Original article

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Inflammatory bowel disease meta-evidence and its challenges: is it time to restructure surgical research?

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Abstract

Aim The aim of this study was to compare the methodological quality and input paper characteristics of systematic reviews and meta-analyses reported in the medical and surgical literature by performing a systematic 'overview of reviews'. Ulcerative colitis (UC) and Crohn's disease (CD) were used as the framework for this comparison as they are relatively common serious conditions, with both medical and surgical options for therapy.

Method Medline, Embase, CINHAL and the Cochrane Database were searched to November 2013. Eligible papers were systematic reviews or meta-analyses that considered a question of therapy in CD or UC. Two independent reviewers selected the papers, extracted the data and scored their methodology using the AMSTAR scoring system. The papers were categorized into medical therapy (M), surgical therapy (S) or medical and surgical therapy (MS) groups. Following retrieval of the sample of meta-evidence papers, the original input studies used in their creation were identified and a search of Medline, Embase, CINHAL and the Cochrane Database was performed. A team of researchers then examined the collection of papers for bibliographic and financial information.

Results Five hundred papers were identified in the meta-evidence search, of which 118 were deemed eligible. There was a difference in the AMSTAR-rated average quality of the papers between the S and M group (S 7.36 *vs* M 8.75, $P = 0.01$). On average S papers were published in journals with a lower impact factor (S 3.26, M 5.04, MS 5.30, $P < 0.001$). S papers also showed more heterogeneity (I^2; S 37%, M 24%, MS 10%, $P < 0.001$). Some 25% of S meta-analyses used data-sets with significant heterogeneity ($I^2 > 75\%$), compared with 8% of M meta-analyses and 3% of the MS meta-analyses. Some 5% of S papers were done on data sets that had I^2 values > 90%. There was no difference in the average number of papers assessed in each group, the average number of patients per meta-paper, the average time covered by the reviews, the average number of papers considered within each meta-analysis, or the average number of patients considered within each meta-analysis. Considering the conclusions of each meta-analysis, S meta-evidence was 50% more likely than M meta-evidence to be unable to make recommendations for practice. A total of 1499 original input papers were identified, of which 283 were used in more than one review. Within the non-repeated papers ($n = 1023$) the average impact factor within the S group was lower than that of the M and the MS groups (3.720 *vs* 11.230 *vs* 7.563, respectively; ANOVA $P < 0.001$). M papers had higher rates of pharmaceutical sponsorship than S papers (M 56% *vs* S 1%) and twice the level of government support (M 16% *vs* S 8%). Of note, 21% of M papers had corporate sponsorship but did not list any conflict of interest.

Conclusion Compared with M meta-analyses, S meta-analyses in the UC and CD domain are more likely to be of poorer methodological quality, are of a greater degree of heterogeneity and less often offer a positive conclusion. The papers used to generate meta-evidence in M papers have a greater degree of corporate and government sponsorship, and are more likely to come from journals with higher impact factors.

Keywords IBD, surgery, gastroenterology

What does this paper add to the literature?

To our knowledge this is the first side-by-side comparison of the quality and characteristics of medical and surgical Level 1 evidence. Our review quantifies a difference in the quality between these fields within the ulcerative colitis and Crohn's disease domains. Furthermore, our review reveals differences in the financial backing and journal impact factor of the studies that are used to compose meta-evidence in each discipline.

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Introduction

Despite success in the use of meta-evidence within medical disciplines, it has been difficult for the surgical specialties to harness their power. There are many reasons for this, including issues related to the researcher, patient, intervention and methodology [1]. In particular, the ethical and practical difficulties of performing adequately blinded, randomized control trials for surgical interventions [2], and the inherent heterogeneity of surgical treatments and surgeon skill [2], present large challenges to the meaningful meta review and analysis of surgical intervention data [3].

In 1996 Horton [4] highlighted the difficulties inherent in conducting original research in the surgical discipline. He asked: 'does surgical research have a future?'. Dixon *et al.* [5] continued this theme in 2005, when they assessed surgical meta-evidence. Of the surgical meta-analyses in their sample 75% had 'serious methodological flaws'. Since then, further systematic reviews of Level 1 evidence in surgery have reported little improvement [1].

While the problems with meta-evidence in the surgical field have been documented [1,3,5], there does not yet appear to have been a side-by-side comparison between medical and surgical meta-evidence. The aim of this study was to attempt to quantify any difference between them and, if present, to examine possible proximal causes.

Method

Search strategy

This study was achieved in two phases. In the first, an assessment of the methodological quality and characteristics of a sample of medical and surgical Level 1 evidence was made. In the second, the characteristics of the initial primary studies were extracted and compared.

Papers for the first phase were limited to systematic reviews or meta-analyses, as defined by the Cochrane Collaboration [6]. Ulcerative colitis (UC) and Crohn's disease (CD) were chosen as the framework for this study as they are relatively common serious conditions [7], with both medical and surgical options for therapy [8]. Papers with other inflammatory bowel diseases were not included. The list of medical therapies considered in this paper was derived from the recommendations of the American College of Gastroenterology Inflammatory Bowel Disease Taskforce, expert consultation and a review of medical literature [7,9,10]. The surgical therapies included were derived from ICD-9-CM procedure codes, along with expert consultation and review of the current surgical literature [8,11,12]. Use of the ICD-9-CM codes has been previously validated [13]. Only papers printed between 2006 and November 2013 were included in the assessment. Paediatric studies were excluded. The search was limited to publications in English. Due to the qualitative nature of the assessment, only full-length papers could be used. The outcome of any included paper was to be related to either medical induction of remission, or maintenance of quiescence in ulcerative colitis or Crohn's disease, or patient outcomes following surgical intervention for UC or Crohn's, including improvement in quality of life scores.

A thorough literature search was made of the electronic databases Medline and Embase via the Ovid interface, Cinahl via Ebsco, and the Cochrane Database of Systematic Reviews. In addition to the search terms identified in Appendix S1, a free search of Medline, Embase and Cinahl was completed using the keywords 'surgery', 'meta analysis' and either 'crohns' or 'ulcerative colitis'. Validated filters for systematic reviews and meta-analyses, specific to each of the databases, were then applied [14]. Following the compilation of the full sample of meta-evidence, we retrieved and examined each of their primary input studies. To be included, we required the article to be available in full and in English.

Data extraction and analysis

Two reviewers (JD and PL) examined the abstracts for the meta-evidence sample. Full text was obtained where abstracts were unable to provide enough information. Updated reviews were used preferentially. The catalogues of 14 university libraries were searched (see Appendix S1). Papers that were deemed suitable for inclusion were placed into one of three groups depending on their interventional focus: medical (M), surgical (S) or medical and surgical (MS). One hundred and eighteen papers were assessed as suitable for inclusion (M = 80, S = 28, MS = 10). A list of the 21 excluded papers, with justifications for exclusion, is given in Appendix S2.

The AMSTAR scoring system was used to assess methodological quality [15]. This consists of 11 individually scored criteria and is well established as a valid means of assessing meta-evidence [16]. AMSTAR is a 'checklist' type tool. A higher total AMSTAR score in a particular paper indicates a more reliable level of methodology [16]. JD and PL scored the papers. Interobserver agreement was assessed using kappa (κ). The following were also recorded: number of papers per review, number of patients included in each review, time span of the papers in years and impact factor of the journal in which the paper was published. The impact factor was retrieved from the Journal of Citation Reports [17]. Additionally, we recorded whether the recommendation of each paper was equivocal or unequivocal. For papers that included meta-analyses, the number of trials, number of patients and heterogeneity scores (I^2) for each were also recorded. Where this information was not obvious the raw data were sought.

All collected data were collated into a Microsoft Excel spreadsheet for statistical analysis [18], which was performed using StatPlus [19]. The information was analysed as unpaired parametric data using one-way ANOVA calculation, with Bonferroni-corrected *post-hoc* two-tailed *t*-test analysis, where indicated. The primary input studies were then identified and retrieved, creating a second sample of papers for analysis. A paper was deemed to be 'unfound' according to the same criteria as previously listed. A total of 1553 primary input papers were identified. Twenty-six could be found in abstract only, 23 could not be found in English and five could not be found. A total of 1499 papers were reviewed. Within this sample the following characteristics were identified: paper title, authors, number of authors, number of patients, year of publication, journal title and impact factor. We also assessed whether the paper listed any financial sponsorship or support and whether any conflict of interest was explicitly declared.

Bibliographic information was retrieved directly from the paper or from abstract information. Financial sponsorship was determined through the listing of acknowledgement of support for a study, financial or otherwise, and through author affiliations.

Results

We identified 500 meta-evidence papers from our initial search. Of these 139 papers were isolated for full-text review based on titles and abstracts. Twenty-one of these were excluded [7,20–43] ($\kappa = 0.920$, 95% CI 0.832–1.000). The 118 included papers [9,10,44–155] covering 193 256 patients were allocated to one of three categories depending on their speciality focus: M (80 papers, 135 375 patients), S (28 papers, 36 521 patients) or MS (10 papers, 24 823 patients). The trial flow diagram representing the inclusion and exclusion process is shown in Fig. 1.

AMSTAR score

Overall quality and the performance of each individual group within the 11 AMSTAR questions are shown in Table 1 ($\kappa = 0.553$, 95% CI 0.422–0.684). A difference was found between the M and S groups (8.75 *vs* 7.36, 95% CI 0.35–2.44, $P = 0.01$). AMSTAR scores of MS *vs* S (8.10 *vs* 7.36, 95% CI −0.97 to 2.46, $P = 0.385$) and M *vs* MS groups (8.75 *vs* 8.10, 95% CI −0.99 to 2.29, $P = 0.432$) were not different (Fig. 2). When plotted over time, the AMSTAR-rated methodological quality improved more consistently in the medical ($r = 0.69$) than in the surgical ($r = 0.32$) literature.

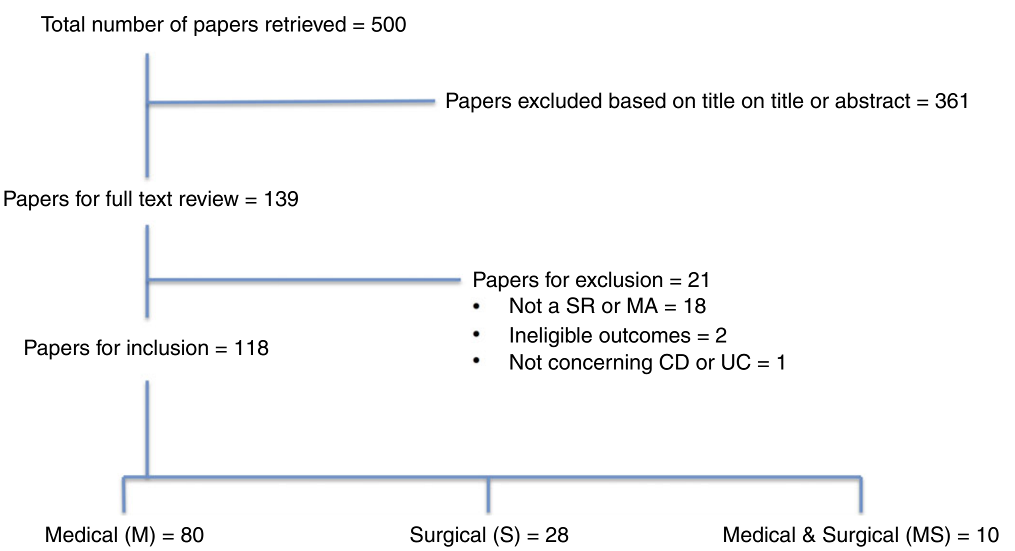

Figure 1 Trials flow diagram (SR, systematic review; MA, meta-analysis).

Table 1 AMSTAR scores.

Question	Surgical (n = 28)	Medical (n = 80)	Medical and surgical (n = 10)	Overall (n = 118)
Was an 'a priori' design provided?	100%	100%	100%	100%
Was there duplicate study selection and data extraction?	89%	80%	67%	82%
Was a comprehensive literature search performed?	93%	88%	89%	91%
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	21%	68%	44%	56%
Was a list of studies (included and excluded) provided?	36%	48%	33%	44%
Were the characteristics of the included studies provided?	100%	99%	100%	99%
Was the scientific quality of the included studies assessed and documented?	64%	76%	67%	74%
Was the scientific quality of the included studies used appropriately in formulating conclusions?	50%	75%	67%	69%
Were the methods used to combine the findings of studies appropriate?	100%	95%	100%	96%
Was the likelihood of publication bias assessed?	36%	66%	67%	61%
Was the conflict of interest included?	46%	81%	78%	72%
Mean AMSTAR score	7.36 (SD 2.23)	8.75 (SD 2.46)	8.10 (SD 2.47)	8.36 (SD 1.86)

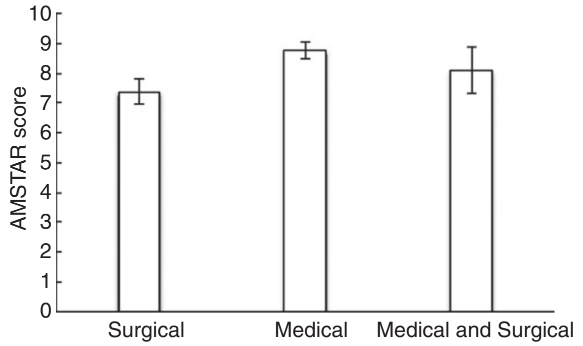

Figure 2 AMSTAR score for included papers (error bars = SEM).

Characteristics of meta-evidence papers

The characteristics of the meta-evidence papers are given in Table 2. There was a difference between the impact factor of journals for M *vs* S (5.042 *vs* 3.265, 95% CI 0.901–2.65, $P < 0.001$) and MS *vs* S (5.296 *vs* 3.265, 95% CI 0.85–3.25, $P = 0.001$), as seen in Fig. 3. There was no difference between the MS *vs* M groups (5.042 *vs* 5.296, 95% CI −1.12 to 1.67, $P = 0.72$). There was a weak to moderate correlation between the impact factor of a journal and the AMSTAR score of its paper ($r = 0.484$). There was also a difference in the heterogeneity score I^2 between the S (37%), M (24%) and MS (10%) groups (ANOVA, $P < 0.001$) as demonstrated in Fig. 4.

Sixteen (57%) of 28 papers in the S group gave unequivocal advice. Twelve were unable to make confident conclusions. In contrast 66 (82%) of 80 M papers were unequivocal (53 positive, 13 negative) and 14 were inconclusive. In the MS group, seven papers were conclusive (78%, all positive) and two were inconclusive. Fisher's exact test showed a difference between the S and M groups ($P = 0.01$).

Characteristics of primary input papers

Of the 1499 papers retrieved, 283 were used more than once, creating 476 repeated papers and 1023 unique papers. The unique papers were divided into

Table 2 Meta-evidence characteristics.

Meta-evidence characteristics	I^2	Impact factor	No. of papers	No. of patients	Time span (years)	Papers per MA	Patients per MA
M group (n = 80)	24% (28%)	5.042 (2.125)	12.33 (10.84)	1735 (1989)	15.1 (12.0)	5 (11.06)	689 (727.33)
S group (n = 28)	37% (33%)	3.265 (1.639)	15.5 (12.19)	1304 (1257)	16.1 (8.6)	5.7 (2.73)	632 (643.47)
MS group (n = 10)	10% (20%)	5.296 (1.405)	15.2 (9.76)	2575 (2335)	14.4 (7.83)	3.77 (2.15)	473 (482.59)
ANOVA P $\alpha < 0.01667$	$P < 0.001$	$P < 0.001$	$P = 0.3815$	$P = 0.2$	$P = 0.9$	$P = 0.4490$	$P = 0.1162$

MA, meta-analysis.
Values are means, values in brackets are ±SD.
$\alpha = 0.05/3$ (i.e. bonferroni correction).

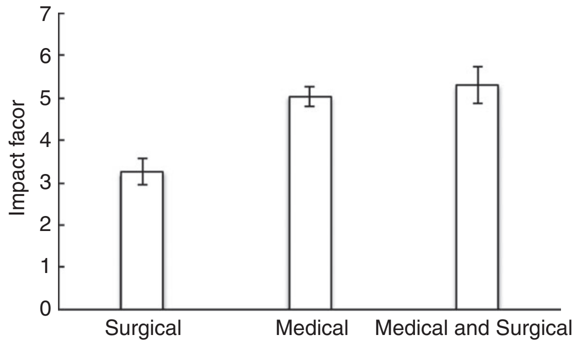

Figure 3 Impact factor of included papers (error bars = SEM).

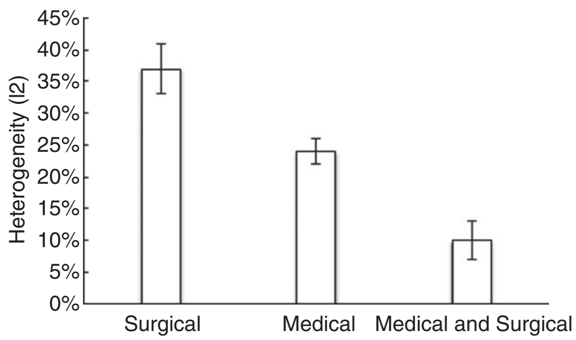

Figure 4 Heterogeneity (I^2) for included papers (error bars = SEM).

M, S and MS groups as in the first phase of this study. The impact factors of the M *vs* S groups were different (11.219 *vs* 3.720, 95% CI 6.263–7.499, $P < 0.001$), the M *vs* MS groups (11.219 *vs* 7.563, 95% CI 1.578–5.735, $P < 0.001$) and the MS *vs* S group (7.563 *vs* S 3.720, 95% CI 3.088–4.597, $P < 0.001$), giving S papers the lowest mean impact score by a factor of 2 to 3. Financial information for the non-duplicate sample is shown in Table 3. In this sample, a conflict of interest was listed in 35% of M papers, 2% of S papers and 12% of MS papers.

Discussion

AMSTAR score

When considering all of the meta-evidence reviewed by this paper, the overall quality was within the 'reasonable' classification. Three improvements may be incorporated to improve quality and validity in Level 1 evidence across the disciplines. First, an investigation of the grey literature is advised. This was completed in only just over half of our sample and notably in just a fifth of S papers. A review of dissertations, conference proceedings or trial registries provides the reviewer with the most up-to-date information and helps minimize exposure to publication bias [156,157]. Secondly, it is recommended that reviews provide a list of excluded papers, along with the list of included ones. A web link to the excluded studies would achieve this. Fewer than half of the papers we reviewed provided a list of excluded studies, limiting the ability of the reader to assess validity and concurrence [6]. Thirdly, we would suggest that a declaration of conflict of interest be included with every publication. In our sample, more than a third of papers did not include this information. Declarations of conflicts of interest provide a clear avenue for authors to communicate any potential sources of funding bias. If there is no conflict, that information is in itself a valuable feature of the paper. Additionally, the inclusion of an assessment of the quality of papers would increase validity in future meta-evidence. In derivative evidence, the distance between the reader and the original source material means transparency is paramount.

AMSTAR scoring within the M group revealed comparative strengths in the use of grey literature, assessment of publication bias and assessment of scientific quality of input material. Compared with surgical Level 1 evidence, there was a difference in overall

Table 3 Financial information in the studies.

Financial support	Pharma co.	Other co.	Government	Charity	University
M group	56%	5%	16%	5%	16%
S group	1%	12%	8%	1%	22%
MS group	14%	6%	22%	6%	49%

methodological quality, with implications for the relative validity of meta-analyses and systematic reviews in current surgical literature. The MS group provides an interesting comparison, where the influence of the medical discipline may be seen on surgical meta-evidence and vice versa. There was no statistically significant difference in the AMSTAR-rated quality of this group when compared with the S group or with the M group. The difference in the temporal trend of AMSTAR-quality M and S meta-evidence suggests that, despite papers detailing methodological weaknesses [1,3,5] and the wide distribution of guidelines and best-practice checklists [15,158], qualitative improvements within the surgical meta-evidence field is slow. The onus remains on the authors, reviewers and editors of papers within the surgical field to work towards continual improvement in the quality of the meta-evidence they produce.

Meta-evidence paper characteristics

According to our research, surgical systematic reviews and meta-analyses within the UC and CD domain are more likely to be published in a journal with a lower impact factor than their medical counterparts. In Australia and the UK, impact factors are linked to government funding. We wonder whether this may create a potential for a financial disadvantage against surgical evidence. Further research into the connection between funding and quality within surgical meta-evidence would help guide this consideration. The average heterogeneity of Level 1 evidence within the S group of this sample was greater than that seen in either the M or MS groups. Higgins *et al.* [159] advised caution in interpreting meta-analyses done on data sets with I^2 results above 75%, indicating a large degree of relevant heterogeneity. A quarter of S meta-analyses within this study were done on such data. This compared with 8% of M meta-analyses and only 3% within the MS group. Five per cent of surgical meta-evidence was based on data sets where the I^2 value was > 90%. In our sample, surgical meta-evidence was over 50% more likely than medical meta-evidence to deliver a paper that was unable to make any meaningful recommendations for practice.

Primary input paper characteristics

In our sample we found a lower level of non-pharmaceutical sponsorship for surgical than medical research. Along with a higher rate of trade sponsorship, M papers were twice as likely as S papers to have received government sponsorship. Additionally, a paper that examined medical and surgical therapies together (i.e. MS papers) was more than twice as likely to receive university support, and three times as likely to have received government sponsorship. It is interesting to note that only 35% of M papers declared an explicit conflict of interest. This is despite 56% of papers having made allusions to some form of corporate sponsorship; 21% of M papers in our sample had corporate sponsorship but were reticent to explicitly list a conflict of interest. Our survey has also revealed differences in the impact factors of the journals in which the original studies were published. This is in keeping with the differences found in our meta-evidence sample. This finding supports the suggestion that the premier academic status afforded to medical meta-evidence may not translate as readily into surgical meta-evidence. It may also go some way to explaining the funding discrepancy between the disciplines.

Strengths and limitations

The strengths of this 'overview-of-reviews' are the large sample of papers, the use of dual independent reviewers in the first phase of the study and the validity of AMSTAR as a quality assessment tool [16]. The methods used in searches and data retrieval have been clearly outlined, with explicit inclusion and exclusion criteria.

The limitations of the study include the inability of AMSTAR to discriminate between poor methodological quality of a study and poor reporting quality within the paper (internal validity). The use of IBD as a framework may introduce selection bias. The limitation of the study selection to English articles only introduces the possibility of language bias. We were unable to perform dual-independent data extraction on the primary input papers and thus there may be bias inherent in these findings.

Our research shows that a reader can expect, on average, surgical meta-evidence in the UC or CD domain to be more heterogeneous and of poorer quality than a study that incorporates a medical therapy, and it will less often offer a firm conclusion. Furthermore, our research has demonstrated large differences in the impact factor of meta-evidence being published in surgical and medical literature, and in the impact factor and financial backing of the original trials used to make that meta-evidence. The findings of this study suggest that, in its current form, surgical meta-evidence in IBD does not have the same utility as medical meta-evidence and caution should be used when applying its findings to inform practice and guide the advancement of the discipline.

We wonder about the effect that funding has on the methodological quality of surgical meta-evidence. Further inquiry may illuminate questions raised from this study. In particular, a methodological quality assessment of the primary input studies of surgical and medical meta-literature may provide more insight into the relative merits of the two. Additionally, an investigation into the relative methodological strengths of surgical meta-evidence on a broader sample base may be useful to confirm or deny the conclusions of this study. Lastly, an exploration on the links between funding and methodological quality within the surgical field would add context to this debate.

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Author contributions

Study conception and design: A. Engel, J. Delaney. Acquisition of data: J. Delaney, P. Laws, phase-two research team. Analysis and interpretation of data: J. Delaney, A. Engel, P. Wille-Jørgensen. Writing and editing manuscript: J. Delaney, P. Wille-Jørgensen, A. Engel.

Conflicts of interest

Potential conflict of interest; none

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Appendix S1. Search terms.
Appendix S2. Excluded papers.
Appendix S3. Characteristics of included papers.