Journal of Crohn's and Colitis, 2018, 600–609
doi:10.1093/ecco-jcc/jjy024
Advance Access publication February 23, 2018
Review Article

Review Article

Burden of Ulcerative Colitis on Functioning and Well-being: A Systematic Literature Review of the SF-36® Health Survey

Aaron Yarlas[a], David T. Rubin[b], Julian Panés[c], James O. Lindsay[d], Séverine Vermeire[e], Martha Bayliss[a], Joseph C. Cappelleri[f], Stephen Maher[a], Andrew G. Bushmakin[f], Lea Ann Chen[g], Marco DiBonaventura[h]

[a]Optum, Johnston, RI, USA [b]University of Chicago Medicine, Inflammatory Bowel Disease Center, Chicago, IL, USA [c]Hospital Clínic de Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain [d]Centre for Immunobiology, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK [e]Department of Gastroenterology, University Hospitals Leuven, Leuven, Belgium [f]Pfizer Inc, Groton, CT, USA [g]New York University School of Medicine, New York, NY, USA [h]Pfizer Inc, New York, NY, USA

Corresponding author: Aaron Yarlas, Optum, 1301 Atwood Avenue, Suite 311N, Johnston, RI 02919, USA. Tel.: [401] 642–9245; email: ayarlas@qualitymetric.com

Abstract

Background and Aims: This review is the first to evaluate the burden of ulcerative colitis [UC] on patients' quality of life by synthesizing data from studies comparing scores from the SF-36® Health Survey, a generic measure assessing eight quality-of-life domains, between UC patients and matched reference samples.

Methods: A systematic review of the published literature identified articles reporting SF-36 domains or physical and mental component summary scores [PCS, MCS] from UC and reference samples. Burden of disease for each SF-36 domain was then summarized across studies by comparing weighted mean differences in scores between patient and reference samples with minimally important difference thresholds.

Results: Thirty articles met pre-specified inclusion criteria. SF-36 scores were extracted from five samples of patients with active disease, 11 samples with a mixture of disease activity, five samples of patients in clinical remission, and 13 samples of patients following proctocolectomy with ileostomy or ileal pouch-anal anastomosis, along with respective reference samples. Clinically meaningful burden was observed in samples with active or mixed disease activity [deficits: PCS = 5.6, MCS = 5.5] on all SF-36 domains except Physical Functioning. No burden was observed in samples in remission or post-surgical patients [deficits: PCS = 0.8, MCS = 0.4] except for the General Health perception domain.

Conclusions: Patients with active UC experience a clinically meaningful burden of disease across most aspects of quality of life. Patients with inactive UC exhibit negligible disease burden and are comparable to the general population on most quality-of-life outcomes. Thus, treatments which effectively induce and maintain remission may restore physical and mental health status.

Key Words: SF-36; ulcerative colitis; burden of disease

1. Introduction

Patients with ulcerative colitis [UC] experience recurring and episodic clinical signs and symptoms, including anaemia, rectal bleeding, diarrhoea, abdominal pain, and fecal urgency.[1] However, patients express concerns that go beyond these clinical manifestations. They report anxieties stemming from a lack of control over their bodily functions, fear of disease progression, hospitalization, or surgery, and fear of not having immediate access to a toilet.[2–4] The issue of toilet access further affects their employment opportunities and work productivity,[4–6] and limits their ability to engage in social and recreational activities.[2,4,6,7] Impaired ability to develop and maintain strong relationships with others may contribute to problems with anxiety, isolation, and depression that are common in this patient population.[8–11] Physicians typically underestimate the burden of UC on patients' daily functioning and well-being[12]; patients are twice as likely as physicians to endorse statements such as 'living with UC is a daily struggle', and 'UC has wrecked important moments in my life'.[13] Thus, fully capturing the burden of UC on the health status of patients with active disease, and accurately evaluating the degree to which treatment alleviates this burden, entails more than merely assessing changes in intestinal symptoms or mucosal inflammation; it also requires measuring changes in patients' functioning and well-being.

The SF-36® Health Survey [SF-36] is a generic patient-reported outcome [PRO] measure that captures multiple aspects of how a respondent feels and functions in their daily life.[14] Because constructs captured by the SF-36 are not specific to a particular health condition or treatment, the interpretation of the burden of a particular condition, such as UC, can be assessed by comparing scores from persons with a condition to scores from a comparable reference, such as a gender- and age-matched control group or the general population. Subsequently, one can understand the impact of treatment or a change in disease status [e.g. achieving disease remission] not merely in a relative sense, such as whether patients' symptoms improve, but also in an absolute sense: whether they become 'well' or normalized.

The objective of the current study was to conduct the first systematic examination of the burden of disease for patients with UC, as measured by SF-36 scores relative to population norms or matched controls. We conducted a review of published studies that reported SF-36 scores from both UC patients and a relevant reference group—a group that is generally healthy and without UC—to assess the magnitude of differences in their SF-36 scores. Burden was examined separately for: samples in which all patients had active disease; samples that included a mix of patients with active and inactive disease; samples of patients in clinical remission; and samples in which patients had undergone surgical treatment [i.e. proctocolectomy with either ileal pouch-anal anastomosis [IPAA], ileorectal anastomosis [IRA], or ileostomy]. Whereas it is generally known that patients with active disease experience functional impairments, the degree to which these impairments are reduced, or fully eliminated, in patients with medical- or surgically-induced remission is not as apparent.

2. Methods

2.1. SF-36® health survey [SF-36]

The SF-36 is a 36-item PRO instrument capturing eight domains of functioning and well-being: Physical Functioning; role limitations due to physical health problems [Role Physical]; Bodily Pain; perception of General Health; Vitality; Social Functioning; role limitations due to emotional health problems [Role Emotional]; and Mental Health. Scores for each domain can be transformed into norm-based *T*-scores, with a mean of 50 and a standard deviation of 10, reflecting normative scores for the US general population. *T*-scores for two global measures—the Physical Component Summary [PCS] and Mental Component Summary [MCS]—are calculated by summing weighted scores from all eight domains.[15] For all scales and summaries, higher scores indicate better health status.

Norm-based algorithms for deriving *T*-scores from raw subscale scores for both the original version of the SF-36 [SF-36v1][16–18] and the updated version [SF-36v2][19,20] have been derived from a representative adult sample from the US general population, who participated in the 1998 National Survey of Functional Health Status.[15] All *T*-scores for the SF-36v1 and SF-36v2 [heretofore, each referred to as 'SF-36'] reported in this paper were calculated using the algorithms based on the 1998 norms dataset.

Thresholds indicating minimal important differences [MIDs] between samples, which can be interpreted as clinically meaningful group differences,[23] have been estimated for each SF-36 scale and summary score using both distribution-based and anchor-based approaches.[15] The MID thresholds recommended by the instrument's developers for between-group differences in SF-36 *T*-scores are 3 points for PCS and MCS and for all domains, with the exception of Role Physical [2 points] and Role Emotional [4 points] domains.[15]

2.2. Systematic literature review

The articles included in this review were identified and selected according to guidelines recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] Statement.[21]

2.2.1. Data sources and search strategy

In July 2017 we conducted searches of several electronic medical databases—PubMed, Embase [OvidSP], Cochrane Register of Controlled Trials [CENTRAL], and BIOSIS Previews—as well as Optum's in-house bibliography that tracks publications using its proprietary survey tools, including the SF-36. The search terms and strings used, which are reported in Supplementary Figure 1 [available as Supplementary data at *ECCO-JCC* online], were designed to capture studies in which the SF-36 was administered to patients with UC or inflammatory bowel disease [IBD] in general.

2.2.2. Article selection

All stages of article selection were conducted by three independent researchers. After each stage, any discrepancies among reviewers regarding the selection decision for each article were discussed until a consensus was obtained.

Initial screening was based on review of record titles, abstracts, and metadata. Records were selected if they met all of the following inclusion criteria: the record pointed to a full article [i.e. not a conference abstract]; the article was published in an English language, peer-reviewed journal; the article described quantitative results from an empirical study; and the article was not clearly irrelevant to the current objectives.

The full text of each article selected during initial screening was reviewed. Articles meeting the following criteria were selected for data extraction: mean or median SF-36 domain scores were reported for a sample or subsample consisting of only UC patients; SF-36 domain scores were also reported from an appropriate reference sample [e.g. matched control sample, general population sample from the same geographical region]; and SF-36 scores were calculated using developer-approved algorithms.

2.3. Data extraction

We extracted mean or median SF-36 domain and/or summary scores from each selected article. For studies using longitudinal designs, we extracted scores from baseline visits only. For articles that presented SF-36 scores in figures rather than numerically in tables or text, we estimated numerical values using WebPlotDigitizer desktop software (version 3.9; available at [http://arohatgi.info/WebPlotDigitizer]).[22] Articles reporting raw domain scores [0–100] were transformed to *T*-scores using Optum's scoring algorithms appropriate to the version used [SF-36v1 or SF-36v2] as derived from the 1998 norm dataset, followed by calculation of PCS and MCS scores using the corresponding weights.[15]

2.4. Assessment of disease burden within each study

We calculated disease burden for UC patient samples within each study by subtracting mean or median SF-36 *T*-scores for the UC patient sample from *T*-scores reported for the study's reference sample. The presence or absence of disease burden was determined by comparing the magnitude of between-sample differences with MID thresholds [i.e. differences above the MID threshold indicated the presence of disease burden].

2.5. Summary of disease burden across studies

Based on reported characteristics of patients at the time that the SF-36 was administered, we classified samples into one of four categories based on pre-specified ad hoc criteria: active disease [≥80% of sample patients had active disease]; mixed disease activity [≥20% and <80% of sample patients had active disease or were in clinical remission]; remission [≥80% of sample patients were in clinical remission]; and post-surgical [sample patients had undergone proctocolectomy with IPAA, IRA, or ileostomy]. For each SF-36 domain and summary measure, we summarized difference scores across studies within each category by calculating unweighted mean values as well as mean values when weighted by the number of patients in the UC sample and when weighted by the combined UC and reference samples. We then compared these summary statistics for each measure with corresponding MID values to assess burden across all samples within the category, and calculated the percentage of samples within each category for which a value exceeding the MID was observed.

3. Results

3.1. Literature search

The number of articles retrieved from each data source, and the number of unique articles excluded from the review during initial screening and full-text review, are presented in Supplementary Figure 2, [available as Supplementary data at *ECCO-JCC* online]. SF-36 scores were extracted from 30 articles that met all selection criteria.[24–53] Table 1 presents descriptions of the UC and reference samples for each selected article.

From these 30 articles, SF-36 scores were reported for a total of 34 independent samples of UC patients [four articles included two samples: one sample of patients with active disease and a sample of patients in remission]. Five samples included patients with active disease,[25,31,36,45,51] and 11 samples included mixed disease activity status among patients.[24,26,28,37–39,41,42,44,50,53] Additionally, four samples included patients in clinical remission,[25,36,43,46] and 14 samples included patients who had undergone surgery: proctocolectomy with IPAA in 11 samples,[27,30,33–35,40,43,47–49,52] proctocolectomy with ileostomy in two samples,[29,32] and proctocolectomy with IRA in one sample.[35]

3.2. Disease burden for samples of patients with active UC

We observed evidence supporting clinically meaningful burden in most SF-36 domains for samples of patients with active disease [Table 2]. Across the five active disease samples, the weighted mean differences in scores exceeded MID thresholds for Role Physical, Bodily Pain, perception of General Health, Vitality, Social Functioning, and Mental Health domains, as well as for PCS and MCS. The mean difference weighted by the combined UC and reference samples, but not by the UC sample alone, exceeded the MID threshold for the Role Emotional domain, whereas neither exceeded the MID threshold for the Physical Functioning domain. Comparisons exceeded MIDs in the majority of samples for both summary scores and for all domains other than Physical Functioning.

3.3. Disease burden for samples of patients with mixed active and inactive UC

Findings for disease burden for mixed disease activity samples are presented in Table 3. Across the eleven samples in this category, both of the weighted mean differences in scores exceeded MID thresholds for Role Physical, Bodily Pain, perception of General Health, Vitality, and Social Functioning domains, as well as for PCS. The mean difference weighted by the combined UC and reference samples, but not by the UC sample alone, exceeded the MID threshold for the remaining domains [Physical Functioning, Role Emotional, and Mental Health] as well as the MCS. Comparisons exceeded MIDs in the majority of samples for both summary scores and for all domains other than Physical Functioning.

3.4. Disease burden for samples of patients with UC in remission

Table 4 presents assessment of disease burden in samples of patients in clinical remission. Across the four remission samples, both of the weighted mean differences in scores exceeded MID thresholds only for the perception of General Health domain, but neither of these differences exceeded the MID threshold for any of the remaining domains nor for either summary measure. Correspondingly, comparisons exceeded MIDs in the majority of samples for only the perception of General Health domain; comparisons exceeded MIDs in two of the four studies for the Vitality domain, and in one or no studies for both summary measures and the remaining domains.

3.5. Disease burden for samples of post-surgical UC patients

Assessment of burden in samples of post-surgical patients is presented in Table 5. As observed for the remission samples, across the 14 post-surgical samples both of the weighted mean differences in scores exceeded MID thresholds only for the perception of General Health domain, with neither of these differences exceeding the MID threshold for any of the remaining domains nor for either summary measure. For no domain and neither summary score did comparisons exceed MIDs for the majority of samples: comparisons exceeded MIDs in five of the 14 samples for the Role Physical, perception of General Health, and Vitality domains, but in three or fewer samples for the remaining domains and summary scores.

Table 1. Sample characteristics of reviewed studies.

Study	Description of UC sample	Disease status of UC sample	Determinant of disease activity status	Description of reference sample
Ahn 2014[24]	49 patients with UC who received a colonoscopy at a hospital in Korea, from 2007 to 2012	Mixed: 21 [43%] active, 28 [57%] in remission	Mayo score[56] [remission defined as an endoscopic subscore of 0]	25 controls with no GI conditions who underwent a routine health check-up [with colonoscopy indicating no GI conditions] at the same hospital during the same time period
Ansari 2008[25]	95 patients with UC who visited a gastroenterology outpatient clinic at a hospital in Iran, from 1999 to 2005	Mixed: 45 [47%] active, 50 [53%] in remission	Mayo score[56] [remission defined as a total score ≤1, with a rectal bleeding subscore of 0 and an endoscopic subscore ≤1]	100 controls who visited an orthopaedic minor trauma outpatient clinic at the same hospital from 2004 to 2005
Barratt 2011[26]	228 patients with UC who visited an outpatient clinic at a hospital in the UK, from 2005 and 2008	Mixed: 62 [27%] active, 166 [73%] in remission	Walmsley's SCCAI[57] [remission defined as SCCAI <5]	348 age- and sex-matched controls with no GI conditions who visited the same outpatient clinic in the same time period
Barton 2001[27]	37 patients with UC who underwent IPAA in the USA, from 1983 to 2000	Post-surgical [IPAA]	Not assessed	US GP sample [Ware, 1994][58]
Bastida 2010[28]	24 inpatients or outpatients with UC at a hospital in Spain [dates not specified]	Mixed [NOS]	Mayo score[56] [remission defined as a total score of 0]	Spanish GP sample [Alonso, 1998][59]
Berndtsson 2004[29]	78 patients with UC who underwent ileostomy [Kock pouch] at a hospital in Sweden, from 1967 to 1974	Post-surgical [ileostomy]	Not assessed	174 age- and sex-matched respondents drawn from a Swedish GP sample [Sullivan, 1995][60]
Berndtsson 2007[30]	268 patients with UC who underwent IPAA in Sweden, from 1982 to 1995	Post-surgical [IPAA]	Not assessed	286 age- and sex-matched respondents drawn from a Swedish GP sample [Sullivan, 1995][60]
Bernklev 2005[31]	348 patients with UC from gastroenterology departments at hospitals in Norway, from 1990 to 1993	Active	Ad hoc single-item measure of symptom severity (inactive disease defined as a score of 0 ['no symptoms'])	Norwegian GP sample [Loge, 1998][61]
Camilleri-Brennan 2001[32]	49 patients with UC who underwent ileostomy [total proctocolectomy] at hospitals in the UK, from 1992 to 1997	Post-surgical [ileostomy]	Not assessed	UK GP sample [Jenkinson, 1993][62]
Carmon 2003[33]	77 patients with UC who underwent IPAA in Israel, from 1990 to 2001	Post-surgical [IPAA]	Not assessed	Israeli GP sample [Lewin-Epstein, 1998][63]
Heikens 2012[34]	30 patients with UC who underwent IPAA at two hospitals in The Netherlands from 2003 to 2008	Post-surgical [IPAA]	Not assessed	Dutch GP sample [Van der Zee, 1993][64]
Heikens 2013[35]	142 patients with UC who underwent IPAA or IRA at two hospitals in The Netherlands from 1998 to 2005	Post-surgical [IPAA or IRA]	Not assessed	Dutch GP sample [Van der Zee, 1993][64]
Hjortswang 2003[36]	292 outpatients with UC who visited hospital colitis clinics in Sweden [dates not specified]	Mixed: 68 [25%] active, 224 [75%] in remission	Physician assessment [active disease defined as symptoms severe enough to require treatment with corticosteroids or 5-ASA]	Swedish GP sample [Sullivan, 1995][60]
Huppertz-Hauss 2016[37]	294 patients with UC in the IBSEN study in Norway contacted 20 years after diagnosis from 2011 to 2014	Mixed: 69 [23%] active, 225 [77%] remission	Walmsley's SCCAI[57] [remission defined as SCCAI ≤2]	Norwegian GP sample [Loge, 1998][61]
Iglesias-Rey 2014[38]	470 patients with UC who visited an IBD unit at a university hospital in Spain, from 2009 to 2010	Mixed: 195 [42%] active, 275 [58%] in remission	Mayo score[56] [remission defined as a total score ≤2]	Spanish GP sample [Alonso, 1998][59]
Jelsness-Jorgensen 2011[39]	92 outpatients with UC who visited clinics in Norway, from 2005 to 2007	Mixed [NOS]	Walmsley's SCCAI[57] [remission or mild-to-moderate active disease defined as SCCAI <10]	Norwegian GP sample [Loge, 1998][61]

Table 1. Continued

Study	Description of UC sample	Disease status of UC sample	Determinant of disease activity status	Description of reference sample
Koerdt 2014[40]	48 patients with UC who underwent IPAA in Germany, from 1996 to 2003	Post-surgical [IPAA]	Not assessed	48 age- and sex-matched controls at least 12 months after undergoing appendectomy for acute appendicitis at the same hospital during the same time period
Langhorst 2007[41]	56 patients with UC recruited through public advertisement in local newspapers and radio in Germany, in 2002	Mixed: 13 [23%] active, 43 [77%] in remission	Rachmilewitz's CAI[65] [remission defined as CAI ≤5]	German GP sample [Bullinger, 1995][66]
McColl 2004[42]	111 patients with UC who visited a hospital in the UK, from 1997 to 1998	Mixed [NOS]	Lichtiger's CAI[67] [disease activity status not defined]	UK GP sample [Jenkinson, 1993][62]
Meijs 2014[43]	58 patients with UC who were in remission after receiving treatment with anti-TNF agents or after undergoing IPAA in The Netherlands, from 2008 to 2011	Remission	Mayo score[56] [remission defined by a partial Mayo score ≤2, with a rectal bleeding subscore of 0 and with no subscore >1]	Dutch GP sample [Ware, 1994][58]
Mokrowiecka 2006[44]	30 patients with UC in Poland [NOS]	Mixed: 23 [77%] active, 7 [23%] in remission	Rachmilewitz's CAI[65] [remission defined as CAI ≤2]	40 healthy volunteers [NOS]
Muir 2001[45]	73 patients with UC, before undergoing IPAA in the USA [dates not specified]	Active	Not assessed	US GP sample [Ware, 1994][58]
Nordin 2002[46]	331 patients with UC who visited an IBD clinic registry in Sweden [dates not specified]	Mixed: 36 [12%] active, 295 [88%] in remission	Relapse status [NOS]	Swedish GP sample [Sullivan, 1995][60]
Pavlides 2014[47]	79 patients with UC who underwent IPAA in the UK, from 1983 to 2012	Post-surgical [IPAA]	Not assessed	UK GP sample [Jenkinson, 1993][62]
Richards 2001[48]	56 patients with UC who underwent IPAA in the UK, from 1985 to 1997	Post-surgical [IPAA]	Not assessed	US GP sample [Ware, 1994][58]
Rokke 2011[49]	134 patients with UC who underwent IPAA in Norway, from 1988 to 2002	Post-surgical [IPAA]	Not assessed	Norwegian GP sample [Loge, 1998][61]
Smith 2002[50]	50 patients with UC from a gastroenterology clinic in the UK [dates not specified]	Mixed [NOS]	Modified CDAI[68] [disease activity status not defined]	50 healthy volunteers from a factory workforce [NOS]
Therkelsen 2016[51]	50 patients with UC recruited from a university hospital in Norway from 2012 to 2014	Active	Modified [4-item version] Rachmilewitz's CAI[65] [CAI ≥3 for study inclusion]	Norwegian GP sample [Loge, 1998][61]
Tiainen 1999[52]	68 patients with UC who underwent IPAA in Finland, from 1985 to 1995	Post-surgical [IPAA]	Not assessed	Finnish GP sample [Aalto, 1999][69]
Zhou 2010[53]	52 patients with UC who visited a hospital in China, from 2005 to 2006	Mixed: 23 [44%] active, 29 [56%] in remission	Walmsley's SCCAI[57] [remission defined as SCCAI <5]	Chinese GP sample [Li, 2003][70]

ASA, aminosalicylic acid; CAI, Colitis Activity Index; CDAI, Crohn's Disease Activity Index; GI, gastrointestinal; GP, general population; IBD, inflammatory bowel disease; IPAA, ileal pouch-anal anastomosis; IRA, ileorectal anastomosis; NOS, not otherwise specified; SCCAI, simple clinical colitis activity index; TNF, tumour necrosis factor; UC, ulcerative colitis.

3.6. Disease burden for active/mixed disease patient samples vs remission/post-surgical patient samples

Given the observed similarity in patterns of burden for the active disease samples and the mixed activity disease samples, we compared weighted mean differences between the two sets of samples to determine whether the magnitude of burden between samples exceeded the MID threshold. No differences exceeded MID thresholds for any domain or either summary measure for either of the weighting sets, indicating that the active and mixed activity samples had the same magnitude of burden, and thus could be combined into a single set of samples [active/mixed UC samples set]. The same approach was used to determine that the remission and post-surgical samples had comparable burden, and thus could also be combined into a single set of samples [remission/post-surgical UC samples set].

We compared the magnitude of burden in SF-36 scores for the active/mixed UC samples set and for the remission/post-surgical UC samples set based on the weighted [by combined samples]

Table 2. Burden of UC for samples of patients with active disease.

Study	*N* [UC sample]	Reference sample [*N*]	Burden of UC [Reference sample score - UC sample score]									
			PCS	MCS	PF	RP	BP	GH	VT	SF	RE	MH
Ansari 2008[25]	45	Control sample [100]	***4.1***	***6.1***	***6.1***	-0.4	***3.1***	***10.7***	***8.2***	***4.5***	-0.4	***10.2***
Bernklev 2005[31]	348	Norwegian GP[61] [2323]	2.2	1.9	0.2	***2.4***	2.2	***5.1***	2.0	1.5	2.8	0.9
Hjortswang 2003[36]	68	Swedish GP[60] [8930]	2.3	***6.9***	-0.8	***3.5***	***3.9***	***8.4***	***5.6***	***6.9***	***5.1***	***4.6***
Muir 2001[45]	20	US GP[58] [1982]	***12.7***	***8.6***	***10.6***	***12.7***	***9.3***	***14.4***	***13.9***	***13.1***	***7.3***	***7.8***
Therkelsen 2016[51]	50	Norwegian GP[61] [2323]	***5.8***	***8.7***	1.1	***7.3***	***7.5***	***11.4***	***10.3***	***8.9***	***5.6***	***7.2***
Mean difference			***5.4***	***6.4***	***3.4***	***5.1***	***5.2***	***10.0***	***8.0***	***7.0***	***4.0***	***6.1***
Weighted mean difference: UC sample[a]			***3.1***	***3.8***	1.0	***3.1***	***3.3***	***6.9***	***4.2***	***3.6***	3.2	***3.0***
Weighted mean difference: total sample[b]			***4.1***	***6.5***	1.1	***5.0***	***4.8***	***9.0***	***6.7***	***7.0***	***4.9***	***4.8***
Percentage of studies in which difference >MID			60%	80%	40%	80%	80%	100%	80%	80%	60%	80%

Values in ***bold italics*** exceed group-level MID.

BP, Bodily Pain; GH, General Health; GP, general population; MCS, Mental Component Summary; MH, Mental Health; MID,: minimally important difference; PCS, Physical Component Summary; PF, Physical Functioning; RE, Role Emotional; RP, Role Physical; SF, Social Functioning; UC, ulcerative colitis; VT, Vitality.

[a]Mean differences were weighted by the size of the UC sample.

[b]Mean differences were weighted by the combined size of the UC and reference samples.

Table 3. Burden of UC for samples of patients with a mixed distribution of active and inactive disease.

Study	*N* [UC sample]	% active	Reference sample [*N*]	Burden [Reference sample score - UC sample score]									
				PCS	MCS	PF	RP	BP	GH	VT	SF	RE	MH
Mokrowiecka 2006[44]	30	76%	Community sample [40]	***12.7***	***6.1***	***9.3***	***15.2***	***9.4***	***14.4***	***6.6***	***8.8***	***8.8***	***7.2***
Jelsness-Jorgensen 2011[39]	92	75%	Norwegian GP[61] [2323]	***4.9***	2.8	2.0	***6.4***	***3.2***	***7.6***	***4.6***	2.3	***4.4***	1.7
Zhou 2010[53]	52	44%	Chinese GP[70] [1688]	***6.8***	-2.8	0.1	***10.3***	***3.2***	***5.1***	-1.2	***4.2***	***4.4***	-8.0
Ahn 2014[24]	49	43%	Control sample [25]	***6.8***	***4.1***	***3.0***	***8.4***	***5.5***	***10.5***	***4.6***	***4.6***	***5.1***	***4.1***
Iglesias-Rey 2014[38]	470	42%	Spanish GP[59] [9151]	***5.2***	***4.4***	2.8	***4.2***	***5.3***	***9.4***	***4.8***	***6.0***	3.9	***3.5***
Langhorst 2007[41]	56	28%	German GP[66] [2914]	2.8	***6.9***	1.1	***2.5***	***4.5***	***8.2***	***7.6***	***4.7***	***6.3***	***4.6***
Barratt 2011[26]a	228	27%	Control sample [348]	***4.2***	0.2	2.1	***4.8***	0.8	***7.2***	***3.2***	***5.5***	-0.1	-0.1
Huppertz-Haus 2016[37]	294	23%	Norwegian GP[61] [2323]	***3.2***	0.2	1.0	***2.2***	2.9	***4.9***	1.6	1.3	0.8	-0.1
Bastida 2010[28]	24	NS	Spanish GP[59] [9151]	***9.5***	***10.1***	***5.7***	***11.5***	***11.4***	***12.6***	***9.3***	***12.4***	***8.3***	***10.3***
McColl 2004[42]	106	NS	UK GP[62] [9332]	***6.3***	***3.8***	***3.1***	***5.5***	***5.0***	***9.5***	***5.2***	***9.5***	1.2	***3.2***
Smith 2002[50]	50	NS	Community sample [50]	2.6	***4.7***	***5.8***	***2.5***	2.7	0.8	2.9	***7.3***	3.2	***5.4***
Mean difference				***5.9***	***3.7***	***3.3***	***6.7***	***4.9***	***8.2***	***4.5***	***6.1***	***4.2***	2.9
Weighted mean difference: UC sample[b]				***4.9***	2.7	2.4	***4.7***	***3.9***	***7.7***	***3.8***	***5.1***	2.8	2.0
Weighted mean difference: total sample[c]				***6.3***	***5.1***	***3.2***	***6.5***	***6.2***	***9.4***	***5.7***	***7.7***	***4.3***	***4.3***
Percentage of studies in which difference >MID				82%	64%	45%	100%	73%	91%	73%	82%	73%	64%

Values in ***bold italics*** exceed group-level MID.

BP, Bodily Pain; GH, General Health; GP, general population; MCS, Mental Component Summary; MH, Mental Health; MID, minimally important difference; NS, not specified; PCS: Physical Component Summary; PF, Physical Functioning; RE, Role Emotional; RP, Role Physical; SF, Social Functioning; UC, ulcerative colitis; VT, Vitality.

[a]Values based on median scores.

[b]Mean differences were weighted by the size of the UC sample.

[c]Mean differences were weighted by the combined size of the UC and reference samples.

mean differences and confidence intervals [CIs, calculated based on weighted standard errors] for differences between UC samples and their respective reference samples [Figure 1]. The results indicate that the magnitude of burden in the active/mixed UC samples set exceeds that for the remission/post-surgery samples set, on all eight domains and both summary scores. Further, for the active/mixed UC samples set, the lower limits of the 95% CIs for weighted mean differences exceed the MID for both summary scores, and for all domains except for Physical Functioning. At the same time, 95% CI limits for the remission/post-surgery UC samples set overlap with or are actually below 0, indicating a complete lack of burden, for both summary scores and for six of the eight domains. For this set of UC samples, clinically meaningful burden of disease is only observed for the perception of General Health domain.

4. Discussion

Findings from this review of published studies comparing SF-36 scores between UC patients and reference samples indicate very different burden profiles between patients with active and inactive disease. Patients with active disease showed deficits relative to controls that exceeded established MID thresholds in all measured aspects of functioning and well-being, with the exception of Physical Functioning. The largest impact of disease was observed on patients' perception of General Health. The impacts of active UC on Role Physical and Social Functioning domains were also substantial. The sizeable burdens of active UC on these latter two domains of functioning are consistent with concerns that are often mentioned by patients, such as decreased performance at work/school, limitations

Table 4. Burden of UC for samples of patients in clinical remission.

Study	*N* [UC sample]	Reference sample [*N*]	Burden [Reference sample score - UC sample score]									
			PCS	MCS	PF	RP	BP	GH	VT	SF	RE	MH
Ansari 2008[25]	27	Control sample [100]	-1.0	-2.3	-1.0	-3.0	-2.0	2.7	-1.0	-6.6	-2.2	-0.2
Hjortswang 2003[36]	224	Swedish GP[60] [8930]	0.0	0.9	-0.8	0.3	-1.8	***3.7***	0.9	-0.1	0.4	0.5
Meijs 2014[43]	29	Dutch GP[58] [1771]	***7.5***	0.5	0.9	**5.0**	***2.6***	***14.5***	***8.5***	***4.9***	-2.8	-0.5
Nordin 2002[46]	331	Swedish GP[60] [8930]	0.1	***3.0***	-1.2	1.5	-1.8	***5.3***	***3.5***	1.6	1.5	2.0
Mean difference			1.6	0.5	-0.5	1.0	-0.8	***6.5***	***3.0***	-0.1	-0.8	0.4
Weighted mean difference: UC sample[a]			0.3	1.8	-1.0	1.0	-1.6	***5.0***	2.6	0.7	0.7	1.2
Weighted mean difference: total sample[b]			0.7	1.7	-0.9	1.2	-1.4	***5.3***	2.7	1.0	0.5	1.0
Percentage of studies in which difference >MID			25%	25%	0%	25%	25%	75%	50%	25%	0%	0%

Values in ***bold italics*** exceed group-level MID.

BP, Bodily Pain; GH, General Health; GP, general population; MCS, Mental Component Summary; MH, Mental Health; MID, minimally important difference; PCS, Physical Component Summary; PF, Physical Functioning; RE, Role Emotional; RP, Role Physical; SF, Social Functioning; UC, ulcerative colitis; VT, Vitality.

[a]Mean differences were weighted by the size of the UC sample.

[b]Mean differences were weighted by the combined size of the UC and reference samples.

Table 5. Burden of UC for samples of patients following surgery-induced remission.

Study	*N* [UC sample]	Surgical procedure	Reference sample [N]	Burden [Reference sample score - UC sample score]									
				PCS	MCS	PF	RP	BP	GH	VT	SF	RE	MH
Barton 2001[27]	37	IPAA	US GP[58] [1982]	0.7	1.9	-0.9	1.6	0.7	2.1	***3.3***	1.7	3.1	-1.2
Berndtsson 2004[29]	61	Ileostomy	Swedish GP[60] [8930]	-0.3	-0.1	-0.8	0.8	-2.6	1.3	0.9	0.2	-0.7	-0.7
Berndtsson 2007[30]	286	IPAA	Swedish GP[60] [8930]	0.0	1.1	-1.3	1.3	-1.3	2.4	2.0	0.3	0.8	-0.1
Camilleri-Brennan 2001[32]	49	Ileostomy	UK GP[62] [9332]	1.1	-1.1	1.8	0.8	-1.6	2.1	-2.3	0.9	-0.7	-0.1
Carmon 2003[33]	77	IPAA	Israel GP[63] [2030]	0.2	2.8	-1.4	1.6	1.6	1.4	2.8	***3.0***	3.5	-0.3
Heikens 2012[34]	30	IPAA	Dutch GP[64] [1063]	-1.2	1.0	-4.2	***2.8***	-1.7	0.0	1.6	0.2	0.2	-0.7
Heikens 2013[35]	71	IRA	Dutch GP[64] [1063]	0.3	1.8	-0.5	1.5	0.1	0.6	2.5	***3.1***	0.4	0.6
Heikens 2013[35]	71	IPAA	Dutch GP[64] [1063]	1.6	0.4	-0.8	***2.1***	-1.1	***3.5***	***4.4***	2.5	-1.7	-1.1
Koerdt 2014[40]	48	IPAA	Control sample [48]	1.2	***3.6***	1.3	***4.5***	-1.0	***3.2***	0.8	***3.4***	***6.6***	0.9
Meijs 2014[43]	29	IPAA	Dutch GP[58] [1771]	***6.7***	-0.1	2.1	***5.5***	2.3	***10.9***	***6.1***	2.2	1.6	-2.6
Pavlides 2014[47]a	79	IPAA	UK GP[62] [9332]	1.8	-3.5	-2.0	-2.4	1.0	***6.7***	0.7	-3.7	-4.6	-2.7
Richards 2001[48]a	56	IPAA	US GP[58] [1982]	0.6	***3.7***	-0.2	***2.6***	0.1	2.8	***3.7***	2.8	0.7	***4.3***
Rokke 2011[49]	133	IPAA	Norwegian GP[61] [2323]	1.6	1.9	-1.5	1.7	0.5	***6.8***	***3.9***	1.1	0.7	0.9
Tiainen 1999[52]	72	IPAA	Finnish GP[69] [2175]	-0.9	-0.8	-2.3	-1.2	-1.5	2.3	-1.0	-1.5	0.0	-1.9
Mean difference				1.0	0.9	-0.8	1.6	-0.3	***3.3***	2.1	1.2	0.7	-0.3
Weighted mean difference: UC sample[b]				0.7	0.9	-1.0	1.3	-0.5	***3.2***	2.1	0.9	0.5	-0.2
Weighted mean difference: total sample[c]				0.8	-0.2	-0.7	0.7	-0.7	***3.3***	1.1	0.1	-0.6	-0.7
Percentage of studies in which difference >MID				7%	14%	0%	36%	0%	36%	36%	21%	7%	7%

Values in ***bold italics*** exceed group-level MID.

BP, Bodily Pain; GH, General Health; GP, general population; IPAA, ileal pouch-anal anastomosis; IRA, ileorectal anastomosis; MCS, Mental Component Summary; MH, Mental Health; MID, minimally important difference; PCS, Physical Component Summary; PF, Physical Functioning; RE, Role Emotional; RP, Role Physical; SF, Social Functioning; UC, ulcerative colitis; VT, Vitality.

[a]Values based on median scores.

[b]Mean differences were weighted by the size of the UC sample.

[c]Mean differences were weighted by the combined size of the UC and reference samples.

in the ability to engage in social activities due to the need for access to a toilet, and the subsequent difficulties for maintaining relationships with others.[2–7]

In contrast, patients with inactive disease [as indicated by assessed clinical remission, or surgically-induced remission] were comparable to healthy controls or general population samples on all domains of physical and mental functioning with the exception of perception of General Health. In other words, achieving an inactive disease state, via clinical remission or using surgery, does not simply reduce the impact of disease on how patients feel and function, but it eliminates the burden altogether, normalizing both physical and mental health status. However, although these patients reported normal levels of functioning and well-being, they still described residual concerns about their health in general. It may be that a longer follow-up of patients with inactive disease would reveal that their general health perceptions also reached normal levels.

In clinical trials, the perspective of patients with UC is often assessed using disease-specific measures of symptoms and their impact on functioning and well-being, such as the Inflammatory Bowel Disease Questionnaire [IBDQ]. The use of disease-specific PRO measures to evaluate treatment benefit is important, as these instruments capture health concepts directly relevant to disease

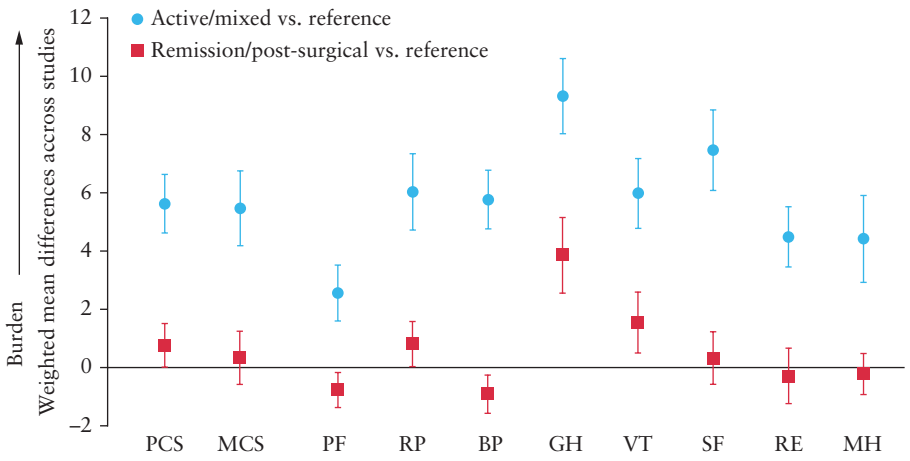

Figure 1. Burden of UC for samples of patients with active disease or a mixed distribution of active and inactive disease relative to samples of patients in clinical remission or surgically-induced remission.

symptoms, and are typically more responsive to improvements in UC patients' clinical and endoscopic disease activity than are generic measures.[54] At the same time, disease measures are, by definition, narrow in scope with respect to the concepts they capture, and typically only assess aspects of health directly related to the affected organ or its treatment. In contrast, generic measures such as the SF-36 capture a broader array of health concepts. An additional benefit of using a generic, normed instrument is the ability to compare health outcomes with persons outside the patient population, such as understanding the relative burden of disease as described here. Thus, disease-specific and generic PRO measures offer complementary information and interpretability for understanding treatment benefit, and as such the inclusion of both types of measures [specifically, the SF-36 and IBDQ] has been recommended for use in clinical trials with UC patients.[55]

There are some limitations to the current study that should be considered when interpreting these findings. For example, we limited our analysis to studies that reported scores from a sample of UC patients as well as from a reference group. Whereas this criterion was helpful in selecting a reasonable number of studies with data relevant to the current objectives, it is possible that patients in studies meeting these criteria are not representative of the UC patient population. For instance, researchers studying patients with active UC who have particularly poor functioning may be more likely to compare patients' outcomes with a reference sample to highlight this burden. On the other hand, researchers studying patients with inactive UC who have particularly good functioning may be motivated to exhibit the benefits of improving health outcomes by comparing patients' outcomes with a reference sample, to demonstrate their similarity.

Additionally, our classification of samples was based on patients' disease status characteristics, but we could not control for any other factors that may have varied between these samples which could account for patterns of disease burden reported here. Thus, we cannot definitively rule out other factors that contribute to the disease burden observed across the sample groups.

5. Conclusion

In conclusion, our synthesis of data from a systematic review of the published literature provides the first clear evidence that UC patients with active disease experience burdens on physical, emotional, and social functioning and well-being, and that normalization of these outcomes is observed in patients with inactive UC. Our findings suggest that treatments for patients with UC which induce and maintain disease inactivity may not simply make patients better, but rather may normalize physical and mental health status.

Funding

This work was supported by Pfizer Inc.

Conflict of Interest

AY, MB, and SM are employees of Optum, who were contracted by Pfizer Inc. in connection with the conduct of the systematic literature review, interpretation of data, and drafting of this manuscript. Optum may receive revenue from the distribution and licensing of the SF-36 for commercial use. DTR has received consulting fees from AbbVie, Amgen, Janssen, Pfizer Inc., Takeda, and UCB; and research grants from AbbVie, Genentech, Janssen, Takeda, and UCB. JP has received consulting fees from AbbVie, Boehringer Ingelheim, Celgene, Ferring, Genentech-Roche, Janssen, MSD, Pfizer Inc., Second Genome, Shire, Takeda, Theravance, TiGenix, and Topivert; research grants from AbbVie and MSD; and speaker fees from AbbVie, Biogen, Janssen, MSD, and Pfizer Inc. JOL has received consulting fees from AbbVie, Celgene, Ferring, Janssen, Merck, Robarts Clinical Trials, Shire, Pfizer Inc., and Takeda; research grants from MSD, Hospira [Pfizer Inc.], Shire, and Takeda; lecture and/or speaker bureau fees from AbbVie, Allergan, Ferring, Janssen, MSD, Shire, and Takeda; and advisory board fees from AbbVie, Atlantic Healthcare, Ferring, Hospira [Pfizer Inc.], Janssen, MSD, NAP, Shire, Pfizer Inc., Takeda, and Vifor. SV has received consulting fees from Takeda, Roche/Genentech, Merck, Centocor, AbbVie, UCB, Pfizer Inc., Ferring, Second Genome, and Galapagos; research grants from Centocor, AbbVie, Takeda, Pfizer Inc., and Merck; and lecture and/or speaker bureau fees from Merck, AbbVie, Takeda, Pfizer Inc., Ferring, Falk, and Centocor. JCC, AGB, and MDB are employees and stockholders of Pfizer Inc. LAC is an employee of New York University School of Medicine, which is contracted by Pfizer Inc. to perform consultative services.

Acknowledgments

The authors would like to thank Paul Healey, Alireza Manuchehri, and Andrew Lovley for their support in the development of this manuscript. Conference presentation: portions of the current work were presented at 12th Congress of the European Crohn's and Colitis Organisation [ECCO], Barcelona, Spain, 15–18 February 2017.

Author Contributions

AY contributed to the study design, the literature review, data extraction and analysis, data interpretation, preparation of figures, and writing of the manuscript. SM contributed to the study design, literature review, data extraction and analysis, preparation of figures, and writing of the manuscript. MB, JCC, and AGB contributed to the study design, data interpretation, and writing of the manuscript. DTR, JP, JOL, SV, LAC, and MD contributed to the data interpretation and writing of the manuscript.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Ford AC, Moayyedi P, Hanauer SB. Ulcerative colitis. *BMJ* 2013;**346**:f432.
2. Sammut J, Scerri J, Xuereb RB. The lived experience of adults with ulcerative colitis. *J Clin Nurs* 2015;**24**:2659–67.
3. Waljee AK, Joyce JC, Wren PA, Khan TM, Higgins PD. Patient reported symptoms during an ulcerative colitis flare: a Qualitative Focus Group Study. *Eur J Gastroenterol Hepatol* 2009;**21**:558–64.
4. Devlen J, Beusterien K, Yen L, Ahmed A, Cheifetz AS, Moss AC. Barriers to mesalamine adherence in patients with inflammatory bowel disease: a qualitative analysis. *J Manag Care Spec Pharm* 2014;**20**:309–14.
5. Jansen F, van Uden-Kraan CF, Braakman JA, van Keizerswaard PM, Witte BI, Verdonck-de Leeuw IM. A mixed-method study on the generic and ostomy-specific quality of life of cancer and non-cancer ostomy patients. *Support Care Cancer* 2015;**23**:1689–97.
6. Wolfe BJ, Sirois FM. Beyond standard quality of life measures: the subjective experiences of living with inflammatory bowel disease. *Qual Life Res* 2008;**17**:877–86.
7. McCormick JB, Hammer RR, Farrell RM, *et al.* Experiences of patients with chronic gastrointestinal conditions: in their own words. *Health Qual Life Outcomes* 2012;**10**:25.
8. Casati J, Toner BB, de Rooy EC, Drossman DA, Maunder RG. Concerns of patients with inflammatory bowel disease: a review of emerging themes. *Dig Dis Sci* 2000;**45**:26–31.
9. Sajadinejad MS, Asgari K, Molavi H, Kalantari M, Adibi P. Psychological issues in inflammatory bowel disease: an overview. *Gastroenterol Res Pract* 2012;**2012**:106502.
10. Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies revisited: a systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. *Inflamm Bowel Dis* 2016;**22**:752–62.
11. Häuser W, Janke KH, Klump B, Hinz A. Anxiety and depression in patients with inflammatory bowel disease: comparisons with chronic liver disease patients and the general population. *Inflamm Bowel Dis* 2011;**17**:621–32.
12. Schreiber S, Panés J, Louis E, Holley D, Buch M, Paridaens K. Perception gaps between patients with ulcerative colitis and healthcare professionals: an online survey. *BMC Gastroenterol* 2012;**12**:108.
13. Rubin DT, Siegel CA, Kane SV, *et al.* Impact of ulcerative colitis from patients' and physicians' perspectives: results from the UC: NORMAL survey. *Inflamm Bowel Dis* 2009;**15**:581–8.
14. Ware JE Jr. Standards for validating health measures: definition and content. *J Chronic Dis* 1987;**40**:473–80.
15. Ware JE Jr, Kosinski M, Bjorner JB, *et al. User's Manual for the SF-36v2 Health Survey*. 2nd edn. Lincoln, RI: QualityMetric Inc.; 2007.
16. Ware JE, Snow KK, Kosinski M, *et al. SF-36 Health Survey Manual and Interpretation Guide*. Boston, MA: The Health Institute; 1993.
17. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey [SF-36]. I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–83.
18. Thalji L, Haggerty CC, Rubin R, *et al. 1990 National Survey of Functional Health Status: Final Report. National Opinion Research Center [NORC]*. Chicago, IL: National Opinion Research Center; 1991.
19. Ware JE Jr. SF-36 health survey update. *Spine* 2000;**25**:3130–9.
20. Maruish ME, editor. *User's Manual for the SF-36v2 Health Survey*, 3rd edn. Lincoln, RI: QualityMetric Inc.; 2011.
21. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9, W64.
22. Rohatgi A. *WebPlotDigitizer*. 3.9. 2015. http://arohatgi.info/WebPlotDigitizer/ Accessed April 21, 2016.
23. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;**10**:407–15.
24. Ahn JY, Lee KH, Choi CH, *et al.* Colonic mucosal immune activity in irritable bowel syndrome: comparison with healthy controls and patients with ulcerative colitis. *Dig Dis Sci* 2014;**59**:1001–11.
25. Ansari R, Attari F, Razjouyan H, *et al.* Ulcerative colitis and irritable bowel syndrome: relationships with quality of life. *Eur J Gastroenterol Hepatol* 2008;**20**:46–50.
26. Barratt SM, Leeds JS, Robinson K, *et al.* Reflux and irritable bowel syndrome are negative predictors of quality of life in coeliac disease and inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2011;**23**:159–65.
27. Barton JG, Paden MA, Lane M, Postier RG. Comparison of postoperative outcomes in ulcerative colitis and familial polyposis patients after ileoanal pouch operations. *Am J Surg* 2001;**182**:616–20.
28. 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.
29. Berndtsson IE, Lindholm E, Oresland T, Hultén L. Health-related quality of life and pouch function in continent ileostomy patients: a 30-year perspective. *Dis Colon Rectum* 2004;**47**:2131–7.
30. Berndtsson I, Lindholm E, Oresland T, Börjesson L. Long-term outcome after ileal pouch-anal anastomosis: function and health-related quality of life. *Dis Colon Rectum* 2007;**50**:1545–52.
31. Bernklev T, Jahnsen J, Lygren I, Henriksen M, Vatn M, Moum B. Health-related quality of life in patients with inflammatory bowel disease measured with the short form-36: psychometric assessments and a comparison with general population norms. *Inflamm Bowel Dis* 2005;**11**:909–18.
32. Camilleri-Brennan J, Steele RJ. Objective assessment of quality of life following panproctocolectomy and ileostomy for ulcerative colitis. *Ann R Coll Surg Engl* 2001;**83**:321–4.
33. Carmon E, Keidar A, Ravid A, Goldman G, Rabau M. The correlation between quality of life and functional outcome in ulcerative colitis patients after proctocolectomy ileal pouch anal anastomosis. *Colorectal Dis* 2003;**5**:228–32.
34. Heikens JT, de Vries J, Goos MR, Oostvogel HJ, Gooszen HG, van Laarhoven CJ. Quality of life and health status before and after ileal pouch-anal anastomosis for ulcerative colitis. *Br J Surg* 2012;**99**:263–9.
35. Heikens JT, de Vries J, de Jong DJ, *et al.* Evaluation of long-term function, complications, quality of life and health status after restorative proctocolectomy with ileo neo rectal and with ileal pouch anal anastomosis for ulcerative colitis. *Colorectal Dis* 2013;**15**:e323–9.
36. 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.
37. Huppertz-Hauss G, Lie Høivik M, Jelsness-Jørgensen LP, *et al.* Health-related quality of life in patients with inflammatory bowel disease 20 years after diagnosis: results from the IBSEN study. *Inflamm Bowel Dis* 2016;**22**:1679–87.
38. Iglesias-Rey M, Barreiro-de Acosta M, Caamaño-Isorna F, *et al.* Psychological factors are associated with changes in the health-related quality of life in inflammatory bowel disease. *Inflamm Bowel Dis* 2014;**20**:92–102.
39. Jelsness-Jørgensen LP, Bernklev T, Henriksen M, Torp R, Moum BA. Chronic fatigue is associated with impaired health-related quality of life in inflammatory bowel disease. *Aliment Pharmacol Ther* 2011;**33**:106–14.
40. Koerdt S, Jehle EC, Kreis ME, Kasparek MS. Quality of life after proctocolectomy and ileal pouch-anal anastomosis in patients with ulcerative colitis. *Int J Colorectal Dis* 2014;**29**:545–54.

41. Langhorst J, Mueller T, Luedtke R, *et al.* Effects of a comprehensive lifestyle modification program on quality-of-life in patients with ulcerative colitis: a twelve-month follow-up. *Scand J Gastroenterol* 2007;**42**:734–45.
42. McColl E, Han SW, Barton JR, Welfare MR. A comparison of the discriminatory power of the Inflammatory Bowel Disease Questionnaire and the SF-36 in people with ulcerative colitis. *Qual Life Res* 2004;**13**:805–11.
43. Meijs S, Gardenbroek TJ, Sprangers MA, *et al.* Health-related quality of life and disability in patients with ulcerative colitis and proctocolectomy with ileoanal pouch versus treatment with anti-TNF agents. *J Crohns Colitis* 2014;**8**:686–92.
44. Mokrowiecka A, Jurek K, Pińkowski D, Małecka-Panas E. The comparison of Health-Related Quality of Life [HRQL] in patients with GERD, peptic ulcer disease and ulcerative colitis. *Adv Med Sci* 2006;**51**:142–7.
45. Muir AJ, Edwards LJ, Sanders LL, *et al.* A prospective evaluation of health-related quality of life after ileal pouch anal anastomosis for ulcerative colitis. *Am J Gastroenterol* 2001;**96**:1480–5.
46. Nordin K, Påhlman L, Larsson K, Sundberg-Hjelm M, Lööf L. Health-related quality of life and psychological distress in a population-based sample of Swedish patients with inflammatory bowel disease. *Scand J Gastroenterol* 2002;**37**:450–7.
47. Pavlides M, Cleland J, Rahman M, *et al.* Outcomes after ileal pouch anal anastomosis in patients with primary sclerosing cholangitis. *J Crohns Colitis* 2014;**8**:662–70.
48. Richards DM, Hughes SA, Irving MH, Scott NA. Patient quality of life after successful restorative proctocolectomy is normal. *Colorectal Dis* 2001;**3**:223–6.
49. Røkke O, Iversen K, Olsen T, Ristesund SM, Eide GE, Turowski GE. Long-term followup with evaluation of the surgical and functional results of the ileal pouch reservoir in restorative proctocolectomy for ulcerative colitis. *ISRN Gastroenterol* 2011;**2011**:625842.
50. Davey Smith G, Watson R, Roger D, *et al.* Impact of a nurse-led counselling service on quality of life in patients with inflammatory bowel disease. *J Adv Nurs* 2002;**38**:152–60.
51. Therkelsen SP, Hetland G, Lyberg T, Lygren I, Johnson E. Effect of a medicinal Agaricus blazei Murill-Based mushroom extract, AndoSan™, on symptoms, fatigue and quality of life in patients with ulcerative colitis in a randomized single-blinded placebo controlled study. *PLoS One* 2016;**11**:e0150191.
52. Tiainen J, Matikainen M. Health-related quality of life after ileal J-pouch-anal anastomosis for ulcerative colitis: long-term results. *Scand J Gastroenterol* 1999;**34**:601–5.
53. Zhou Y, Ren W, Irvine EJ, Yang D. Assessing health-related quality of life in patients with inflammatory bowel disease in Zhejiang, China. *J Clin Nurs* 2010;**19**:79–88.
54. Yarlas A, Yen L, Hodgkins P. The relationship among multiple patient-reported outcomes measures for patients with ulcerative colitis receiving treatment with MMX ® formulated delayed-release mesalamine. *Qual Life Res* 2015;**24**:671–83.
55. D'Haens G, Sandborn WJ, Feagan BG, *et al.* A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007;**132**:763–86.
56. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;**317**:1625–9.
57. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut* 1998;**43**:29–32.
58. Ware J, Kosinski M, Keller S. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. 4th edn. Boston, MA: The Health Institute; 1994.
59. Alonso J, Regidor E, Barrio G, Prieto L, Rodríguez C, de la Fuente L. Population reference values of the Spanish version of the Health Questionnaire SF-36. *Med Clin [Barc]* 1998;**111**:410–6.
60. Sullivan M, Karlsson J, Ware JE Jr. The Swedish SF-36 Health Survey–I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. *Soc Sci Med* 1995;**41**:1349–58.
61. Loge JH, Kaasa S. Short form 36 [SF-36] health survey: normative data from the general Norwegian population. *Scand J Soc Med* 1998;**26**:250–8.
62. Jenkinson C, Coulter A, Wright L. Short form 36 [SF36] health survey questionnaire: normative data for adults of working age. *BMJ* 1993;**306**:1437–40.
63. Lewin-Epstein N, Sagiv-Schifter T, Shabtai EL, Shmueli A. Validation of the 36-item short-form Health Survey [Hebrew version] in the adult population of Israel. *Med Care* 1998;**36**:1361–70.
64. van der Zee KI, Sanderman R. *Het meten van de algemene gezondheidstoestand met de RAND-36: Een handleiding [Measuring the general health condition with the RAND-36: A manual]*. Groningen, The Netherlands: Noordelijk Centrum voor Gezondheidsvraagstukken, Rijksuniversiteit Groningen; 1993.
65. Rachmilewitz D. Coated mesalazine [5-aminosalicylic acid] versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989;**298**:82–6.
66. Bullinger M. German translation and psychometric testing of the SF-36 Health Survey: preliminary results from the IQOLA Project International Quality of Life Assessment. *Soc Sci Med* 1995;**41**:1359–66.
67. Lichtiger S, Present DH, Kornbluth A, *et al.* Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;**330**:1841–5.
68. Helzer JE, Stillings WA, Chammas S, Norland CC, Alpers DH. A controlled study of the association between ulcerative colitis and psychiatric diagnoses. *Dig Dis Sci* 1982;**27**:513–8.
69. Aalto A, Aro AR, Teperi J. *RAND 36 as a Measure of Health-related Quality of Life*. Helsinki: Stakes, Research Reports 101; 1999.
70. Li L, Wang HM, Shen Y. Chinese SF-36 Health Survey: translation, cultural adaptation, validation, and normalisation. *J Epidemiol Community Health* 2003;**57**:259–63.