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**TITLE PAGE**

**Title:** Systematic Review with Meta-analysis: The Effect of Tobacco Smoking on the Natural History of Ulcerative Colitis.

**Short "running" title:** Effects of Tobacco Smoking on Ulcerative Colitis.

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**Abbreviations:**

| | |
|---|---|
| CI | confidence interval |
| IPAA | ileal pouch-anal anastomosis |
| IBD | inflammatory bowel disease |
| MeSH | medical subject headings |
| OR | odds ratio |
| UC | ulcerative colitis |

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**ABSTRACT**

**Background:** Tobacco smoking is associated with a reduced risk of developing ulcerative colitis (UC). A high proportion of UC patients perceive a benefit in disease outcomes secondary to smoking. However, the effects of smoking on the natural history of UC are uncertain.

**Aim:** To conduct a systematic review and meta-analysis of the effects of tobacco smoking on the natural history of UC.

**Methods:** A search of MEDLINE, EMBASE and EMBASE classic was carried out (up to December 2015) to identify observational studies reporting data on smoking and rates of colectomy, flare of disease activity, proximal disease extension, and development of pouchitis following panproctocolectomy and ileal pouch-anal anastomosis in patients with UC. Dichotomous data were pooled to obtain odds ratios (ORs), with 95% confidence intervals (CIs).

**Results:** The search identified 16 eligible studies: five (2615 patients) studying colectomy; four (620 patients) reporting on flare of disease activity; four (687 patients) examining proximal disease extension; and three (355 patients) assessing development of pouchitis. Compared with non-smokers, the odds of colectomy (OR = 0.89; 95% CI 0.62-1.26), flare of disease activity (OR = 1.26; 95% CI 0.65-2.44), proximal extension of disease (OR = 0.57; 95% CI 0.20-1.66), or the development of pouchitis (OR = 0.57; 95% CI 0.21-1.53) were not significantly lower in smokers.

**Conclusions:** Smoking may not improve the natural history of UC. Given the health benefits of smoking cessation and the lack of clear benefit in UC, smoking cessation advice should be incorporated into guidance on the management of UC.

## INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD), of chronic relapsing remitting nature. It is characterized by superficial, diffuse, and continuous inflammation of the rectum, and can extend proximally to the colon to a variable extent. (1) The incidence of UC is 1.2 to 20.3 cases per 100,000 per year, and is highest in developed countries in Northern Europe and North America. (2) The disease usually starts in young adulthood, and can have a high economic cost. A systematic review estimated an annual per patient cost of between $6,217 and $11,377 in the United States. (3)

The pathophysiology of UC remains uncertain. Research focusing on an immunological etiology has found that altered immune responses result in the generation of pro-inflammatory cytokines. (4) Others have found that patients with UC have an imbalance between their enteric bacteria and host immune system. (5) Genetics may also contribute to the pathogenesis of UC, with multiple risk loci now reported in association with the disease. (6)

Since the 1980s, it has been well established that tobacco smokers are less likely to develop UC than non-smokers. (7) A systematic review and meta-analysis of studies examining the relationship between tobacco smoking and the development of UC found that non-smokers had a nearly three-fold increased odds of developing the disease. (8) However, evidence for the role of tobacco smoking in the clinical course of UC is less definitive, with conflicting evidence as to whether this influences the likelihood of needing surgery, rates of relapse of disease activity, (9-14) proximal extension of disease location, or the development of pouchitis in patients having undergone panproctocolectomy and ileal pouch-anal anastomosis (IPAA) for acute severe or chronic refractory disease. (15, 16)

We have therefore conducted a systematic review and meta-analysis to examine the effect of tobacco smoking on the clinical course of UC. If tobacco smoking does lead to a

less complicated disease course in UC, then this may provide the impetus for researchers to investigate the components of tobacco that are beneficial in UC. However, if there is no effect of tobacco smoking on the natural history of UC, then healthcare professionals can be confident in encouraging smoking cessation in patients with UC, due to the multiple other health benefits provided by quitting smoking.

## METHODS

### Search Strategy and Study Selection

A literature search of MEDLINE, EMBASE and EMBASE Classic (from 1947 to December 2015) was carried out to identify observational studies with longitudinal follow-up studying the effects of smoking on the natural history of UC. Eligible studies had to include ≥50 unselected adult patients (≥16 years of age) with UC, and report data on the effect of smoking status at study entry and subsequent need for any surgery, flare of disease activity (defined as the presence of active disease at endoscopy, elevation in clinical disease activity indices, or by physician's global assessment), proximal disease extension (defined as the extension of proctitis to left-sided colitis or extensive disease, or the extension of left-sided colitis to extensive disease), or the development of pouchitis following panproctocolectomy and IPAA. Prospective studies, or retrospective studies analysing prospectively collected data, were included. The diagnosis of UC had to be confirmed using histology, radiology, or endoscopic methods. Cases of inflammatory bowel disease unclassified (IBD-U) were excluded. These eligibility criteria were defined prospectively and are summarised in Table 1.

The literature search was performed using the words: ulcerative colitis, inflammatory bowel disease, colitis, or pouchitis (both as a medical subject heading (MeSH) and free text term). These terms were combined using the set operator AND with: tobacco, tobacco products, or smoking (both as a medical subject heading (MeSH) and free text term), cigarettes, or smoker* (as free text terms). There were no language restrictions applied to the search and any foreign articles were translated. All titles and abstracts identified by the search were assessed for inclusion, and a recursive search of the bibliographies of selected articles was carried out. Two investigators judged eligibility on the selected articles independently,

and a third investigator resolved any disagreements that emerged.

**Data Extraction**

Data extraction was carried out by two investigators, independently, using a Microsoft excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, US). Data extracted included total number of patients with ulcerative colitis who were current smokers, ex-smokers, or non-smokers, and the numbers in each group that required surgery, had a flare of disease activity, experienced proximal extension of their disease location, or developed pouchitis. A third investigator resolved any disagreements in data extraction. Additional information collected included country of origin, number of participating centers, type of setting (primary, secondary, or tertiary care), type of study (prospective, or retrospective analysis of prospectively collected data), outcomes assessed, whether patients were consecutively recruited, total sample size, mean age of included individuals, and proportion of males. The quality of each study was then assessed using the Newcastle-Ottawa scale, (17) and scored from a possible total of 9, with higher scores indicating higher quality.

**Data Synthesis and Statistical Analysis**

The degree of agreement between the two investigators, in terms of judging study eligibility, was measured using a Kappa statistic. Data in the studies identified were analysed according to the reported outcomes of interest, including need for surgery, flare of disease activity, proximal disease extension, or development of pouchitis. The proportions of patients with each of these outcomes of interest were compared between current smokers, ex-smokers (where reported), and non-smokers using an odds ratio (OR) with a 95% confidence interval (CI). Heterogeneity between studies was assessed using the $I^2$ statistic with a cut off of 50%,

(18) and the $\chi^2$ test with a P value <0.10, as the threshold to define a statistically significant degree of heterogeneity.

Data were pooled using a random effects model, (19) in order to give a more conservative estimate of the effect of tobacco smoking on the natural history of UC. We used StatsDirect version 2.7.2 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled ORs with 95% CIs. We assessed for evidence of publication bias by applying Egger's test to funnel plots, (20) where sufficient studies had been identified. (21)

## RESULTS

The search generated 4664 citations, with 198 potentially relevant papers retrieved for detailed analysis (Figure 1). Sixteen articles were ultimately found to be eligible, and were included in our analysis. (12, 14, 16, 22-34) Agreement between reviewers was substantial (Kappa statistic = 0.90). The characteristics of each individual study, including study quality according to the Newcastle-Ottawa scale, are provided in Table 2.

### Need for Colectomy According to Smoking Status

Need for colectomy was analysed in five studies, including a total of 2615 patients with UC (Figure 2). (14, 22-25) The studies included information on colectomy in 488 smokers compared with 2127 non-smokers. In total, 50 (10.3%) smokers underwent colectomy due to UC, compared with 401 (18.9%) non-smokers. However, the odds of colectomy were not significantly lower in smokers (OR = 0.89; 95% CI 0.62 to 1.26) with no significant heterogeneity between studies ($I^2$ = 2.9%, P = 0.39). There were too few studies to assess for publication bias. Due to the lack of heterogeneity, analyses were repeated with a fixed effects model and showed a similar result.

Four of these studies reported data on colectomy in current smokers, ex-smokers, and non-smokers. (14, 22-24) These studies contained a total of 2490 patients, 426 of whom were smokers, 736 ex-smokers, and 1328 non-smokers. In these studies, 31 (7.3%) smokers required a colectomy compared with 96 (7.2%) non-smokers, and 70 (9.5%) ex-smokers. There was no difference in the odds of requiring colectomy between current and non-smokers (OR = 1.00; 95% CI 0.63 to 1.59), with no significant heterogeneity between studies ($I^2$ = 6.8%, P = 0.36). When current smokers and ex-smokers were compared the pooled OR for colectomy was 0.89 (95% CI 0.56 to 1.42). No significant heterogeneity was observed between the studies ($I^2$ 0%, P = 0.44). Finally, when ex-smokers were compared with non-

smokers the OR for colectomy was 1.24 (95% CI 0.89 to 1.73), again with no heterogeneity between studies ($I^2$ 0%, P = 0.68). There were too few studies to assess for publication bias in all these analyses. Due to the lack of heterogeneity between studies in all three analyses, these were repeated with a fixed effects model and showed similar results.

**Flare of Disease Activity According to Smoking Status**

Four studies reported data on flare of disease activity, containing a total of 620 patients with UC (Figure 3). (12, 26-28) Overall, 77 (48.1%) of 160 smokers experienced a flare of disease activity during longitudinal follow-up, compared with 193 (42.0%) of 460 non-smokers (OR = 1.26, 95% CI 0.65 to 2.44), with significant heterogeneity between studies ($I^2$ 54.8%, P = 0.08). There were too few studies to assess for publication bias. Only one of these studies reported data on ex-smokers, (12) with 80 (44.7%) of 179 ex-smokers experiencing a flare of disease activity, compared with 44 (45.4%) of 97 current smokers, and 98 (42.1%) of 233 non-smokers.

**Proximal Extension of Disease According to Smoking Status**

Proximal disease extension was reported in four studies, including 687 patients with UC (Figure 4). (29-32) There were 45 (41.7%) of 108 smokers who experienced an extension of their disease, compared with 262 (45.3%) of 579 non-smokers (OR = 0.57; 95% CI 0.20 to 1.66), although there was significant heterogeneity between the studies ($I^2$ 73.2%, P = 0.01). There were too few studies to assess for publication bias, and none of these four studies provided data on disease extension among ex-smokers.

**Development of Pouchitis Following IPAA According to Smoking Status**

Three studies reported the development of pouchitis in a total of 355 patients with UC who had undergone panproctocolectomy and IPAA. (16, 33, 34) All three studies reported data on ex-smokers. In total, 20 (30.3%) of 66 current smokers developed pouchitis, compared with 84 (41.2%) of 204 non-smokers, and 28 (32.9%) of 85 ex-smokers. There was no difference in the odds of developing pouchitis in current smokers compared with non-smokers (OR = 0.57; 95% CI 0.21 to 1.53) with borderline significant heterogeneity between the studies ($I^2$ = 47.5%, P = 0.26). When current smokers were compared with ex-smokers, the OR for developing pouchitis was 0.80 (95% CI 0.14 to 4.52), with significant heterogeneity between studies ($I^2$ = 78.1%, P = 0.01). Finally, when ex-smokers were compared with non-smokers, the OR was 0.63 (95% CI 0.28 to 1.44), with borderline significant heterogeneity between studies ($I^2$ 50.6%, P = 0.13). There were too few studies to assess for publication bias in all these analyses.

## DISCUSSION

In this systematic review with meta-analysis we investigated the impact of tobacco smoking on the disease course of UC. Data were pooled from longitudinal follow-up studies that reported rates of colectomy, flare of disease activity, proximal disease extension, or development of pouchitis following panproctocolectomy and IPAA among smokers, ex-smokers and non-smokers. In all our analyses, tobacco smoking did not appear to have a significant impact on the rates of any of these outcomes, suggesting that it is not associated with an altered disease course in UC.

A comprehensive search of the medical literature was conducted to identify relevant studies, including a recursive search of the bibliographies of eligible studies, and translation of foreign language articles where appropriate. In addition, attempts were made to contact authors for additional data as required, although only one author responded to provide these. (28) Two investigators assessed study eligibility and extracted data independently, with a third investigator resolving any disagreements between the two. The quality of eligible studies was assessed using the Newcastle-Ottawa scale, with 11 out of the 16 articles scoring 7 or more out of a possible 9. Furthermore, analysis was performed using a random effects model in order to provide a more conservative estimate of the effect of smoking on the natural history of UC.

There are several limitations of this study. Firstly, the fact that the majority of eligible studies were conducted in tertiary referral centres means that these results may not be applicable to patients with UC in primary or secondary care. In addition, our analysis was based upon extraction of raw data from included studies, meaning that other confounding variables could not be adjusted for. These could include, for example, psychological co-morbidity, which is prevalent in IBD populations, (35, 36) may influence the natural history of UC, (37) and is independently associated with higher rates of smoking. (38) In addition,

only three of the 16 studies reported any assessment of disease extent or severity among smokers and non-smokers specifically, which could have affected our results, and there was variation in the amount of follow-up studies, meaning that the effect of duration of smoking on these outcomes could not be studied. Furthermore, the methods employed in the individual included studies were not uniform. The classification of smokers in these studies differed and not all studies provided extractable data on current smokers, ex-smokers, and non-smokers. It is possible that pooling of ex-smokers and current smokers in some of these studies may have occurred, and this could have led to an underestimation of the protective effect of smoking in these analyses. However, wherever possible, individual comparison of current, ex-, and non-smokers was undertaken in order to limit this effect and, when these additional analyses were conducted, there remained no significant association between current smoking and colectomy, or current smoking and the development of pouchitis when compared with ex-smokers and non-smokers. Furthermore, the number of studies fulfilling our inclusion criteria was relatively small, especially for pouchitis where only 270 patients were included, and there was significant heterogeneity observed in some analyses. A final limitation is a potential lack of power in the meta-analysis. As UC is largely a disease of non-smokers, (7) the total number of smokers in the identified studies was smaller than that of non-smokers. This may have contributed to the non-statistically significant results we observed. Certainly in some of our analyses the absolute proportions of smokers experiencing the event of interest was lower than that of non-smokers.

The impact of tobacco smoking, as a protective modifiable environmental risk factor for the development of UC is well described. Indeed, a systematic review and meta-analysis by Calkins et al. described a nearly three-fold increase in lifetime odds of developing UC in non-smokers compared with smokers, with ex-smokers also having increased odds of developing UC compared with non-smokers. (8) However, there is conflicting evidence

regarding the effect of smoking on the natural history of UC, with previous studies suggesting that smokers experience a more benign disease course compared with non-smokers, an assertion which is supported by an international consensus statement regarding the diagnosis and management of UC, (39) although this is refuted by others. (40) Moreover, because of the detrimental effects of smoking on overall morbidity and mortality, controlled trials of smoking in UC are unethical, (41) therefore restricting research examining this issue to studies of an observational design, with the inherent limitations associated with them.

Our study is a contemporaneous analysis of observational studies examining the effect of tobacco smoking on colectomy rates and flares of disease activity in UC and, to our knowledge, is the first systematic review and meta-analysis to investigate the effect of smoking on proximal disease extension and the development of pouchitis in patients who have undergone panproctocolectomy and IPAA for acute severe colitis, or chronic refractory disease. A previous systematic-review and meta-analysis investigated the effect of smoking on overall rates of colectomy in UC, and reported a statistically significant reduction in the odds of colectomy among current smokers. (42) However, four of the five studies examined did not fulfil our inclusion criteria, due to recruiting highly selected groups of patients with acute severe colitis only, (43, 44) use of a retrospective study design, (45) or a lack of available raw data for extraction. (46)

As a consequence of the hitherto assumed benefit of smoking in UC, in part due to the findings of historical observational studies investigating the effects of smoking on active UC, (47, 48) clinical trials of nicotine containing products, including transdermal patches and chewing gum, as therapeutic options in the management of UC have been conducted previously. (49, 50) These studies are small, and have largely inconclusive results, with some reporting the use of nicotine products as superior to placebo, but showing no definite advantage over conventional UC pharmacotherapy, (49, 51) and others suggesting a lack of

benefit entirely. (50, 52) These results imply that any benefit of tobacco smoking may not be attributable to nicotine directly, but to some other component of tobacco smoke. The conflicting results from these studies, and the results of this systematic review and meta-analysis, suggest that further clinical trials of nicotine therapy may not be warranted.

Our results have important implications for clinical practice, especially as the deleterious effects of tobacco smoking on cardiovascular and cerebrovascular health, (53) respiratory function, (54) and the incidence of several cancers are well described. (55, 56) This is of particular importance as these effects may be ameliorated with smoking cessation. (57) Given that the proportion of patients who believe that tobacco smoking has a beneficial impact on long term outcomes in UC is almost 40%, (58) our results imply that patients whose smoking habit is reinforced by a perceived benefit, in terms of disease outcomes, expose themselves to an increased risk of smoking-related illness, without any tangible benefit in the long-term management of their disease. These data therefore reinforce the need for smoking cessation advice, not only in Crohn's disease, where the detrimental effects of smoking on disease course are clear, (59) but in all IBD patients, and support the requirement for this advice to be included in future iterations of international guidelines on the management of UC which is, to date, lacking. (60)

In summary, this systematic review and meta-analysis has demonstrated that tobacco smoking, when compared with non-smoking, does not appear to have any effect on colectomy rates in UC. Furthermore, smoking was not associated with any reduction in the rates of flare of disease activity, proximal disease extension, or the development of pouchitis in the small, heterogeneous group of studies that were included in these latter analyses. Given the high morbidity and mortality associated with smoking, and the high proportion of patients who may, falsely, perceive a benefit of smoking on disease outcomes in UC, these data reinforce the need for smoking cessation advice to be provided to all patients with IBD.

## AUTHORSHIP

Guarantor of the article: DJ Gracie

Author contributions: NT, ACF and DJG conceived the study. NT, ACF and DJG collected all data. ACF and DJG analysed and interpreted the data. NT, ACF and DJG drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the article.

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**Table 1: Eligibility criteria.**

| |
|---|
| Prospective studies, or retrospective analysis of prospectively collected data, with longitudinal follow-up<br>≥50 unselected adult patients with UC (aged ≥16 years)<br>Diagnosis of UC based on histological, radiological, or endoscopic criteria<br>Examined the effect of smoking on the natural history of UC including:<br>• Need for colectomy<br>• Flare of disease activity<br>• Proximal extension of disease location<br>• Development of pouchitis in patients having undergone panproctocolectomy and IPAA |

**Table 2: Characteristics of Studies Reporting the Effects of Tobacco Smoking on the Natural History of Ulcerative Colitis.**

| Study name and year | Country (no. of centres) | Setting | Method of assessment of smoking status | Outcome studied | No. of patients (% male) | Duration of follow up | Analysis | Quality Score* |
|---|---|---|---|---|---|---|---|---|
| **Merrett 1996 (16)** | UK | Tertiary | Interview | Development of pouchitis | 101 (58.4%) | 1 year | Prospective | 7 |
| **Stahlberg 1996 (34)** | Sweden | Tertiary | Unclear | Development of pouchitis | 147 (57.7%) | 54 months | Prospective | 6 |
| **Russel 1998 (23)** | Europe | Tertiary | Unclear | Colectomy | 905 (56.0%) | 1 year | Prospective | 6 |
| **Meucci 2000 (29)** | Italy | Tertiary | Questionnaire | Disease extension | 273 (58.2%) | 5.3 years | Retrospective analysis of prospectively collected data | 6 |
| **Levenstein 2000 (26)** | Italy | Tertiary | Interview | Flare of disease | 62 53.2% | 1.8 years | Prospective | 8 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Bitton 2001 (27)** | USA & Canada | Tertiary | Unclear | Flare of disease | 74 (43.2%) | 1 year | Prospective | 8 |
| **Kuisma 2004 (33)** | Finland | Tertiary | Questionnaire | Development of pouchitis | 107 (50.5%) | 7.5 years | Prospective | 5 |
| **Chatzicostas 2006 (31)** | Greece | Tertiary | Interview | Disease extension | 62 (60.1%) | 60 months | Prospective | 7 |
| **Aldhous 2007 (22)** | Scotland | Tertiary | Questionnaire | Colectomy | 499 (50.9%) | 5.6 years | Retrospective analysis of prospectively collected data | 7 |
| **Hoie 2007 (24)** | Europe | Tertiary | Interview | Colectomy | 509 (52.3) | 10 years | Prospective | 7 |
| **Hoie 2007 (12)** | Europe | Tertiary | Interview | Flare of disease | 509 (52.3) | 2 years | Prospective | 8 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Haritunians 2010 (25)** | USA | Tertiary | Unclear | Colectomy | 861 (53.0%) | 48-95 months | Retrospective analysis of prospectively collected data | 5 |
| **Anzai 2015 (32)** | Japan | Tertiary | Database | Disease extension | 66 (54.5%) | 14 years | Retrospective analysis of prospectively collected data | 7 |
| **Hosseini 2015 (28)** | Iran | Tertiary | Questionnaire | Flare of disease | 154 (51.3%) | 1 year | Prospective | 9 |
| **Waterman 2015 (30)** | Canada | Tertiary | Unclear | Disease extension | 286 (42.0%) | 5 years | Retrospective analysis of prospectively collected data | 6 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Lunney 2015 (14)** | Australia | Secondary and tertiary care | Secure record (e.g. surgical records) | Colectomy | 577 (50.8%) | 9 years | Retrospective analysis of prospectively collected data | 7 |

* The Newcastle-Ottawa scale was used to assess study quality. From a possible total score of 9, higher scores indicate higher quality.

**Figure 1: Flow Diagram of Studies Identified in the Systematic Review and Meta-analysis.**

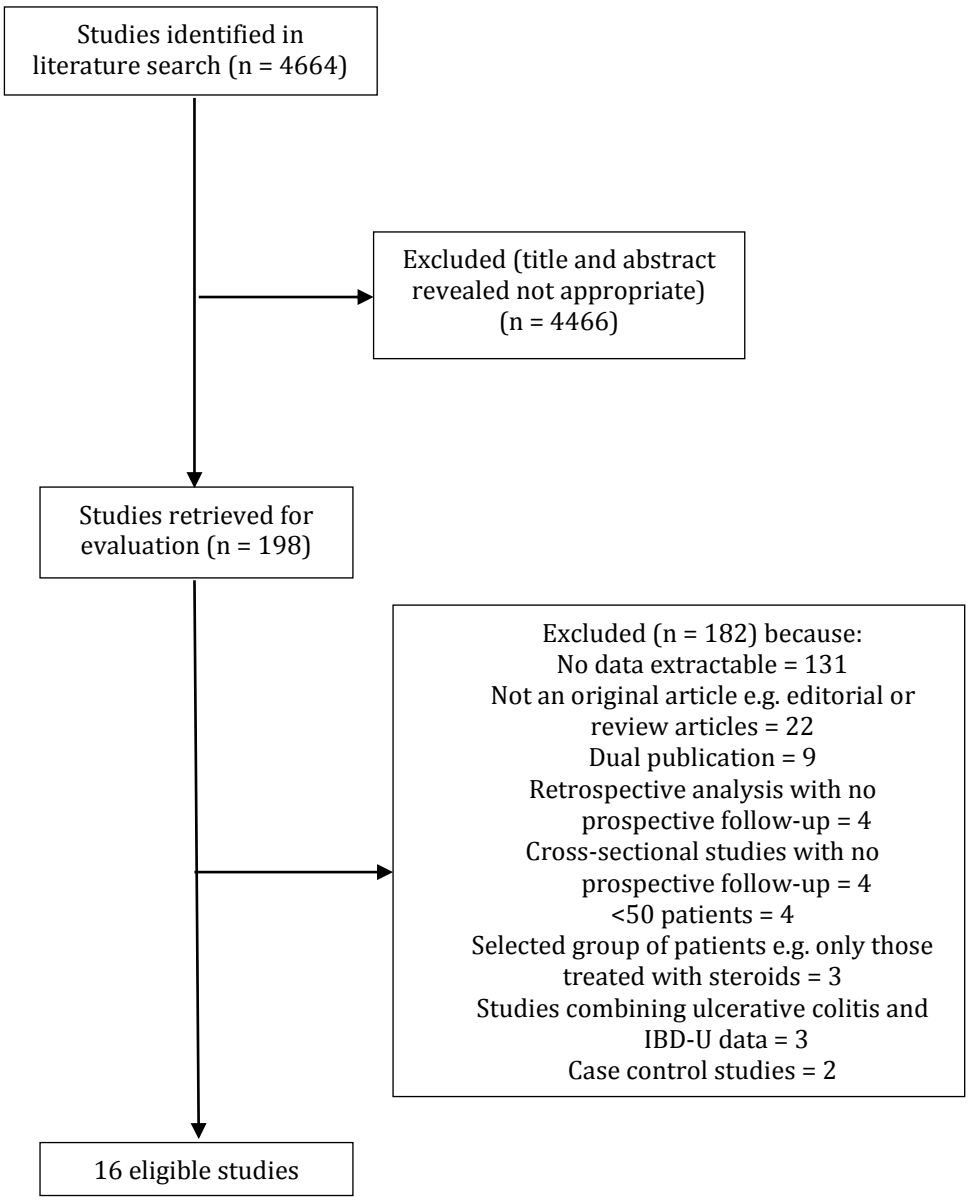


**Figure 2: Forest Plot of Effect of Smoking on Need for Colectomy.**

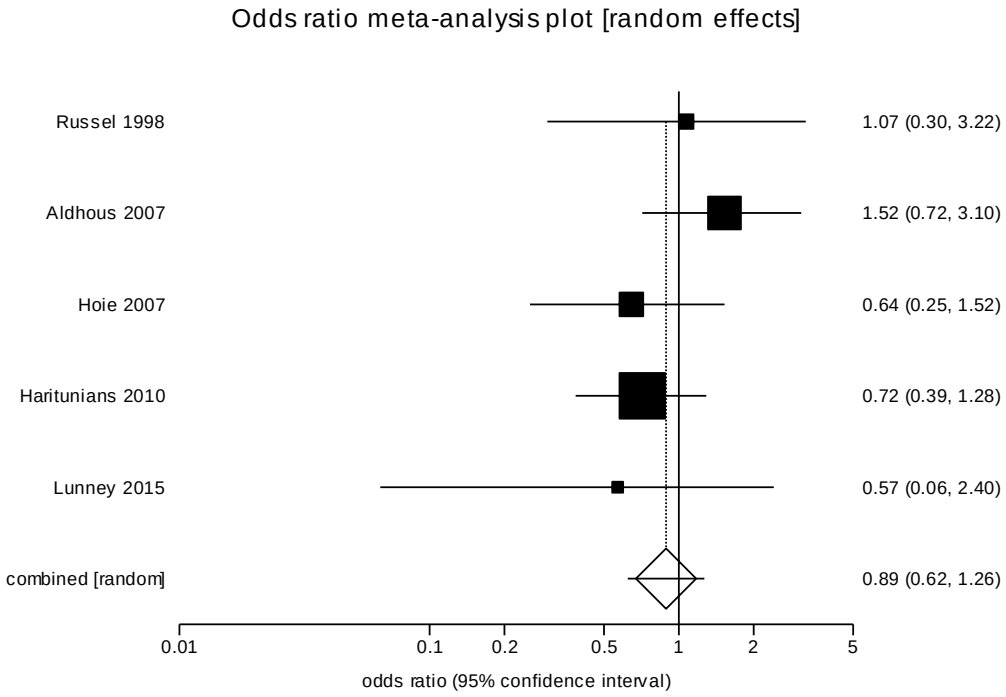


**Figure 3: Forest Plot of Effect of Smoking on Flare of Disease Activity.**

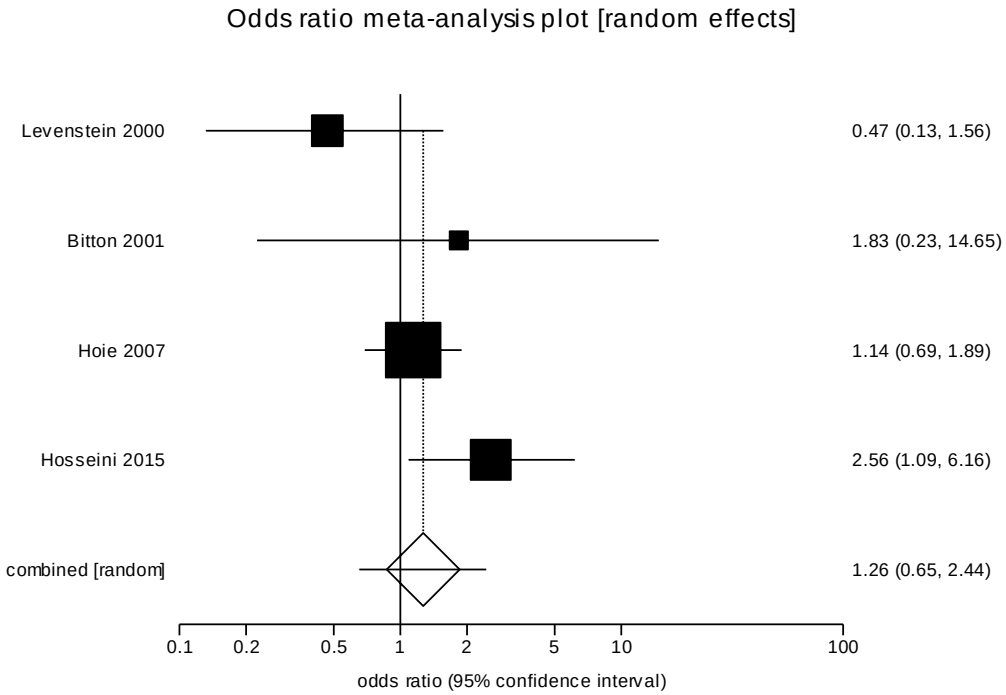
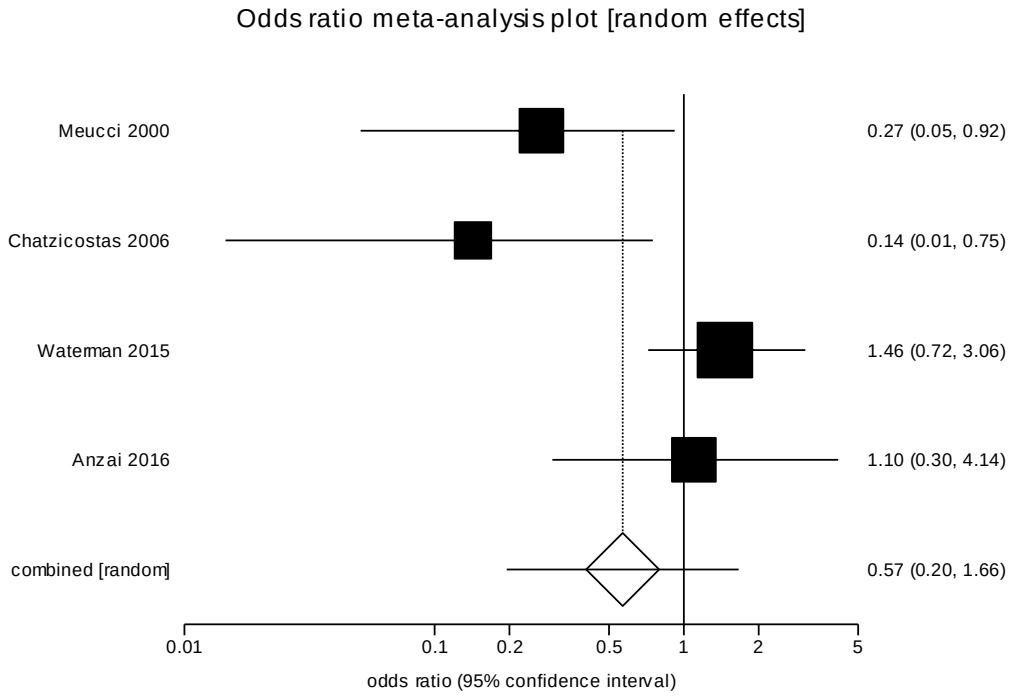


**Figure 4: Forest Plot of the Effect of Smoking on Proximal Extension of Disease.**



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4-5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6 and 26 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | N/A |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 and 26 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6-7 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7-8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 7-8 |

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | N/A |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9 and 30 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 27-29 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 27-29 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 31-33 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 9-11 and 31-33 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | N/A |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | N/A |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 12 and 15 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 12-13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13-15 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 16 |