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Review Article

Review Article

Placebo Effect on the Health-related Quality of Life of Inflammatory Bowel Disease Patients: A Systematic Review With Meta-analysis

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Abstract

Background and Aims: Placebo effect in health-related quality of life [HRQoL] of inflammatory bowel disease [IBD] patients has been poorly characterised. This systematic review and meta-analysis aimed to assess: i] mean improvements in IBDQ [Inflammatory Bowel Disease Questionnaire] and SF-36 [36-Item Short Form Health Survey] scores among placebo-treated IBD patients; and ii] the proportion of placebo-treated patients achieving IBDQ-defined response and remission and correspondent odds ratios [OR].

Methods: Literature search was performed using four databases. Mean differences and ORs were computed using the random-effects model. Univariate and multivariate regressions were performed to evaluate the weight of different factors on the placebo effect.

Results: From the 328 identified records 26 were included in the study, comprising 2842 placebo-treated IBD patients. Pooled mean differences on IBDQ following placebo administration were above the clinically meaningful improvement [≥16 points] in ulcerative colitis [UC] patients during the induction regimen (17.67; 95% confidence interval [CI]: 12.90, 22.44) and during maintenance in both Crohn's disease [CD] [27.60; 95% CI: 14.29, 40.91] and UC patients [27.50; 95% CI: 18.73, 36.27]. The treatment regimen was the only significant variable in multivariate analysis, with lower placebo-related IBDQ improvements during induction. Maintenance trials' inclusion criteria were also relevant. The proportions of placebo-treated patients achieving IBDQ-defined response and remission were 0.42 [95% CI: 0.49, 0.56] and 0.31 [95% CI: 0.28, 0.34], respectively, with 0.49 and 0.40 the ORs for response and remission. Significant improvements were also observed on SF-36 score.

Conclusions: Herein we prove that placebo effect on HRQoL is meaningful, providing insights about implications for clinical trials' design and interpretation and for IBD management.

Key Words: Health-related quality of life; inflammatory bowel disease; patient-reported outcomes; placebo

1. Introduction

Inflammatory bowel diseases, comprising ulcerative colitis [UC] and Crohn's disease [CD], are believed to be triggered by an aberrant chronic immune response to the gut microbiome, catalysed by environmental and genetic factors,[1,2] and are estimated to affect up to 0.5% of the general population in the Western World.[3]

The clinical course of the IBD is characterised by periods of relapse and remission and only a minority of patients experience a chronic, continuous disease course.[4,5] Medical approaches to bowel and non-bowel manifestations of IBD may be associated with side effects such as eye, bone, gastrointestinal, or liver dysfunction, as well as an overall impairment in the immune system with an increased risk of infections and autoimmune reactions.[6] In fact, both disease-related and therapy-related factors are known to induce a wide spectrum of physical, psychological, and social issues that impair IBD patients' quality of life.[4]

Most of the IBD-focused clinical studies conducted in recent decades aimed to assess the efficacy of disease-modifying drugs on outcomes such as disease activity, need for hospitalisation and/or surgery, and side effects.[7] However, the Food and Drugs Administration [FDA] and the European Medicines Agency [EMA] have recently attributed a pivotal role to health-related quality of life [HRQoL] measures, emphasising that these should be included in drug development clinical trials.[8,9] Indeed, assessing the HRQoL allows the performance of pharmacoeconomic analyses, which may be useful to guide future clinical decision making and health care policy.[10]

In the particular case of IBD, outcomes reported by patients in clinical trials are mostly focused on health-related quality of life [HRQoL], and are combined with data from the generic Short Form-36 questionnaire [SF-36] and a specific disease scale, such as the Inflammatory Bowel Disease Questionnaire [IBDQ].[7]

The placebo response is defined as the change that occurs in response to an inert or sham treatment used as a pharmacological control.[11] Even though the underlying mechanisms remain cryptic, the placebo response is thought to have a complex neurobiological basis, resulting from the interaction of expectation and conditioning.[12] Some authors consider that the influence of psychological health in gastrointestinal conditions stems from the brain-gut axis.[13] In what concerns IBD, two recent meta-analyses[12,14] have pointed out that the placebo intervention is associated with improvements in clinical outcomes [response and remission] in both induction and maintenance trials. The impact of placebo interventions in subjective IBD outcomes is expected to be greater than that observed in objective endpoints.[13] Still, and to our best knowledge, no studies have been published on the effect of placebo in IBDs' HRQoL.

This paper aims to systematically review the published evidence regarding the placebo effect in the HRQoL of IBD patients, as well as to understand which factors underlie such an effect. The specific objectives were to analyse the placebo-treated patients concerning: i] mean IBDQ and SF-36 scores before and following placebo administration; and ii] the proportion of patients achieving IBDQ-defined response and remission, as well as the odd ratios for these two outcomes [ORs] calculated for placebo versus all active interventions.

2. Materials and Methods

2.1. Search strategy

This study was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] Guidelines[15] and the Cochrane Collaboration Guidelines for reporting meta-analyses.[16]

Literature search included studies published until February 2018 using four electronic databases: PubMed [https://www.ncbi.nlm.nih.gov/pubmed/], Web of Science [http://www.isiwebofknowledge.com], Cochrane Central Register of Controlled Trials [http://www.cochranelibrary.com/], and Science Direct [www.sciencedirect.com]. The words or medical subject heading terms used were: ['placebo'] AND (['inflammatory bowel disease*'] OR ['colitis, ulcerative'] OR ['crohn's disease']) AND (['quality of life'] OR ['IBDQ'] OR ['SF-36'] OR ['inflammatory bowel disease questionnaire']). In order to ensure that all pertinent articles were included, the reference lists of the selected studies and previously published reviews were manually reviewed.

2.2. Eligibility criteria of randomised controlled trials

The following inclusion criteria were used: i] placebo-controlled randomised controlled trials [RCTs] assessing the effect of pharmacological interventions in HRQoL of adult patients with UC or CD; and ii] IBD diagnosis based on clinical, radiographic, endoscopic or histological criteria. The HRQoL scales considered in this study were the SF-36 and the IBDQ.

All studies that fulfilled at least one of the following conditions were excluded: i] systematic reviews, guidelines, comments, editorials, and letters; ii] studies involving patients with diseases other than CD and UC; iii] trials of probiotics, antibiotics, complementary therapies, or devices; and iv] articles written in languages other than English. No restriction in terms of publication dates was applied. Whenever full-text articles were unavailable, abstracts were included if considered critically relevant.

2.3. Study selection and data collection process

Two reviewers [MME and JA] carried out studies' screening and data extraction independently. Discrepancies were settled by consensus. Whenever the title and abstract clearly indicated that the study failed to meet the previously defined selection criteria, the report was immediately excluded from further analysis. The full text was analysed in all other studies.

The following information was collected from the selected studies: authors' name; publication year; cohorts' geographical origin; disease and severity; treatment regimen; duration of treatment and follow-up; number of patients enrolled in the intervention and placebo groups; concomitant therapies [medications allowed in the placebo arm]; dose and route of administration of the drugs being assessed; criteria used in the definition of clinical activity; scales used to assess HRQoL; HRQoL mean values at baseline and following placebo therapy according to IBDQ and SF-36; and the proportion of patients achieving remission and presenting the minimum clinically important difference according to the IBDQ.

The IBDQ scale was specifically designed to assess overall HRQoL in IBD patients and comprises data from four dimensions [bowel symptoms, systemic symptoms, social function, and emotional function]. The scores of this scale range from 32 to 224, with higher scores indicating better HRQoL. An increase of no less than 16 points was considered a clinically meaningful improvement [IBDQ response] and remission was defined as a total IBDQ score of ≥170 points.[17] The validity and reliability of this psychometrically validated instrument for measuring disease-specific HRQoL in patients with IBD have been previously established.[18] On the other hand, the SF-36 is a generic HRQoL comprising 36 items that are divided into two main domains (mental component summary [MCS] and physical component summary [PCS]) and eight subscales

[physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health].[19] The use of the SF-36 scale for the IBD context was also previously validated. However, fewer consensuses exist regarding the clinically meaningful differences for this HRQoL assessment scale. Having taken into account the variations and other authors' recommendations,[20,21] the range 3 to 5 points in SF-36 score was considered a clinical meaningful change.

2.4. Risk of bias assessment

Funnel plots were analysed to detect potential publication bias and/or presence of systematic heterogeneity. The asymmetry of funnel plots comprising: i] all studies; ii] studies published before 2008; and iii] published since 2008 was assessed using the Eggers Test.

Afterwards, the quality assessment tool [QATSDD] was applied to each study by two authors in an independent fashion. This tool comprises 16 items that are scored from 0 to 3, reflecting intelligibility in the description of aims and setting, data quality, methodology, and self-assessment of each study.[22] Of the 16 QATSDD criteria, 14 were used in this systematic review; the two excluded items concern qualitative studies only. The overall quality score was obtained by dividing each study's total score by the maximum possible score [42 points].

2.5. Statistical analysis

Data were evaluated using random-effects meta-analysis methodology, which assumes that the estimations of the different studies are not identical but similar and follow some distribution.[23] The I^2 was used to evaluate the trials' heterogeneity: values above 50% were considered to indicate a substantial level of heterogeneity.[23] The stability of the estimations and the weight of each study in the heterogeneity analysis were assessed through sensitivity analysis, omitting one study at a time in a stepwise fashion. Review Manager version 5.3 was used to generate the forest and funnel plots and to calculate mean differences and corresponding 95% CIs, in order to compare the change of HRQoL scores before and after treatment with placebo. This software was also used to obtain the pooled proportion of IBDQ-defined response or remission and 95% confidence intervals [CIs] for the studies in which those rates were provided, as well as to calculate the odds ratios [Ors] for response or remission [placebo versus all active interventions] following CochranMantelHaenszel statistics.

For mean differences in HRQoL scores, univariate linear regression models were used in order to evaluate the effect of different factors on placebo effect: i] publication year; ii] cohort's country of origin; iii] number of patients in the placebo arm; iv] type of IBD; v] treatment regimen [induction or maintenance]; vi] class of drug in the intervention arm; vii] route of administration; viii] percentage of women in the placebo arm; and ix] concomitant medication. The inclusion criteria of maintenance trials [previous clinical response only to the intervention versus response to intervention or placebo] were also evaluated through univariate linear regression models. In order to have a more thorough understanding of the factors influencing mean differences in HRQoL among placebo-treated patients, multivariate linear regression modelling was performed using the enter method. The studied variables were: i] number of patients receiving placebo; ii] treatment regimen; and iii] class of drug in the intervention arm. Such analyses were performed using the Software Statistical Package for the Social Sciences [SPSS] version 25.0 [IBM, Armonk, NY, USA]. All *p*-values were two-sided and had a 5% significance level.

3. Results

3.1. Bibliographic search and study selection

The selection strategy followed in this systematic review is summarised in Figure 1. The database search yielded 328 records of which 55 were immediately excluded: 53 for being duplicates and two that were not written in English. The remaining 273 studies were evaluated by title and abstract screening and 210 were excluded: 96 whose outcomes were not within the scope of this systematic review, 79 that were not RCTs, 24 that did not involve IBD patients, nine that focused on non-pharmacological therapies, and two that were consensus papers. A total of 63 papers were then considered for full text analyses, from which 37 were excluded: 26 whose outcomes were not within the scope of this systematic review, eight that did not disclose results concerning the placebo arm, and three that used scales other than the IBDQ and SF-36 for the HRQoL assessment. Overall, 26 studies matched our inclusion criteria [Table 1]. From these, 22 were used for IBDQ mean-difference analysis, seven were used for SF-36 mean-difference analysis, seven were used for the assessment of the proportion of patients with clinically meaningful improvement in IBDQ and its corresponding OR, and six were used to calculate the proportion of patients in the placebo arm who achieved IBDQ remission and the corresponding OR.

3.2. Description of studies

The main characteristics of the 26 studies included in this systematic review are described in Table 1. One can observe considerable variation concerning the year of publication [from 1995[24] to 2017[19]] and the cohorts' geographical origin: 10[17,19,24–31] studies enrolled patients from USA and/or Canada, 11[32–42] enrolled patients from several countries, three[43–45] enrolled patients from Japan, and two[46,47] enrolled European patients.

Regarding the IBD type, 15[24–26,28–30,33–35,37,38,41–44] of the selected RCTs addressed patients with CD, all of them with moderate to severe activity. The remaining 11[17,19,27,31,32,36,39,40,45–47] studies addressed patients with UC, most of them with moderate to severe disease [only two studies[31,47] addressed UC patients with mild disease activity]. The classification systems used for the patients' clinical evaluation were rather similar. Indeed, Crohn Disease Activity Index [CDAI] was used in all CD trials, whereas in nine[17,19,27,31,32,39,40,45] out of the 11 UC studies the researchers used the Mayo Scoring System.

Concerning the therapeutic regimens, 17[17,24,26,27,29–32,35,36,38,39,41,42,44,46,47] trials evaluated the induction stage, five[19,28,33,34,37] analysed the maintenance stage, and four studies assessed both.[25,40,43,45] The mean [± standard deviation] treatment duration was 8.70 ± 3.48 and 51.11 ± 9.43 weeks for induction and maintenance regimens, respectively.

Overall, 2842 patients receiving placebo were included in this systematic review: 54.5% of them were CD patients and 45.5% of them were UC patients. The number of patients in the placebo arm of each trial varied widely [ranging from 20[46] to 331[32]]. The drug in the intervention arm was a biologic therapy in 19 RCTs: adalimumab in four[34,40,43,45]; natalizumab in three[25,28,38]; infliximab in three[36,37,46]; certolizumab[33,35] and golimumab[39,48] in two; vedolizumab,[19] fontolizumab,[41] antibody targeting $\alpha_4\beta_7$ integrin,[30] keratinocyte growth factor-2[31] and recombinant IL-10[42] in one trial each. Corticosteroids were used in two[29,44] studies and tofacitinib,[17] rosiglitazone,[27] sargramostim,[26] and methotrexate[24] in the remaining four RCTs. In all but two[24,29] RCTs, patients were allowed to take concomitant medications which were, in most cases, aminosalicylates, immunosuppressants, or corticosteroids.

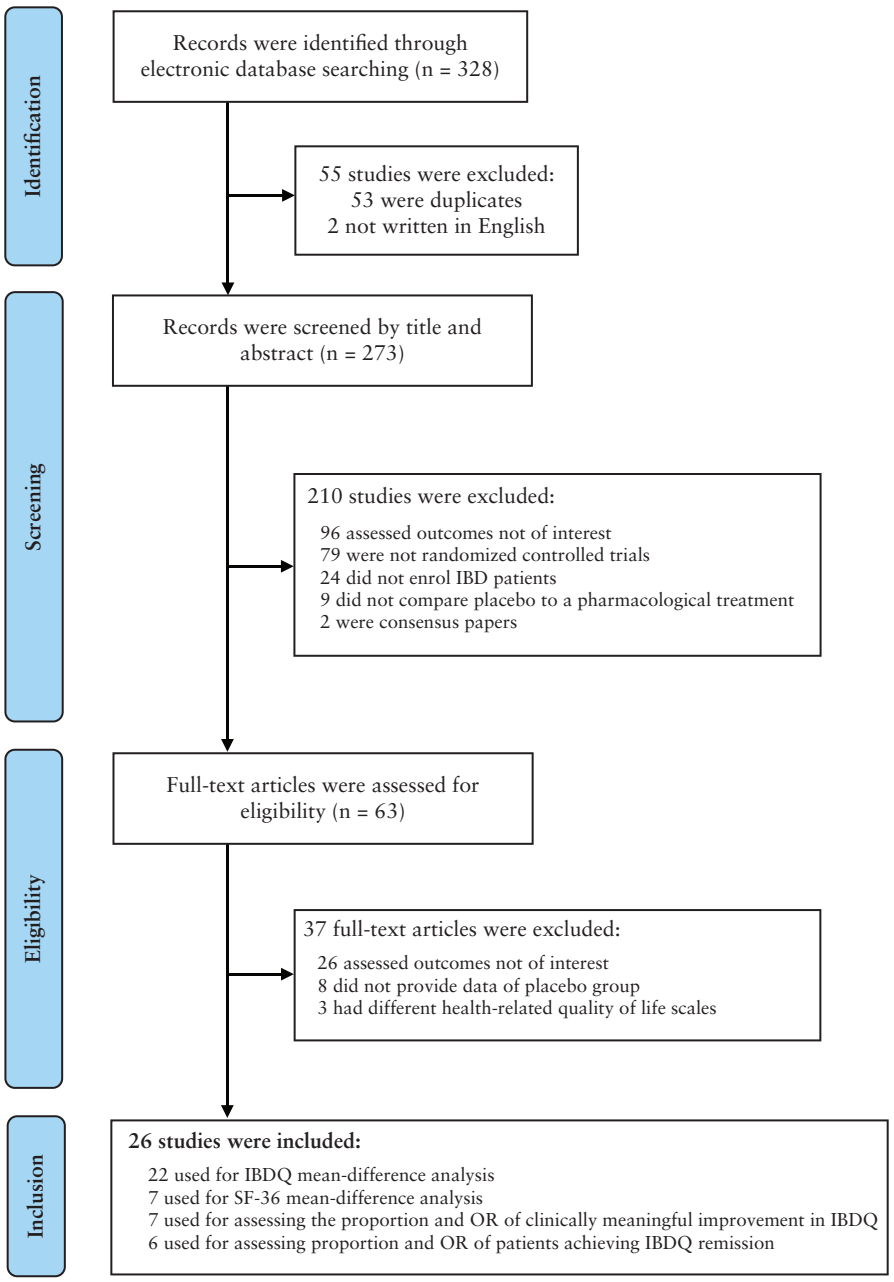

Figure 1. Flow diagram of studies selection and data collection process.

The scales used for assessing patients' HRQoL were roughly the same among all studies: all of them provided data on the IBDQ, 10[19,25,26,28,33,34,36,37,42,43] used the SF-36, four[26,28,33,34] applied the visual analogue scale [VAS], and three[19,28,33] used the European Quality of Life-5 Dimensions [EQ-5D]. Whereas the IBDQ scale was specifically designed to assess the overall HRQoL in IBD patients, the remaining three scales are generic HRQoL instruments that assess a wide range of dimensions and are applicable to several health states and conditions.[17]

The quality assessment tool [QATSDD] scores are listed in Table 1 as percentages of the maximum possible score. These quality scores ranged from 54.8%[29] to 88.1%,[32] yielding an average [± standard deviation] quality score of 75.4 ± 9.6%. The highest scores were obtained for the parameters 'explicit theoretical framework', 'clear description of research setting', and 'description of procedure for data collection', whereas the lowest scores were found for the parameters 'statistical assessment of reliability and validity of measurement tools' and 'strengths and limitations critically discussed'. Overall, the methodological quality was moderate to high, suggesting a low to moderate risk of biased results.

3.3. Mean differences on IBDQ scores

Data concerning the mean IBDQ differences before and after placebo administration were pooled from 22 RCTs. In general, the distribution of trials on the funnel plot was asymmetrical, according to the results obtained with the Eggers test [$p = 0.008$], suggesting the existence of publication bias. On the other hand, when the studies from the past decade are separated from those remaining, it is observed that asymmetry exists among the studies published before 2008 [$p = 0.017$] but not among those published since then

Table 1. Characteristics of the studies included in the systematic review

Study	Country	Disease	Treatment phase	Treatment duration	Population	Concomitant therapy	Intervention	HRQoL scale	Clinical evaluation	QAT score [%]
Feagan *et al.*, 2017	USA	UC Moderate to severe	Maintenance	52 weeks	Placebo arm: 126 patients [total *n* = 373]	Induction with 300 mg vedolizumab [IV]; immunosuppressants, CCT	Responders to vedolizumab: i] placebo; ii] vedolizumab 300 mg every 4 weeks or every 8 weeks	IBDQ SF-36 EQ-5D	Mayo Scoring System	83.33
Rutgeerts *et al.*, 2015	Several countries	UC Moderate to severe	Induction	6 weeks	Placebo arm: 70 patients [total *n* = 276]	Aminosalicylates, immunosuppressants, CCT	i] placebo; ii] golimumab [IV] doses 1, 2, or 4 mg/kg	IBDQ	Mayo Scoring System	78.57
Panés *et al.*, 2015	USA	UC Moderate to severe	Induction	8 weeks	Placebo arm: 48 patients [total *n* = 144]	Aminosalicylates, CCT	i] placebo; ii] tofacitinib 0.5, 3, 10, or 15 mg [oral]	IBDQ IBD-PRTI	Mayo Scoring System	73.81
Suzuki *et al.*, 2014	Japan	UC Moderate to severe	Induction Maintenance	8 weeks 52 weeks	Placebo arm: 96 patients [total *n* = 273]	Aminosalicylates, immunosuppressants, CCT	i] placebo; ii] adalimumab [SC] 160 mg at Week 0, 80 mg at Week 2, or 80 mg at Week 0, 40 mg at Week 2, followed by 40 mg every other week beginning at Week 4	IBDQ	Mayo Scoring System	85.71
Sandborn *et al.*, 2014	Several countries	UC Moderate to severe	Induction	6 weeks	Placebo arm: 331 patients [total *n* = 1064]	Aminosalicylates, immunosuppressants, CCT	i] placebo; ii] golimumab [SC] 100/50 mg, 200/100 mg, or 400/200 mg at Weeks 0 and 2	IBDQ	Mayo Scoring System	88.10
Sandborn *et al.*, 2012	Several countries	UC Moderate to severe	Induction Maintenance	8 weeks 52 weeks	Placebo arm: 246 patients [total *n* = 494]	Aminosalicylates, immunosuppressants, CCT	i] placebo; ii] adalimumab [SC] 160 mg [Week 0], 80 mg [Week 2], then 40 mg every other week	IBDQ	Mayo Scoring System	83.33
Suzuki et *al.*, 2013	Japan	CD Moderate to severe	Induction	8 weeks	Placebo arm: 22 patients [total *n* = 63]	Aminosalictylates; some cases enteral nutrition	i] placebo; ii] budesonide 9 mg or 15 mg [oral]	IBDQ	CDAI	69.05
Watanabe *et al.*, 2012	Japan	CD Moderate to severe	Induction	4 weeks	Placebo arm: 23 patients [total *n* = 90]	Aminosalicylates, immunosuppressants, CCT, enteral nutrition, anti-TNF [others than ADA]	i] placebo; ii] adalimumab 80/40 mg or 160/80 mg [SC] at Weeks 0 and 2	IBDQ SF-36	CDAI	76.19
			Maintenance	52 weeks	Placebo arm: 25 patients [total *n* = 50]		Responders to induction [placebo or adalimumab]: i] placebo; ii] adalimumab 40 mg [SC] every week			
Reinisch *et al.*, 2010	Several countries	CD Moderate to severe	Induction	16 weeks	Placebo arm: 40 patients [total *n* = 200]	Aminosalicylates, immunosuppressants, CCT	i] placebo; ii] fontolizumab 1.0 or 4.0 mg/kg [IV] on Days 1 and 29, followed by maintenance doses [0.1 or 1.0 mg/kg, SC] of fontolizumab every 4 weeks	IBDQ	CDAI	80.95
Dudley-Brown *et al.*, 2009	USA	CD Moderate to severe	Induction	12 weeks	Placebo arm: 250 patients [total *n* = 509]	Aminosalicylates, immunosuppressants, CCT, anti-TNF	i] placebo; ii] natalizumab 300 mg [IV] every 4 weeks	IBDQ SF-36	CDAI	88.10
			Maintenance	60 weeks	Placebo arm: 171 patients [total *n* = 339]		Responders to natalizumab: i] placebo; ii] natalizumab 300 mg [IV] every 4 weeks			

Table 1. *Continued*

Study	Country	Disease	Treatment phase	Treatment duration	Population	Concomitant therapy	Intervention	HRQoL scale	Clinical evaluation	QAT score [%]
Feagan *et al.*, 2009	Several countries	CD Moderate to severe	Maintenance	26 weeks	Placebo arm: 210 patients [total *n* = 425]	Induction with 400 mg certolizumab pegol [SC], aminosalicylates, immunosuppressants, CCT, anti-TNF	Responders to certolizumab: i] placebo; ii] certolizumab pegol 400 mg [SC] every 4 weeks	IBDQ SF-36 EQ-5D VAS	CDAI	85.71
Valentine *et al.*, 2009	USA and Canada	CD Moderate to severe	Induction	22 weeks	Placebo arm: 41 patients [total *n* = 87]	Aminosalicylates, immunosuppressants, CCT, anti-TNF	i] placebo; ii] sargramostim 6 mg/kg [SC] once a day	IBDQ SF-36 VAS	CDAI	71.43
Loftus *et al.*, 2008	Several countries	CD Moderate to severe	Maintenance	52 weeks	Placebo arm: 114 patients [total *n* = 383]	Induction treatment with adalimumab 80/40 mg [SC]; aminosalicylates, immunosuppressants, CCT	Responders to adalimumab: i] placebo; ii] adalimumab 40 mg [SC] every other week or weekly	IBDQ SF-36 VAS	CDAI	83.33
Lewis *et al.*, 2008	USA	UC Moderate to severe	Induction	12 weeks	Placebo arm: 53 patients [total *n* = 105]	Aminosalicylates, immunosuppressants, CCT	i] placebo; ii] rosiglitazone 4 mg orally twice daily	IBDQ	Mayo Scoring System	64.29
Rutgeerts *et al.*, 2008	Several countries	CD Moderate to severe	Induction	12 weeks	Placebo arm: 73 patients [total *n* = 292]	Aminosalicylates, immunosuppressants, CCT, anti-TNF	i] placebo; ii] certolizumab pegol [SC] 100, 200, or 400 mg	IBDQ	CDAI CRP	80.95
Feagan *et al.*, 2008	Canada	CD Moderate to severe	Induction	8 weeks	Placebo arm: 58 patients [total *n* = 185]	Aminosalicylates, antibiotics	i] placebo; ii] MLN0002 [humanised monoclonal antibody targeting $\alpha_4\beta_7$ integrin] 0.5 or 2.0 mg/kg [IV] on days 1 and 29	IBDQ	CDAI	69.05
Feagan *et al.*, 2007 A	USA and Canada	CD Moderate to severe	Maintenance	60 weeks	Placebo arm: 171 patients [total *n* = 339]	Induction with natalizumab 300 mg; aminosalicylates, immunosuppressants, CCT	Responders to natalizumab: i] placebo; ii] natalizumab 300 mg [IV] every 4 weeks	IBDQ SF-36 EQ-5D VAS	CDAI	85.71
Feagan *et al.*, 2007 B	Several countries	UC Moderate to severe	Induction	8 weeks	Placebo arm: 244 patients [total n = 728]	Aminosalicylates, immunosuppressants, CCT	i] placebo; ii] infliximab 5 or 10 mg/kg [IV], Weeks 0, 2, and 6	IBDQ SF-36	Mayo Scoring System	78.57
Zahn *et al.*, 2006	Germany	UC Mild, moderate or severe	Induction	12 weeks	Placebo arm: 30 patients [total *n* = 60]	No steroids and/or immunosuppressive agents within 3 months	i] placebo; ii] phosphatidylcholine	IBDQ	CAI EAI	61.90
Feagan *et al.*, 2003	Several countries	CD Moderate to severe	Maintenance	54 weeks	Placebo arm: 110 patients [total *n* = 335]	Infliximab [5 mg/kg at induction]; aminosalicylates, immunosuppressants, CCT	Responders to infliximab: i] placebo; ii] infliximab 5 or 10 mg/kg [IV], Weeks 0, 2, and 6	IBDQ SF-36	CDAI	69.05
Probert *et al.*, 2003	UK and Germany	UC Moderate to severe	Induction	6 weeks	Placebo arm: 20 patients [total *n* = 43]	Aminosalicylates, immunosuppressants, CCT	i] placebo; ii] infliximab 5 mg/kg at Week 0 and Week 2	IBDQ	UCCS Baron score CRP	78.57

Table 1. *Continued*

Study	Country	Disease	Treatment phase	Treatment duration	Population	Concomitant therapy	Intervention	HRQoL scale	Clinical evaluation	QAT score [%]
Sandborn *et al.*, 2003	USA	UC Mild to moderate	Induction	6 weeks	Placebo arm: 28 patients [total *n* = 88]	Aminosalicylates, immunosuppressants, CCT	i] placebo; ii] scaled doses [1, 5, 10, 25 or 50 μg/kg of repifermin [keratinocyte growth factor-2] on 5 consecutive days [IV]	IBDQ	Mayo Scoring System	73.81
Ghosh *et al.*, 2003	Several countries	CD Moderate to severe	Induction	6 weeks	Placebo arm: 63 patients [total *n* = 244]	Aminosalicylates, immunosuppressants, CCT	i] placebo; ii] one infusion of natalizumab 3 mg/kg [IV] followed by placebo; two infusions of natalizumab 3 mg/kg; or two infusions of natalizumab 6 mg/kg	IBDQ	CDAI	59.52
Schreiber *et al.*, 2000	Several countries	CD Moderate to severe	Induction	4 weeks	Placebo arm: 66 patients [total *n* = 329]	Aminosalicylates, immunosuppressants, CCT, metronidazole	i] placebo; ii] human recombinant IL-10 [1, 4, 8, and 20 μg/kg [SC] daily	IBDQ SF-36	CDAI	78.57
Irvine *et al.*, 2000	Canada	CD Moderate to severe	Induction	10 weeks	Placebo arm: 66 patients [total *n* = 258]	Not allowed	i] placebo; ii] oral budesonide [1.5 mg, 4.5 mg, or 7.5 mg] twice daily for 8 weeks, then 2 weeks at a lower dose [6.0 mg]	IBDQ	CDAI	54.76
Feagan *et al.*, 1995	USA and Canada	CD Moderate to severe	Induction	16 weeks	Placebo arm: 47 patients [total *n* = 141]	Not allowed	i] placebo; ii] 25 mg of methotrexate [IM] weekly	IBDQ	CDAI	57.14

Adalimumab [ADA]; Clinical Activity Index [CAI]; Endoscopic Activity Index [EAI]; corticosteroids [CTT]; Crohn's disease [CD]; Crohn's Disease Activity Index [CDAI]; European Quality of Life-5 Dimensions [EQ-5D]; Inflammatory Bowel Disease Patient-Reported Treatment Impact [IBD-PRTI]; Inflammatory Bowel Disease Questionnaire [IBDQ]; intramuscular [IM]; intravenous [IV]; Quality Assessment Tool [QAT]; 36-item Short Form health survey [SF-36]; subcutaneous [SC]; tumour necrosis factor [TNF]; ulcerative colitis [UC]; Ulcerative Colitis Clinical Score [UCSS]; C-reactive protein [CRP]; Visual Analogue Scale [VAS].

[p = 0.666; Supplementary Figure 1, available as Supplementary data at *ECCO-JCC* online].

Mean differences ranged from -4.00 [95% CI: -5.72, 2.28][24] to 45.30 [95% CI: 39.49, 51.11][33] and the pooled mean difference was 18.76 [95% CI: 11.52, 26.01; I^2 = 96, p < 0.001] [Supplementary Figure 2, available as Supplementary data at *ECCO-JCC* online]. The values obtained differed widely among studies and the sensitivity analysis did not reduce the heterogeneity. Considering that the rigour of IBD trials has increased considerably in recent decades, we decided to pool into two sub-group studies published more than 10 years ago [before 2008, n = 10] and those published since then [n = 12]. However, no significant differences were found [I^2 = 3.2, p = 0.310] [Supplementary Figure 2, available as Supplementary data at *ECCO-JCC* online].

To assess which factors were associated with this heterogeneity, univariate and multivariate analyses were carried out [Table 2]. The following factors were found to be significant on the univariate analysis: i] number of patients in the placebo arm using 100 as the cut-off [p = 0.021]; ii] treatment regimen [induction or maintenance; p = 0.002]; and iii] drug classes used in the intervention arm [biologic versus others, comprising the remaining six drug types; p = 0.050]. Significant estimates were also found for placebo-treated patients' concomitant medication [corticosteroids or immunosuppressants]. However, such information was available in a small number of studies [n = 14], making it difficult to include in multivariate models and precluding accurate interpretation. Therefore, multivariate analysis was performed, considering the factors found to be significant on univariate linear regression and whose data were available in 22 studies [number of patients in the placebo arm, treatment regimen, and interventions' drug class]. The only significant factor in multivariate analysis was the treatment regimen, with lower placebo-related IBDQ improvements in the induction phase [beta = -14.32; 95% CI: -28.15, -0.48; p = 0.043]. Trials were then stratified according to the treatment regimen: the pooled IBDQ mean differences before and after placebo administration were 14.90 [95% CI: 8.12, 21.68] during the induction and 27.66 [95% CI: 16.23, 39.09] during the maintenance phases of therapy, with significant heterogeneity being observed within the two groups [Supplementary Figure 3, available as Supplementary data at *ECCO-JCC* online]. Significant differences were registered regarding maintenance trials' inclusion criteria: patients who achieved previous clinical response only to the drug versus patients achieving response to either drug or placebo [beta = 30.16; 95% CI: 6.29, 54.03; p = 0.013].

Trials were further stratified according to IBD type, and four different settings were evaluated: i] CD patients in the induction therapeutic regimen; ii] UC patients in the induction regimen; iii] CD patients in the maintenance regimen; and iv] UC patients in the maintenance therapeutic regimen [Figure 2]. The pooled mean IBDQ differences concerning CD were 13.23 [95% CI: 4.47, 21.99] and 27.60 [95% CI: 14.29, 40.91] for induction and maintenance phases,

Table 2. Univariate and multivariate analyses of the factors contributing to IBDQ improvement following placebo administration.

	Univariate		Multivariate	
	beta [CI 95%]	***p*-Value**	**beta [CI 95%]**	***p*-Value**
Publication year				
<2008	-8.297 [-18.17, 1.58]	0.095		
>2008	Reference			
Country of origin				
Japan	Reference			
USA	12.83 [-13.74, 39.40]	0.324		
Europe	5.50 [-25.32, 36.42]	0.710		
Several countries	12.63 [-13.81, 39.07]	0.271		
Number of patients in the placebo arm				
<100	**-11.25 [-20.69, -1.88]**	**0.021**	0.77 [-12.27, 13.81]	0.903
>100	Reference			
Disease				
Crohn's disease	1.505 [-9.45, 12.470]	0.777		
Ulcerative colitis	Reference			
Treatment regimen				
Induction	**-15.70 [-25.04, -6.37]**	**0.002**	**-14.32 [-28.15, -0.48]**	**0.043**
Maintenance	Reference			
Class of drug				
Biologic	**12.43 [0.02, 24.84]**	**0.050**	8.04 [-3.71, 19.80]	0.168
Other	Reference			
Route of administration				
Parenteral	Reference			
Oral	0.115 [-18.26, 18.49]	0.990		
Sex of the patients in the placebo arm[a]				
Percentage of women	0.379 [-0.207, 0.965]	0.191		
Concomitant medication[a]				
Corticosteroids	**0.230 [0.070, 0.390]**	**0.008**		
Immunosuppressants	**0.358 [0.083, 0.632]**	**0.014**		
Aminosalicylates	0.051 [-0.142, 0.245]	0.579		

The bold entries marked the statistically significant values (p < 0.05).

IBDQ, Inflammatory Bowel Disease Questionnaire; CI, confidence interval.

[a]Information regarding placebo-treated patients was available in 20 studies; the percentages of patients receiving corticosteroids, immunosuppressants, and aminosalicylates was provided in 14, 16, and 14 trials, respectively.

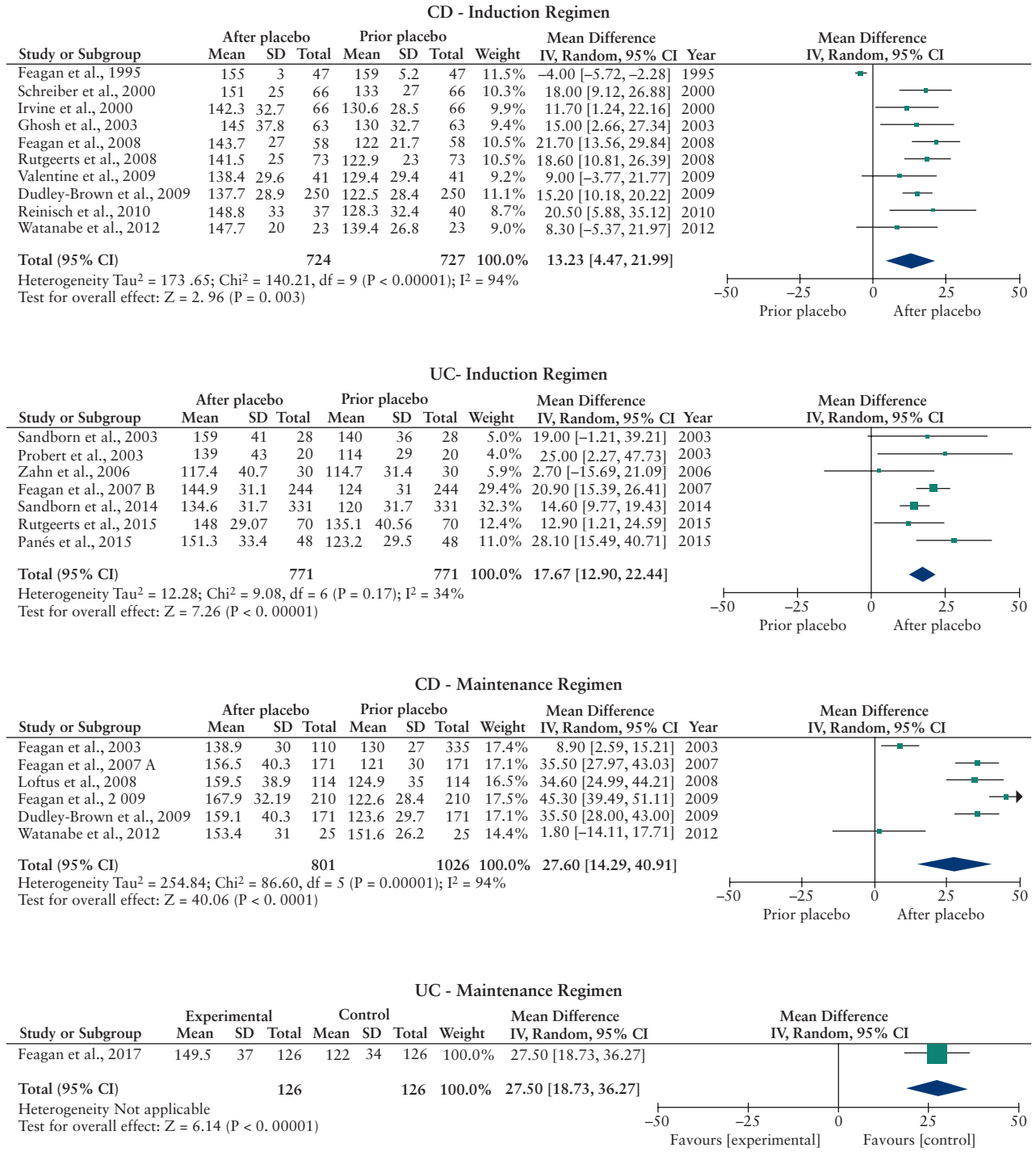

Figure 2. Mean differences and 95% confidence interval [CI] on Inflammatory Bowel Disease Questionnaire [IBDQ] scores before and after placebo administration [stratified by IBD type and therapeutic regimen].

respectively. Significant heterogeneity was observed amongst studies emphasising both CD treatment regimens: induction [I^2 = 94%; p < 0.001; n = 10] and maintenance [I^2 = 94%; p < 0.001; n = 6]. For UC, the pooled mean difference on IBDQ scores obtained for the seven studies assessing placebo effect on induction was 17.67 [95% CI: 12.90, 22.44] and no significant heterogeneity was found [I^2 = 34%; p = 0.17]. Regarding the maintenance regimen, a single trial was included addressing UC patients, and the mean IBDQ difference was 27.50 [95% CI: 18.73, 36.27].

3.3. Mean differences on SF-36 score

Even though data regarding SF-36 score were available in 10 trials, the values reported in three[19,26,43] of them were not complete enough to allow pooling mean differences before and after placebo administration. From the remaining seven studies, three assessed changes on SF-36 score of patients in the induction phase of the treatment [two with CD[25,42] and one with UC].[36] Considering the relatively low number of studies, these studies were stratified following the same

strategy used for IBDQ data [according to the type of IBD and therapeutic regimen]. The pooled mean differences obtained for the trials on the induction regimen of CD[25,42] were 8.39 [95% CI: 6.79, 9.99] for the mental component summary [MCS] and 3.03 [95% CI: 1.89, 4.18] for the physical component summary [PCS]. The mean differences obtained for the induction regimen of UC[36] were 5.00 [95% CI: 2.30, 7.70] for MCS and 6.00 [95% CI: 3.57, 8.43] for PCS.

Four studies[28,33,34,37] presented the SF-36 scores before and following placebo administration in the setting of the maintenance regimen of CD therapy, and the pooled mean differences were 6.84 [95% CI: 2.62, 11.06] and 6.65 [95% CI: 3.53, 9.78] for MCS and PCS, respectively [Figure 3]. Significant heterogeneity was observed between the four studies.

3.4. IBDQ response and remission

Information regarding the number of patients in the placebo arm who experienced a minimum clinically important difference on IBDQ score [IBDQ response defined as a ≥16-point increase from baseline] was retrieved from five[17,19,28,33,36] studies. The pooled proportion of patients with IBDQ response was 0.42 [95% CI: 0.34, 0.49] [Supplementary Figure 4, available as Supplementary data at *ECCO-JCC* online]. These proportions ranged from 0.13 [95% CI: 0.07, 0.21][45] to 0.65 [95% CI: 0.58, 0.72].[28] The global OR for achieving IBDQ response in the placebo-treated patients was 0.49 [95% CI: 0.42, 0.57], favouring the effect of intervention [Supplementary Figure 5, available as Supplementary data at *ECCO-JCC* online]. No heterogeneity was observed among these five RCTs [$I^2 = 4$; $p = 0.400$].

Information concerning the proportion of placebo-treated patients achieving IBDQ remission [defined as a total score ≥170 points] was retrieved from six[17,19,25,28,33,35] RCTs: the pooled proportion was 0.31 [95% CI: 0.28, 0.34] [Supplementary Figure 6, available as Supplementary data at *ECCO-JCC* online]. There were no significant differences between trials, which may be related to the considerable intra-study variability. The pooled OR for IBDQ remission among patients in the placebo arm was 0.40 [95% CI: 0.31, 0.53], once again favouring the intervention [Supplementary Figure 7, available as Supplementary data at *ECCO-JCC* online]. No significant heterogeneity was observed among the RCTs [$I^2 = 52$; $p = 0.060$].

4. Discussion

The placebo arm of RCTs allows controlling for placebo responses and other incidental factors including detection biases, natural waxing and waning of symptoms, and regression to the mean.[49,50] Even though placebos are designed to be inert and physiologically ineffective, recent evidence suggests that they may produce effects beyond those expected from diseases' natural history and clinical course,[12] precluding the detection of the intervention effects.[14] Recent studies[32,51] have highlighted an increase of placebo response rates in IBD trials conducted over the years, and the impact of placebo on objective clinical outcomes of IBD patients was recently analysed in detail.[12,14] However, even though greater changes are expected to occur in subjective outcomes, as far as the authors know there are no systematic data on the effect of placebo in health-related quality of life measures.

The results obtained for differences in IBDQ score following placebo administration were above the minimum clinically important difference [16 points] in three settings: maintenance therapeutic regimen of CD patients, and induction and maintenance therapeutic phases of UC patients. There was a trend towards higher improvement in IBDQ mean scores following placebo administration during maintenance regimen. Also, the maintenance regimen was the only significant factor in the multivariate analysis. This finding is important for future study design and sample size calculation, as some IBD RCTs are integrated trials that include both induction and maintenance regimens and a second randomisation following induction therapy.[52] These usually have an 'enrichment design', in which patients responding to placebo during induction are excluded from the maintenance period, and placebo non-responders are re-randomised to receive intervention or placebo.[53] Consequently, integrated trials

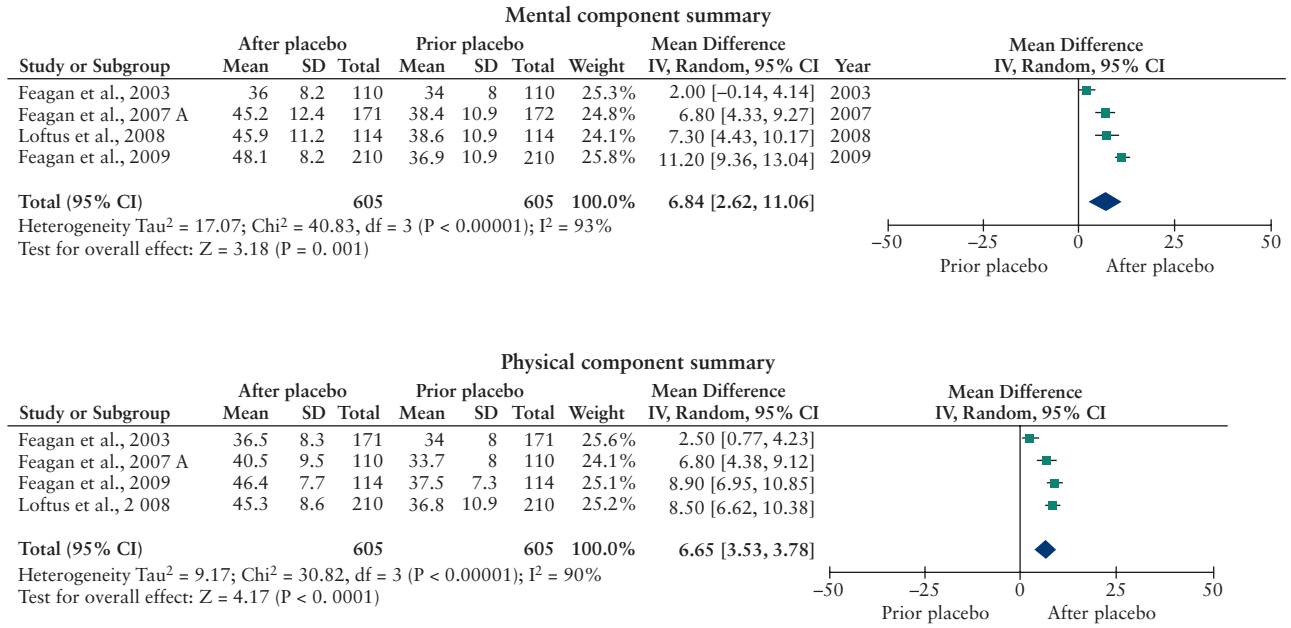

Figure 3. Mean differences and 95% confidence interval [CI] in 36-item Short Form health survey [SF-36] scores (mental component summary [MCS] and physical component summary [PCS]) before and after placebo administration in the maintenance regimen of Crohn's disease [CD] patients' therapy.

must include enough patients to ensure an adequate sample size for the maintenance regimen.

In order to explore the higher HRQoL improvement during the maintenance phase, the design of the trials was investigated. Six[19,25,28,33,34,37] of the seven studies just included patients with previous clinical response to pharmacological treatment during induction. The pooled mean difference on IBDQ for these trials differed from that reported on the single study that included patients that responded to either drug or placebo during the induction regimen. Even though the small number of studies hampers interpretation, this may suggest that the higher IBDQ values of placebo-treated patients during maintenance may be affected by a previous pharmacological response at induction which modulates both clinical course and patients' expectations.

The univariate analysis revealed that heterogeneity among trials could be related to the number of patients in placebo arm. Indeed, studies enrolling less than 100 placebo-treated patients systematically presented lower IBDQ mean difference values, suggesting that a small population size may not have the necessary power for detecting a minimally important effect.[54]

In addition, changes in IBDQ mean scores were statistically superior in the placebo arms of the trials assessing the effect of biologic therapies. This may be due to the higher patient expectations regarding the efficacy of biologic therapy, which may contribute to the placebo response.[11,55] Another factor that has to be underscored is that biologic trials were far more likely to allow concomitant medication [aminosalicylates, immunosuppressants, or steroids], which may contribute to the more robust placebo response in those trials. In fact, the univariate analysis suggested that those drugs could be factors influencing in a positive way the placebo effect in IBDQ scores, particularly corticosteroids and immunosuppressants. However, the reduced number of studies providing information on the percentage of placebo-treated patients receiving such medications hampers further interpretation.

It has been suggested that there is a trend towards higher placebo effect when the placebo is administered intravenously or subcutaneously rather than orally.[56] Significant differences for the variable 'route of administration' were not observed in our meta-analysis, which may be related to the fact that only two[17,29] trials assessed orally administered drugs.

Limited information was available regarding changes on SF-36 score following placebo administration. A difference of three to five points in SF-36 score, regarded as a meaningful change,[20,21] was observed in the pooled results of the trials assessing induction regimen of CD [for MCS scale], in the trial addressing the induction regimen of UC [for both MCS and PCS], and in the results pooled for the studies concerning the maintenance regimen of CD [MCS and PCS].

The pooled proportions of placebo-treated patients achieving IBDQ response and remission were 0.42 and 0.31, respectively. These values are higher than those available in the literature regarding clinical response and remission in UC[12] and CD[14,57] assessed using the Ulcerative Colitis Disease Activity Index, Mayo Activity Score, or Crohn's Disease Activity Index. Indeed, even though there is reasonable correlation between objective endpoint responses and HRQoL, some studies suggest that placebo effects are greater in patients' perception of their own improvement and self-rated measures, when compared with objective measures of disease activity.[58]

The ORs of placebo-treated patients for achieving response and remission according to the IBDQ were lower than 1, meaning that the interventions analysed in all included trials are superior when compared with placebo in what comes to improve HRQoL.

This study has some methodological limitations. First, there was significant heterogeneity among studies used for the mean differences analysis in what concerns induction and maintenance regimens of CD [both using IBDQ and SF-36 scales]. However, the exclusion of each study individually neither eliminated the heterogeneity nor changed considerably the pooled estimations. Yet, univariate analysis suggested that some factors might contribute to the high degree of heterogeneity, namely the number of patients in the placebo arm, the treatment regimen, and the type of drug used in the intervention. The variables used in the multivariate analysis were selected based on significance in the univariate regression. However, even though 'concomitant medication' was significant in the univariate analysis, it was not considered in the multivariate analysis since the number of studies reporting this variable was too small to include three study-level covariates in the model. The only significant factor influencing placebo-related IBDQ improvement in the multivariate analysis was the treatment regimen [maintenance versus induction]. Further investigation on heterogeneity would require access to individual participant data in order to compare subgroups within each trial and then combine these across trials.[59]

Second, as the number of studies providing information on the proportion of patients who achieved IBDQ response and/or remission was small, the data of patients with CD and UC in induction and maintenance regimens were pooled together.

Third, due to the limited availability of data and large variations in trials' characteristics, some factors that could theoretically influence placebo effect on HRQoL could not be assessed, namely age distribution of the patients included in the placebo arm, baseline disease activity, disease duration preceding trial inclusion, duration of follow-up, and number of follow-up visits. Other factors that might influence the response and remission in the placebo arm were the smoking habits, psychological factors [including optimism, suggestibility, empathy, and neuroticism] as well as the psychiatric background of patients.[60] The information available regarding those characteristics was scarce, precluding further evaluation.

In brief, this systematic review and meta-analysis demonstrated that there is a clinically meaningful improvement in IBDQ mean scores following placebo administration and a significant improvement in SF-36 scores during both induction and maintenance regimens. Also, the pooled proportions of patients achieving response and remission according to IBDQ were 42% and 31%, respectively. Our results demonstrate that the placebo effect on IBD patients' HRQoL cannot be discarded during the design and analysis of a clinical trial. Still, and as expected, the ORs obtained for placebo arm were significantly below the reference when compared with the intervention arm [0.49 and 0.40 for IBDQ response and remission, respectively].

Understanding the placebo effect on measures of patient-perceived benefit, particularly on HRQoL, is of paramount importance,[52] considering that regulatory authorities [the FDA and EMA] are in the process of redefining clinical trials' endpoints, and inclusion of patient-reported outcomes as co-primary endpoints is very likely.[12] However, even though restoring quality of life is a therapeutic objective, the potential utility of patient-reported outcomes in clinical practice is yet to be determined.

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Conflict of Interest

FM served as speaker and received honoraria from Merck Sharp & Dohme, Abbvie, Vifor, Falk, Laboratórios Vitória, Ferring, Hospira, and Biogen. The other authors have no conflict of interests to disclose.

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Author Contributions

MME and JAf were involved in data acquisition, analysis, and interpretation, and in manuscript drafting; IR, PL, ET, and LC helped with data interpretation and manuscript drafting; CCD coordinated the statistical analysis; FM was involved in study concept and design, data interpretation, and manuscript drafting. All authors read and approved the manuscript.

Supplementary Data

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

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