka-Walus and colleagues[3] found that rates of anxiety and depression were higher in individuals with IBD than in healthy controls (anxiety 19.1% vs 9.6%, depression 21.2% vs 13.4%). Work life can also be adversely affected by the disease, resulting in absenteeism, reduced work hours, and changes in career choice, contributing to financial burden.[4–6]

In early research, health-related quality of life (HRQoL) was rarely examined in clinical trials as either a dependent variable or end point, but with advances in clinical trial designs and the influence of regulatory agencies seeking patient-reported outcomes as primary end points, quality of life (QoL) and related psychosocial measures are of growing significance.[7] QoL is broadly defined by the World Health Organization as an individual's subjective evaluation that they are living in

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accordance with their values, expectations, goals, and standards with regard to their environmental, social, and cultural contexts.[8] QoL is often evaluated using either generic measures, such as the EUROHISQoL,[9] or illness-specific QoL measures such as the Inflammatory Bowel Disease Questionnaire (IBDQ).[10]

Over the past 4 decades, studies using quality of life end points in IBD have increased quite dramatically. Within a recent 10-year period, there were more than 100 publications involving QoL in IBD each year, doubling in number in 5 years, and doubling again in the most recent 5 years (2009–2014), currently totalling more than 400 unique publications each year since 2013.

Several nonsystematic reviews of the IBD literature have explored QoL, using either generic or illness-specific (HRQoL) measures. In an early review of QoL in IBD, Casellas and colleagues[11] found that individuals with IBD reported poorer QoL than healthy individuals or those with other health conditions. Hashimoto,[12] in their review of the IBD QoL literature, concluded that while disease activity plays an important role in QoL, psychosocial conditions and how a patient views these are also relevant determinants of QoL.

Given the significant number of studies relating to QoL in IBD and the inherent complexity of the IBD QoL research, a systematic review using standardized, rigorous methodology and a priori planned comparisons was done to synthesize the extensive IBD literature and address specific questions about QoL in IBD. The following paper is the first of a 2-part systematic review and meta-analyses exploring 5 key comparisons relating to QoL in IBD. Part I examines between-disease comparisons of (1) IBD and the healthy/general population and (2) IBD and other medically ill patient groups. Part II examines within-disease comparisons of (3) active and inactive disease, (4) UC and CD, and (5) change of QoL over time. In this paper (Part I), we identify, analyze, and critique the current evidence in relation to QoL and IBD in relation to the first 2 comparisons, while Part II[13] will review comparisons 3, 4, and 5.

In this paper, 2 questions were reviewed:

Question 1: Is QoL in IBD similar to or different than that reported for healthy/general population controls?

Question 2: Is QoL in IBD similar to or different than that reported in other groups of medically ill patients?

METHODS

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42015026139).

Types of Studies

Studies meeting the selection criteria listed below were included.

Inclusion criteria

- Studies concerning IBD (including Crohn's disease, ulcerative colitis, and indeterminate colitis) diagnosed using any well-established criteria;
- Studies examining quality of life;
- Studies with either adult or pediatric populations;
- Controlled studies, including randomized controlled trials (baseline data only), with prospective, retrospective, or cross-sectional designs;
- Peer-reviewed papers.

Exclusion criteria

- Studies focusing on other psychological variables such as depression, anxiety, distress, coping, or personality, without specific quality of life measures;
- Interventional studies (eg, medication trials);
- Studies in languages other than English;
- Conference abstracts or any short papers with incomplete data presented;
- Incomplete data presented (eg, QoL subscales only);
- Nonvalidated QoL scales;
- Case reports, case series, or qualitative research;
- Reviews or opinion papers;
- Animal studies.

Search Methodology

Sources

Studies were identified through systematic searches of the following databases: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to Present; PsycINFO (Ovid) 1806 to September Week 5 2015; Ovid Nursing Database 1946 to September Week 4 2015; CINAHL Plus with full text (EBSCOhost); EMBASE (Embase.com); Informit Health Collection & Informit Humanities & Social Sciences Collection and the full Cochrane Library, including the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, and Cochrane Central Register of Controlled Trials.

Search strategy

Search strategies were developed by an experienced medical librarian (HW) in consultation with SK and combined the following general concepts: (inflammatory bowel disease or Crohn's disease or colitis or proctocolitis or enteritis or duodenitis or ileitis or pouchitis or enterocolitis or proctitis) and quality of life. An initial strategy combining both MeSH Terms and text words was developed for Ovid Medline (Fig. 2) and then adapted as appropriate for the other databases, taking into account database-specific subject headings and syntax.

Searches were run between October 7 and 21, 2015, and results were limited to English language but not limited by date. Full search strategies for all databases are available on request. Search results from all databases were exported into Endnote bibliographic management software, and duplicates were manually removed, with the most complete record retained. See Appendix 1 for the detailed systematic search strategies.

Data collection and analysis

The systematic review was undertaken based upon the recommended PRISMA statement guidelines (http://www.prisma-statement.org; Appendix 2 for completed PRISMA checklist). In the first phase, 2 reviewers independently screened the titles and abstracts identified by the search to determine whether they met the inclusion criteria. Any disagreements were resolved by discussion with a third reviewer. In the second phase, the full papers of those identified in phase 1 were independently evaluated by 2 reviewers to determine if they included data to address any 1 or more of the 4 questions that were the focus of the review. That is, after checking general selection criteria, papers were screened again to verify whether information required to respond to a particular question was reported in the study. For example, for Question 1, studies were reviewed to determine whether QoL data were available for IBD and healthy comparison groups, with disagreements resolved through discussion with a third reviewer.

Data extraction

Extracted data included authors, year of publication, country of origin, design, setting, participant characteristics (IBD subtype, age, sex, disease activity status) and sample size, outcome measures, and results for main outcome measures.

Data synthesis

We provided a narrative synthesis of the findings from the included studies, structured around QoL associated with IBD, calculating means for the IBD and the appropriate comparator groups. In addition, meta-analyses or statistical evaluations in relation to each of the 2 review questions were conducted. For the meta-analyses, results could only be pooled when there were more than 2 studies looking at the same outcome within each question, provided there were sufficient data for the number of participants, means and standard deviation per group, and that the studies were conducted within the same population (adult or pediatric). Some studies did not provide the data in the format that was required for analysis. In these cases, standard formulas[14] for calculating standard deviations from test statistics, confidence intervals, and *P* values and for combining data from more than 2 groups were applied, and data were transformed following standard formulas[15] into the appropriate format. Once the data were in the required format (as identified in Supplementary Tables 1 and 2), random effects meta-analyses were undertaken with a random effects model using the method of DerSimonian and Laird[16]; given that most studies used different measures of QoL, standardized mean differences (SMDs) were reported. SMD was chosen as it is a common measure reported in meta-analyses and expresses the intervention effect in standard units rather than the original units of measurement.

The I^2 statistic was used to assess heterogeneity between studies. This statistic is more effective than the X^2 statistic when there are small numbers of studies included in a meta-analysis[17]. To aid interpretation, an I^2 value of 25% was considered low heterogeneity, 50% moderate and 75% high heterogeneity. To calculate pooled correlation coefficients, all r values were transformed to the Fisher's z scale ($z = 0.5 \times \ln\left(\frac{1+r}{1-r}\right) = 01 + r$; $SE_z = \sqrt{\left(\frac{1}{n-3}\right)} =$), and analyses were performed on the transformed values. The pooled estimate and associated confidence interval were then back-transformed to the original scale representing the correlation coefficient ($r = \frac{e^{2z}-1}{e^{2z}+1}$).

Quality and risk of bias assessment

Two reviewers independently inspected the full articles identified for inclusion for each question to evaluate study quality. Any disagreement was discussed with a third reviewer. The quality appraisal of the studies was assessed using a scale developed a priori for the specific needs of this study (Appendix 3), based on recommendations from Sanderson[18] regarding key domains to assess in critical appraisal. The scale included evaluation of (1) appropriate selection of participants, (2) appropriate measurement of variables, and (3) appropriate control of confounding variables. We also consulted with IBD experts not involved in this review regarding the scale and piloted it with a subsample of studies before undergoing the quality appraisal of the included articles. Quality scores were interpreted as follows: If the mean quality score for the question was between 0% and 30% on the rating scale, it was considered low; if it was between 31% and 60%, it was considered moderate; and if it was between 61% and 100%, it was considered high.

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 (Fig. 1), leaving 466 included for full review. A total of 30 unique studies (23 adult, 7 pediatric) were included in the final review, with 19 studies for question 1 and 15 studies for question 2. Studies used in questions 1 and 2 can be found in the supplemental tables 1 and 2.[34-54]

Study Characteristics

Question 1: QoL in IBD vs healthy/general population controls: As shown in Supplementary Table 1, 19 studies (n = 7154, 21% CD, mean age = 27.2 years, 49% female)

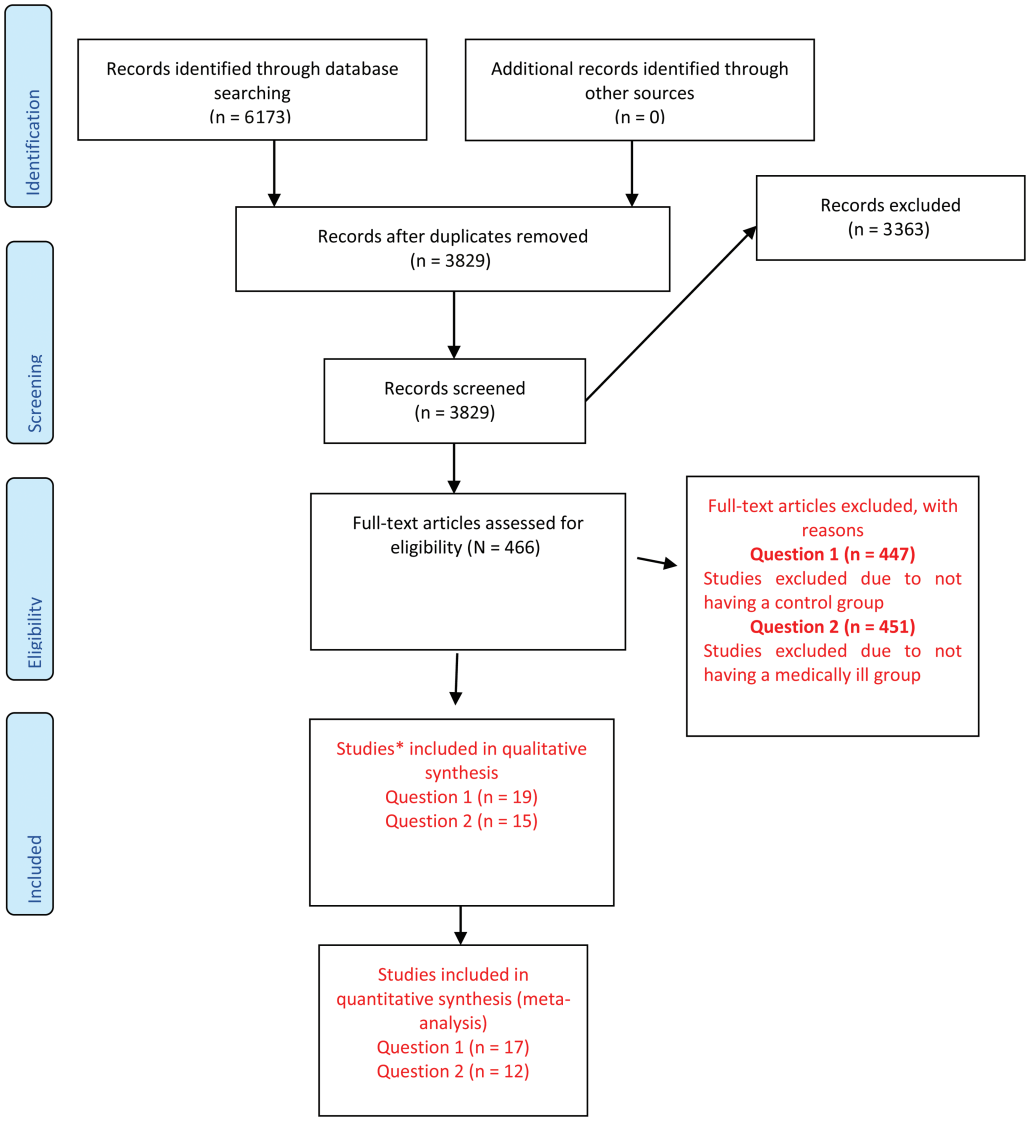

Figure 1. PRISMA flow diagram.

examined differences in QoL between IBD patients and healthy or general population controls. Of these included, 2362 were IBD participants (samples ranged from 19 to 368, 58% CD, mean age = 30.8 years, 47% female), and 4934 were healthy controls (samples ranged from 19 to 1441, 0% CD, mean age = 25.21 years, 51% female). Twelve studies were from Europe, 6 from North America, and 1 from Asia. Seventeen were cross-sectional and 2 were prospective cohort studies. Of the 19, 5 studies included pediatric/adolescent populations (IBD: n = 296, mean age = 13.6 years, 47% female; healthy/general controls: n = 1323, mean age = 12.4 years, 53% female); 14 studies were in adult populations (IBD: n = 2066, mean age = 35.4 years, 47% female; healthy/general controls: n = 3611, mean age = 33.4 years, 51% female). In terms of QoL measurement, the most common measure was IBDQ (n = 4 full, n = 2 short version), followed by PedsQL (n = 4), SF36 (n = 2), and SF12 (n = 2). All other measures (ie, PGWB, CHQ-PF50, WHOQoL-100, EQ-5D, IMPACT III, ACSA, LSI, CGQL, PIBDQL, EORTC QLQ-C30, and an unnamed but validated scale[19]) were each used in 1 study only (the total exceeds 19 as some studies used >1 scale).

Question 2: QoL in IBD vs medically ill controls: As shown in Supplementary Table 2, 15 cross-sectional studies from 17 papers met the inclusion criteria in relation to this question. Of these, 9 were based in Europe, 5 in North America, and 1 in Australia. Five of the 15 were based on child/adolescent samples. In total, there were 3453 participants across these studies, of which 1269 had IBD (samples ranged from 34 to 237, mean age = 31.2 years, 54% female), and the remaining 2184 had various other medical conditions (samples ranged from 34 to 474, mean age = 33.2 years, 60% female). The most common comparative sample was another gastrointestinal condition (such as

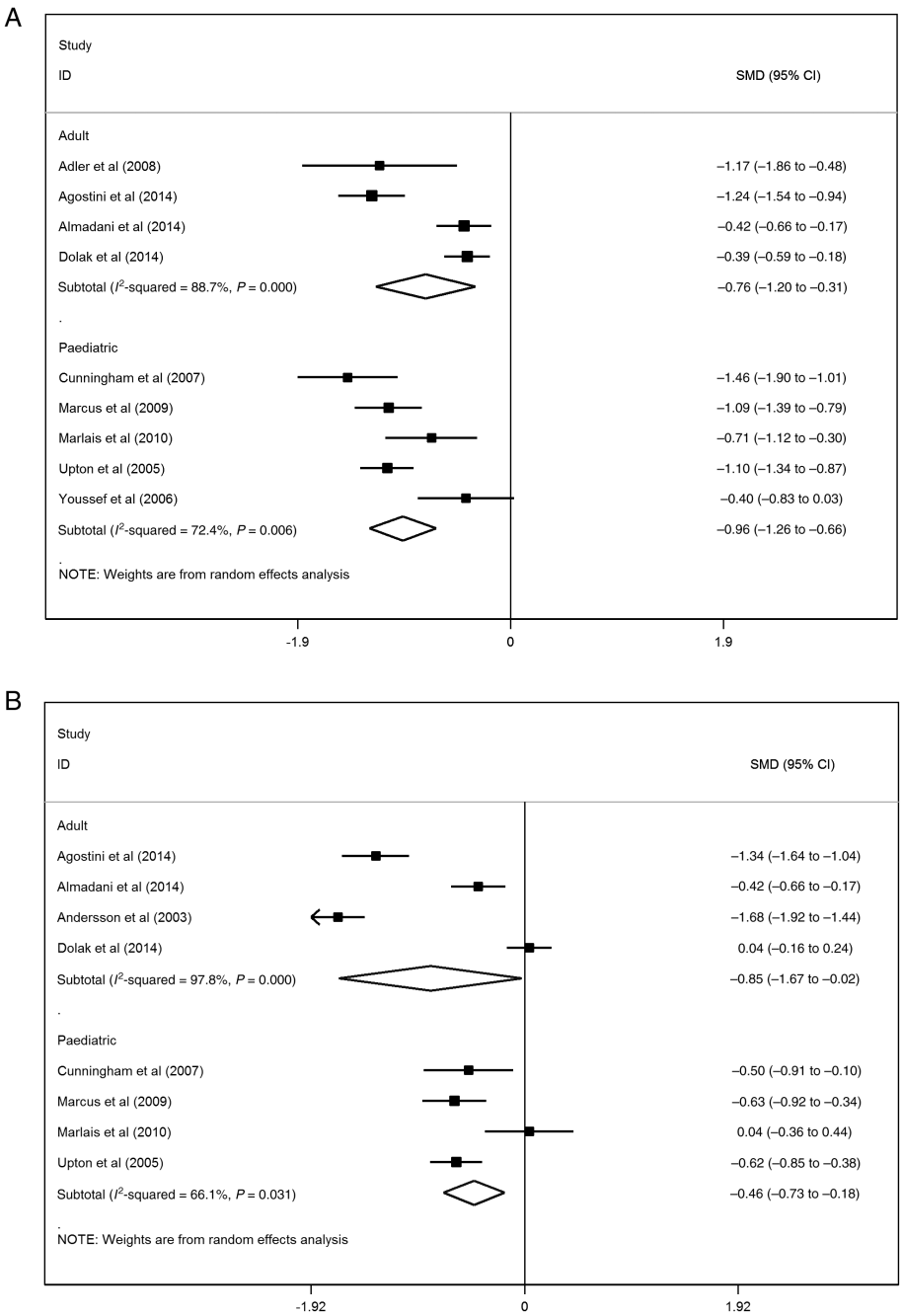

FIGURE 2. Physical (A) and mental (B) component QoL scores pooled by pediatric and adult populations.

irritable bowel syndrome, chronic constipation, or gastroesophageal reflex disease; used in 8 adult or child studies), although multiple other medically ill comparators were also used, such as those with epilepsy, rheumatoid arthritis, renal disease, asthma, and multiple sclerosis. For the 10 adult studies, the IBS-QoL (n = 2, IBSQoL-H n = 1) or a version of the Medical Outcomes Study (MOS) QoL measure (SF-36 n = 2; SF-12 n = 1) was used most frequently, with other measures used only once (ie, IBDQ-32, 15D, ACSA, LSI, F-QoL, CWHOQoL-100C; total exceeds 10 as some studies used >1 scale). For the 5 studies with children (IBD: n = 271, mean age = 14.3 years, 44% female; medically ill controls: n = 1125, mean age = 11.4 years, 51% female), the generic PedsQL 4.0 was used uniformly, with a minor difference in version.

Quality of Life Study Outcomes

Question 1: QoL in IBD vs healthy/general population controls: All 19 studies reported poorer QoL levels in IBD

participants compared with healthy controls on at least 1 measure of QoL, although some of the individual studies did not show statistically significant differences; 2 studies did not provide sufficient data to be included in any of the meta-analyses.[20, 21] Studies reporting physical and mental QoL scores were combined separately for pediatric and adult samples (Fig. 2). The pooled estimate for the pediatric samples was –0.96 (95% confidence interval [CI], –1.26 to –0.66) for physical scores (n = 5 studies and 1617 participants) and –0.46 (95% CI, –0.73 to –0.18) for mental scores (n = 4 studies and 1534 participants). The pooled estimate for the adult samples was –0.76 (95% CI, –1.21 to –0.31) for physical scores (n = 4 studies and 2092 participants) and –0.85 (95% CI, –1.67 to –0.02) for mental scores (n = 4 studies and 2447 participants). Thus, all analyses demonstrated that the pooled mean QoL scores (both mental and physical QoL) were lower in all IBD samples relative to the healthy or general population comparison groups. Interestingly, pooled physical QoL scores were lower in pediatric samples compared with adult samples, and the reverse was demonstrated for mental QoL scores; however, there were relatively low numbers of studies included in each analysis, and there were high I^2 values, suggesting high heterogeneity among the studies.

There were sufficient numbers of studies for adult populations to pool the total scores for both generic and IBD-specific QoL scores (Fig. 3). The pooled estimate for the generic total QoL scores (n = 3 studies and 1515 participants) was –0.25 (95% CI, –0.36 to –0.15), and for IBD-specific QoL scores (n = 5 studies and 1153 participants), it was –0.85 (95% CI, –1.14 to –0.56). Although both types of measures highlighted poorer QoL in IBD patients compared with healthy controls, greater differences in QoL were demonstrated by the IBD-specific QoL measures compared with generic QoL measures.

Question 2: QoL in IBD vs medically ill controls: There were 5 pediatric studies providing sufficient data on physical, mental, or total generic QoL measures (both child and parent) to be included in at least 1 of the meta-analyses.[22–26] The QoL scores for those with IBD were compared with a variety of groups with different medical illnesses. All pooled estimates demonstrated a better QoL for those with IBD compared with medically ill controls, but none of the results were statistically significant. The pooled estimate was 0.14 (95% CI, –0.13 to 0.40) for physical QoL (n = 5 studies and 1246 participants), 0.21 (95% CI, –0.20 to 0.61) for mental QoL (n = 4 studies and 1153 participants), and 0.28 (95% CI, –0.09 to 0.64) for total scores (n = 5 studies and 1396 participants) on generic QoL measures. The pooled estimates for child-reported outcomes were slightly lower than parent-completed outcomes, but were comparable (Fig. 4).

Three adult studies did not provide sufficient data to be included in any of the meta-analyses related to this question.[27–29] The remaining 7 adult studies had sufficient data to pool the studies in at least 1 meta-analysis undertaken to answer this question (Fig. 5). Three studies used IBD-specific measures, and all had gastrointestinal controls; the pooled estimate (n = 3 studies and 463 participants) was found to be 0.17 (95% CI, –0.81 to 1.16).

Four studies reported both generic physical and mental QoL scores, with 3 having gastrointestinal controls and 1 study having nongastrointestinal (non-GI) controls. There was little difference observed in the overall pooled estimates for generic physical QoL (n = 4 studies and 662 participants; –0.03; 95% CI, –0.51 to 0.45) and for generic mental QoL (n = 4 studies and 662 participants; 0.10; 95% CI, –0.06 to 0.26).

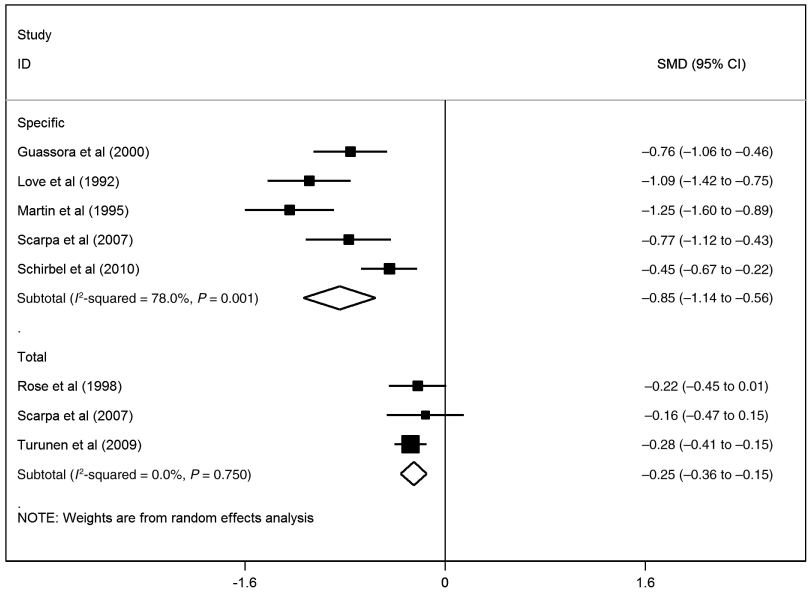

FIGURE 3. Generic and specific QoL scores for adult populations.

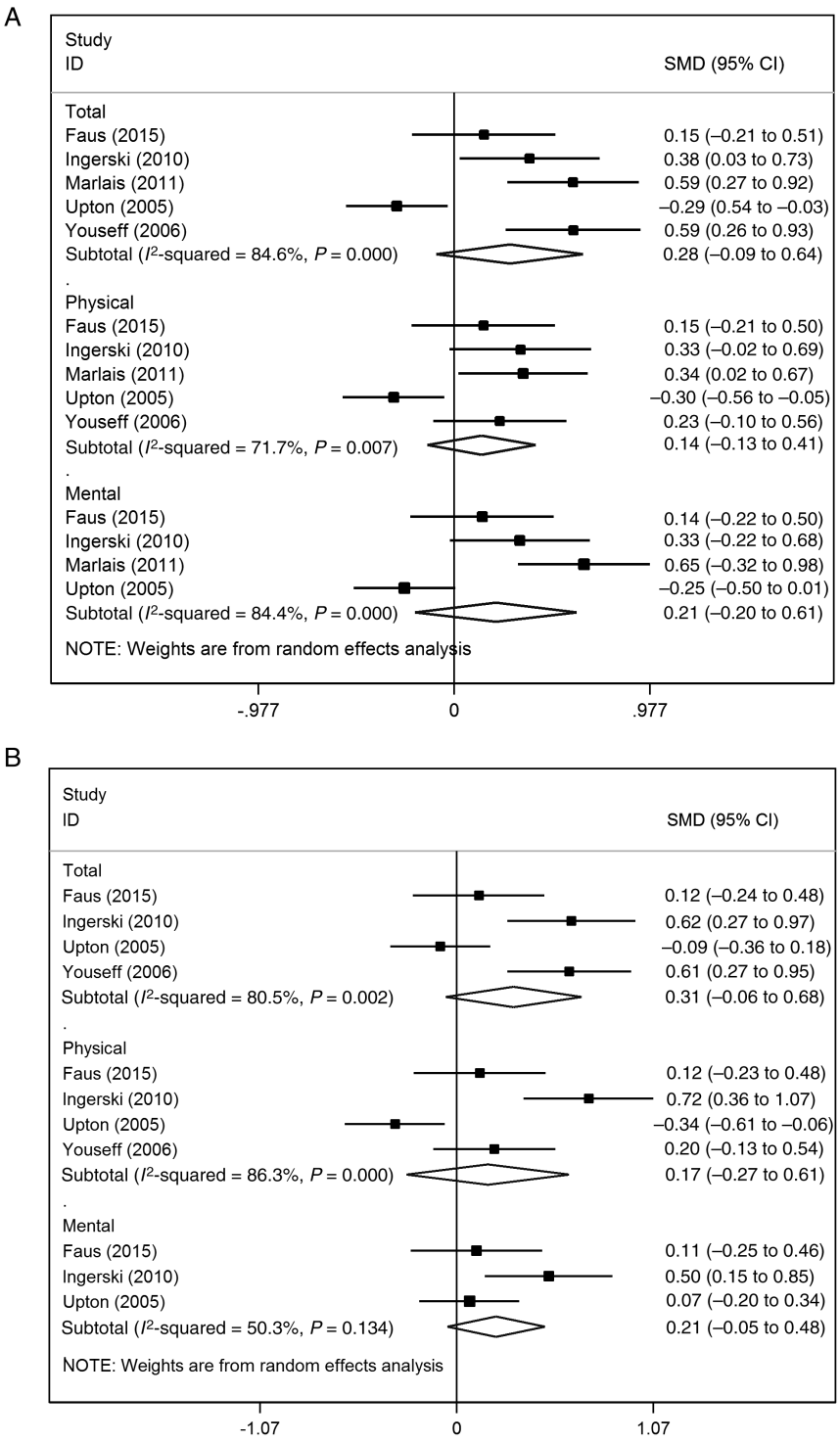

FIGURE 4. Generic total, physical, and mental QoL scores for pediatric populations comparing measures completed by the child (A) and parent (B).

Quality Appraisal

Quality scores for each study are presented in Supplementary Tables 1 and 2.

Question 1: IBD vs healthy/general population controls: Quality ranged from 1 to 7 of a maximum 8 points, with a mean of 3.2, indicating moderate quality. Overall, 3 studies of 19 (15.79%) scored 5 or higher on the quality appraisal scale.

Question 2: IBD vs medically ill controls: Quality ranged from 1 to 5 of a maximum 8 points, with a mean of 2.9,

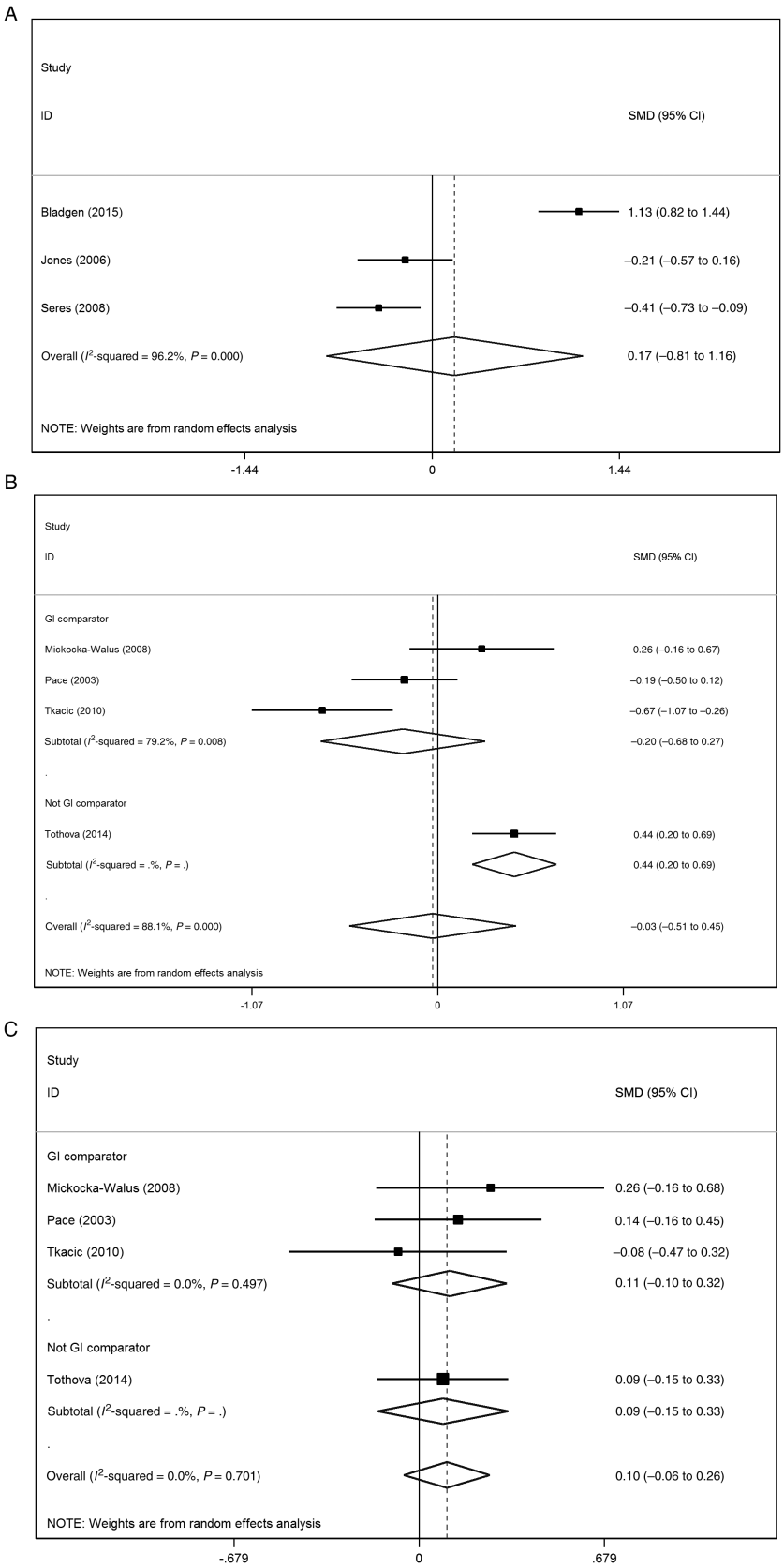

FIGURE 5. IBD-specific total (A) and generic mental (B) and physical (C) QoL scores for adult populations comparing GI and non-GI controls.

indicating low to moderate quality. Overall, only 1 of 15 studies (6.67%) scored 5 or higher on the quality appraisal scale.

DISCUSSION

QoL is an important indicator of patient outcomes in both observational and interventional studies in the IBD literature. The relevance of QoL in IBD is exemplified by the annual increase in the number of publications evaluating QoL over the past several years, with currently more than 400 QoL IBD publications per year. This paper (the first of 2 examining QoL in IBD) provides the first systematic review relating to broad comparisons of QoL in IBD and healthy or chronically ill individuals, including both adult and pediatric populations. We also explored the potential differences in generic vs IBD-specific QoL measures across the IBD literature.

The review clearly supported that QoL was significantly lower for those with IBD relative to healthy individuals without IBD, based on examination of the eligible studies and on pooled mean scores, with moderate quality of evidence. The review also demonstrated that this difference held for both mental and physically focused QoL, and across children and adults. The outcome compared with other medically ill controls was less clear cut. There were no evident differences in QoL between adults with IBD and those with other medical conditions. QoL may be better for children with IBD compared with those with other GI or chronic medical conditions, as the individual studies and pooled mean estimates indicated higher QoL in IBD. While the estimates were nonsignificant, study quality was generally low to moderate.

It is not surprising that QoL is significantly poorer for both adults and pediatric cohorts with IBD, when compared with healthy individuals who do not have to contend with a chronic illness, and this review confirms this as a very robust finding. Decreased QoL may well be a consequence of factors such as disruption to usual life activities, given the impact of the disease on education, employability, and social and interpersonal functioning (eg, sexuality, intimacy, body image satisfaction), as well as stigma and disability.[30] Poorer social and interpersonal functioning, self-perception, and self-esteem are likely to be associated with IBD-related complications such as chronic changes in bowel function, surgical scars, and ostomy, which in turn can adversely impact QoL. The detrimental impact of IBD on QoL is consistent with findings regarding QoL for other chronic illnesses,[31] and for gastrointestinal conditions specifically,[32] highlighting that the burden disease can contribute to day-to-day functioning.

This review summarized the findings from QoL comparisons of IBD participants with individuals with other types of GI illnesses such as irritable bowel syndrome, and with other types of inflammatory diseases such as rheumatoid arthritis, hepatitis, and multiple sclerosis. However, it is difficult to conclude where QoL lies for those with IBD relative to individuals with other diseases, based on the studies available and considered in this review, particularly considering the heterogeneity of the studies. For example, the multiple studies comparing irritable bowel syndrome (IBS) with IBD variously concluded that QoL was poorer in IBD, better in IBD, or the same as IBS. Study quality was an issue as most studies used convenience samples, and only 2 studies matched samples on personal characteristics (age, sex) even though matching for demographics is critical when comparing across disease types.[33] Further, very few studies aimed to account for disease characteristics such as activity or duration across the comparative groups. For example, QoL may well be better for individuals with cancer in remission than for those with active IBD due to the interference of ongoing symptoms in the latter group. Future studies addressing QoL in IBD should take heed of these observations when designing much needed controlled studies.

There were few studies that allowed direct comparison of IBD-specific and generic QoL measures. The pediatric QoL studies all included a generic QoL measure. In the adult studies, where both generic and disease-specific QoL measures were used, they resulted in similar conclusions; however, the pooled estimates were more pronounced for IBD-specific measures, suggesting the former may have more utility or sensitivity in understanding the impact of the disease on QoL. Nevertheless, generic QoL measures facilitate direct comparison across different types of disease conditions with the same metric, and thus may be most practical to use in that context.

CONCLUSIONS

This systematic review confirmed that QoL for children and adults with IBD is poorer relative to healthy individuals, and generally similar to those with other medical conditions, with the potential exception that QoL may be better for children with IBD than other medical conditions. Generic QoL measures may be most practical to use in cross-disease comparisons, but they could underestimate IBD impact. Overall, these conclusions need to be qualified by recognizing heterogeneity and the modest quality level of the studies reviewed. Discussion of the limitations and recommendations for future research regarding QoL is provided in Part II of this systematic review.

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