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Systematic Review and Meta-analysis: Association Between Acetaminophen and Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Risk of Crohn's Disease and Ulcerative Colitis Exacerbation

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Abstract

Background—Unlike acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) have generally been thought to be associated with increased risk of inflammatory bowel disease (IBD) exacerbation.

Aim—To carry out a systematic review and meta-analysis of previous studies examining the association between acetaminophen and NSAIDs including cyclooxygenase (COX-2) inhibitors use, and risk of crohn's disease (CD) and ulcerative colitis (UC) exacerbation.

Methods—We identified published manuscripts and abstracts through March 1, 2017 by systematic search of Medline, Embase, Cochrane and other trial registries. Quality assessment was done using Newcastle-Ottawa scale and random effects meta-analysis using pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated.

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None to declare

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Authors Contributions

OM – study design, acquisition of data, statistical analysis, drafting of the manuscript

WM - acquisition of data, critical revision of the manuscript

PL – study concept, critical revision of the manuscript

HK- study design, statistical analysis, drafting of the manuscript

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Findings—18 publications between years 1983 and 2016 were identified. For the meta-analysis, pooled RRs of disease exacerbation with NSAIDs use were (1.42, 95% CI, 0.65 – 3.09), $I^2=60.3\%$ for CD, and (1.52, 95% CI, 0.87 – 2.63), $I^2=56.1\%$ for UC. The corresponding values for acetaminophen use were (1.40, 95% CI, 0.96 – 2.04), $I^2=45.6\%$ for UC, and (1.56, 95% CI, 1.22 – 1.99), $I^2=0.0\%$ for IBD. Sensitivity analyses limited to studies with low risk of bias showed a significantly increased risk of CD exacerbation (1.53, 95% CI, 1.08 – 2.16) but not UC (0.94, 95% CI, 0.36 – 2.42) with NSAIDs use.

Conclusion—Contrary to generally accepted belief, we did not find a consistent association between NSAIDs use and risk of CD and UC exacerbation. There was also no consistent evidence for association with acetaminophen although further studies are needed.

INTRODUCTION

Unlike acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) have generally been thought to be associated with increased risk of inflammatory bowel disease (IBD) exacerbation. Use of NSAIDs is known to be associated with mucosal ulceration in the gastrointestinal tract.[1–3] In addition, chronic use of NSAIDs has previously been linked to development of Crohn's disease (CD) and ulcerative colitis (UC).[4–7] In clinical practice, patients with established IBD are encouraged to avoid the use of NSAIDs because of the concern for their potential adverse effects on disease activity and instead are encouraged to use acetaminophen for management of pain. Although several studies have examined the link between NSAIDs use and IBD exacerbation, the results have been conflicting.[6, 8, 9] We therefore sought to conduct a systematic review and meta-analysis of prior studies examining the relationship between acetaminophen, NSAIDs and cyclooxygenase (COX-2) inhibitors use, and risk of IBD exacerbation. Such comprehensive examination of prior studies may ultimately help inform clinical recommendations for patients with established IBD.

METHODS

Search Strategy

We conducted a systematic literature search using a predetermined and registered protocol (Supplementary Material) in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement.[10, 11] For electronic database search, we used medical subject headings (MeSH) and text words related to acetaminophen, NSAIDs, cyclooxygenase (COX-2) inhibitors, CD, and UC for MEDLINE (PubMed interface, 1974–March 2017) (Supplementary Material) and Embase subject headings (Emtree) for EMBASE. Similar search strategies using related text words were employed for ongoing or recently completed trials and systematic reviews in Cochrane Central Register of Controlled Trials (Wiley interface, current issue), The International Clinical Trials Registry Platform Search Portal, ClinicalTrials.gov, and PROSPERO. All the keywords were used to search the titles and abstracts. The reference lists of relevant articles were also reviewed for any additional articles not captured through the primary search method.

Selection Criteria

Two reviewers (O.M. and W.M.) identified articles eligible for further review by performing an initial screen of identified abstracts and titles. Articles were eliminated in this initial screening if there were case series, case reports, animal studies, studies on aspirin or 5-Aminosalicylates derivatives, or studies not reported in English language. Full-texts of the remaining articles were retrieved and reviewed. Articles were considered for inclusion in the second screening if they reported original data from a study of eligible design, including randomized controlled trials (RCTs), non-randomized clinical trials, prospective and retrospective cohort studies, and case-control or nested case-control studies of patients with established IBD. We also included studies that examined both adults and children if data for adults were reported separately. The observed agreement between reviewers for eligibility of articles on initial screening was 97.0%, corresponding to moderate agreement ($k=0.79$) and in the second screening was 98.1%, corresponding to strong agreement ($k=0.87$).[12] Disagreements between reviewers were resolved by consensus with third party experts (H.K. and P.L.).

Data Extraction

Our primary outcome was defined as IBD disease activity or complications while our primary exposure was use of acetaminophen, NSAIDs, or COX-2 inhibitors. There were significant variations in the outcome variable measures among studies, which included rates of hospitalizations and exacerbation, and changes in disease-specific activity index scores. Other variables extracted included study design, duration and frequency of exposure, publication year, and information on key indicators of study quality using Newcastle-Ottawa scale (NOS). We extracted reported odds ratios (ORs), hazard ratios (HRs), rate ratios (RRs) and incidence rate ratios (IRRs) with their respective 95% confidence intervals (CIs) or data enabling the calculation of these association measures. Both adjusted and unadjusted values were extracted; though, when available, the adjusted estimates were used.

Statistical Analysis

Meta-analysis summary estimates (RR) and 95% CIs were obtained by pooling effect estimates (RRs, IRRs, HRs and ORs) from all the eligible studies using fixed- or random-effects meta-analysis according to the method of Desimonian and Laird.[13] Given the relatively modest prevalence of IBD and its complications, the OR is a good approximate of the RR under the rare outcome assumption.[14] To assess for heterogeneity of RRs across studies, I^2 statistics were calculated.[15] Given the small number of studies included in the meta-analysis, random effect models were used when there was moderate heterogeneity between studies, defined as I^2 value $\geq 30\%$. [15] We assessed for publication bias using Egger's test, and funnel plot for analysis with ten or more studies.[16] Subgroup analysis was performed for UC, CD and IBD when outcomes were reported separately by the primary authors. Consistent with prior studies, we used a cutoff score of 7 for NOS to define studies with low risk of bias[17, 18], and performed sensitivity analysis assessing the risk of disease exacerbation restricted to these studies. Additionally, we examined the associations among cohort studies. All analyses were performed using STATA 14 (StataCorp. 2015) statistical software package.

RESULTS

Literature Search

Our search strategy resulted in 8378 unique citations: 1412 from Medline, 6966 from Embase and 4 from in-article references (Figure 1). Of these, 552 and 7695 citations were excluded by review of titles and abstracts during the first screen on account of duplication and relevance, respectively. After full text review of 135 articles, 111 articles were excluded including 1 abstract that examined the association between aspirin and not NSAIDs and risk of IBD exacerbation.[19] A total of 24 studies were included in the final systematic review. 18 of these studies examined NSAIDs use and IBD exacerbation including five studies that reported non-suitable association measure for meta-analysis, eight studies looked at COX-2 inhibitor use, and six studies examined acetaminophen use and IBD exacerbation including one without suitable association measure for meta-analysis. There were multiple entries for studies that reported separate results for different exposure categories.

Study characteristics and quality

Studies undertaken to elucidate the relationship of NSAIDs use and IBD disease activity or complications are outlined in Tables 1 and 2. There were a total of 18 studies, 9 case-control, 8 cohort studies and 1 non-randomized clinical trial, published between years 1983 and 2016. Nine studies evaluated IBD complications in quiescent disease ranging from symptomatic relapses confirmed on sigmoidoscopy and disease flares requiring steroids to emergency admissions.[6, 20–27] Nine studies examined worsening disease activity level using physician global assessment of disease activity or objective indices like Harvey-Bradshaw, Manitoba or Mayo scores.[8, 9, 28–34] The number of participants per study ranged from 60 to 1940 for a total of 6276 participants across studies pooled for the meta-analysis. 13 studies were included in the meta-analysis, 5 cohort[9, 23, 25, 27, 29] and 8 case-control studies.[6, 8, 20, 21, 26, 28, 31, 32] Crude RRs were calculated for 3 studies that presented raw data.[20, 21, 26] Table 3 outlines studies evaluating COX-2 inhibitor use and IBD exacerbation. These include 1 case-control study [8], 2 cohort studies [35, 36], 3 non-randomized clinical trials[33, 37, 38] and 2 RCTs.[39, 40] Similarly, Table 4 outlines characteristics of acetaminophen studies which included 1 non-randomized clinical trial[33], and 2 cohort[9, 27] and 3 case-control studies.[8, 21, 26] Due to the inherent qualitative differences among studies, we conducted quality assessment using Newcastle-Ottawa scale (Supplementary Tables 1 and 2). Studies with a score ≥ 7 were considered to have low risk of bias, consistent with prior definitions.[6, 8, 9, 25, 27, 29, 31]

Meta-analysis of NSAIDs use and IBD exacerbation

A total of 13 studies were included in the meta-analysis with multiple entries for studies with distinct CD and UC results (Figures 1 and 2). The results of the meta-analysis are outlined in Figure 2. Among the five studies examining the association between NSAIDs use and risk of CD exacerbation, substantial heterogeneity was observed ($I^2=60.3\%$). The pooled RR of CD exacerbation using the random effects model was 1.42; 95% CI (0.65 – 3.09). We observed moderate heterogeneity across the eight studies that examined the association between NSAIDs use and UC exacerbation ($I^2=56.1\%$). The pooled RR of UC exacerbation was 1.52; 95% CI (0.87 – 2.63) using the random effect model. Lastly, we

examined the association between NSAIDs use and IBD exacerbation among 9 studies that reported effect estimates and observed a non-statistically significant increase in risk (RR= 1.29; 95%CI 0.92 – 1.80). However, there was substantial heterogeneity across the studies (I^2 =63.2%).

Systematic Review of NSAIDs use and IBD exacerbation

We also performed a systematic review of studies not included in our meta-analysis (Table 2). Bonner et. al.[30] evaluated the influence of NSAIDs use on disease activity among 426 CD and 203 UC patients over a 5-year follow up. Information on disease activity was collected using the modified Harvey Bradshaw score for CD and Lichtiger index for UC. NSAIDs use was defined as over the counter or prescription use within 3 days of every clinic visit, the time when information on disease activity was collected, and usage was categorized into non-users, low-dose and high-dose users. For CD, average MHB score was 4.07 for the non-user group, 4.24 for low-dose NSAIDs (p=0.46) and 4.78 for high dose group (p=0.0072 versus no-NSAIDs) while for UC, corresponding scores were 5.64, 5.46 (p=0.74), and 6.20 (p=0.69), respectively.

Takeuchi et. al.[33] conducted two non-randomized clinical trials examining the risk of IBD relapse following administration of non-selective NSAIDs compared to acetaminophen in patients with quiescent disease. In the first trial, use of NSAIDs was associated with frequent early clinical relapse in IBD. Specifically, disease exacerbations occurred in 9 (28%) of those receiving naproxen, 5 (24%) of those receiving indomethacin and 5 (17%) patients receiving diclofenac. These numbers were significantly different than the rate of relapse in the acetaminophen group (0 out of 26 patients). In the second trial, 4 (20%) patients each in the naproxen and nabumetone treated groups experienced disease exacerbation compared to only 1 (5%) in acetaminophen group.

Feagins et. al.[24] conducted a case-control study in 33 IBD patients with symptom flares and 23 IBD patients in clinical remission as controls, no statistically significant difference in the frequency of NSAIDs use was observed between cases and controls. Similarly, Riley et. al.[22] and Jejuna et. al.[34] in their respective cohort studies on UC and CD did not find significant difference in NSAIDs use among patients with active disease and those in remission.

Systematic Review of COX-2 inhibitors use and IBD exacerbation

Our study captured 8 articles evaluating selective COX-2 inhibitor use and IBD exacerbation (Table 3). We did not conduct a meta-analysis because of insufficient data. Specifically, three of the studies had no comparator group,[35, 36, 38] one study utilized patients with dyspepsia as controls[37] while another study used acetaminophen exposure as control.[33] Studies by Mahadevan et. al.[35], Reinisch et. al.[38] and Takeuchi et. al.[33] showed that only two out of 27, zero out of 32 and one out of 20 IBD patients experienced exacerbation with use of celecoxib, rofecoxib, and nimesulide, respectively. Similarly, Hensley et. al.[8] study showed that only one out of seven patients experienced IBD relapse with use of celecoxib or etoricoxib. In contrast, a retrospective cohort study by Matuk and colleagues [36] and an open label trial by Biancone et. al.,[37] demonstrated that IBD patients had high

rate of disease exacerbation (39% and 20%, respectively) with use of celecoxib or rofecoxib. El Miedany et. al.[39] reported a multicenter, double-blinded, placebo-controlled study of the safety of etoricoxib among 146 patients with rheumatologic manifestations of IBD. Participants, who were aged 18–65 years with varying degrees of disease activity, were given 60–120mg/day of etoricoxib or placebo. At 3 months, there were no significant changes in disease activity index between the treatment and control groups, (RR=0.92; 95% CI 0.37- 2.32). Lastly, Sandborn and colleagues conducted a multicenter, randomized, double-blinded, controlled trial involving 222 UC patients who were in clinical remission and were given 200mg of oral celecoxib, a selective COX-2 inhibitor, or placebo twice daily for 14 days. The study found no association between use of celecoxib and risk of disease exacerbation (RR = 0.73, 95% CI 0.17 – 3.18).[40]

Meta-analysis of acetaminophen use and IBD exacerbation

A total of 5 studies were included in the meta-analysis as shown in Figure 3. Moderate heterogeneity was observed ($I^2=45.6\%$) among the three studies that examined the association between acetaminophen use and risk of UC exacerbation. The pooled RR of UC exacerbation using the random effects model was 1.40; 95% CI (0.96 – 2.04). We observed no heterogeneity among the two studies that examined the association between acetaminophen use and IBD exacerbation ($I^2=0.0\%$). The pooled RR of IBD exacerbation showed a statistically significant increase in risk 1.56; 95% CI (1.22 – 1.99) using the random effect model. Only one study, Long et. al,[9] reported a separate result for acetaminophen use and CD exacerbation (RR = 1.72, 95% CI 1.11 – 2.68).

Systematic Review of acetaminophen use and IBD exacerbation

Results of two non-randomized clinical trials by Takeuchi et. al[33] examining the risk of IBD relapse following administration of acetaminophen demonstrated only one disease exacerbation in the 46 patients with quiescent IBD, which was lower than the rate observed in the NSAIDs group (27 out of 143 patients).

Sensitivity analyses

We considered the possibility that quality of studies may have been a major source of substantial heterogeneity observed across the studies and therefore performed sensitivity analysis limiting our studies to those with a score of ≥ 7 on the Newcastle-Ottawa scale (Figure 4). The risk of CD exacerbation was increased and statistically significant with NSAIDs use (RR = 1.53, 95% CI 1.08 – 2.16 and $I^2=0.0\%$). In contrast, we did not observe an association between NSAIDs use and risk of UC exacerbation (RR = 0.94, 95% CI 0.36 – 2.42 and $I^2=64.7\%$) or risk of IBD exacerbation (RR =1.15, 95% CI 0.89 – 1.49 and $I^2=44.9\%$). We also performed sensitivity analysis limiting our population to cohort studies and observed similar results (Figure 5). The pooled RR of IBD exacerbation with NSAIDs use was 1.22, 95% CI 0.90 – 1.66 with moderate heterogeneity ($I^2=58.1\%$). There were insufficient data for separate analyses on CD and UC as only two cohort studies reported separate results for UC [9, 23] and one study for CD.[9]

Publication bias

We assessed for presence of publication bias using Egger's test and found no evidence for publication bias (p-values of Egger's test = 0.952 for CD, 0.699 for UC and 0.239 for IBD).

DISCUSSION

In this systematic review and meta-analysis of prior studies, we found no consistent association between acetaminophen, NSAIDs or COX-2 inhibitor use and risk of CD and UC exacerbation. However, among studies with low risk of bias, NSAIDs use appeared to be associated with increased risk of exacerbation in CD, but not UC. Although we observed significant heterogeneity between the studies, likely due to variation in outcome ascertainment, we found no evidence for publication bias.

American College of Gastroenterology guidelines for management of IBD recognize NSAIDs as potential triggers for disease exacerbation, highlighting the ongoing concern regarding the use of these medications in patients with established disease [41]. Although, it's well-established that NSAIDs may cause de novo damage throughout the gastrointestinal tract, [42–45] the precise mechanism through which NSAIDs promote IBD exacerbation remains largely unknown. Prior studies have suggested that inhibition of intestinal prostaglandin synthesis due to dual inactivation of COX-1 and COX-2 enzyme isoforms may in part be responsible.[33, 46] It is however unclear whether COX-1 inhibition is primarily responsible for mucosal injury and whether patients taking COX-2 inhibitors have similar potentially increased risk of exacerbation compared to those consuming non-selective NSAIDs.[47] In our systematic review, we did not see a consistent association between COX-2 inhibitors and risk of IBD exacerbation.

The observed heterogeneity in our analyses was likely due to variation in study design and outcome definition. For example, the less stringent case-control study by Bonner et. al.[28], which included irritable bowel syndrome (IBS) patients as controls and utilized a subjective global assessment of disease activity, showed an inverse association between NSAIDs use and risk of CD exacerbation while studies by Evans et. al.[6], Hensley et. al.[8] and Long et. al.[9], which appeared to have the most rigorous study designs suggested a positive association. However, even in well-designed, studies, there were significant limitations in definition of outcomes. For example, in the study by Evans et. al.[6], exacerbation was defined as emergency admission to hospital. This definition is unlikely to capture the majority of CD exacerbations that are managed in the outpatient settings.[48] In contrast, Hensley et. al.[8] and Long et. al.[9] utilized objective disease activity index to measure outcome, which may be a more sensitive method to capturing short term influence of NSAIDs on disease activity.

Our meta-analysis findings of no statistically significant association between NSAIDs use and risk of UC and IBD exacerbation, even among studies with low risk of bias, are in keeping with results of randomized controlled trials (RCT) by Sandborn et. al. and El Miedany et. al., and systematic review works by Forrest et. al. and Kefalakes et. al.[39, 40, 49, 50] Similarly, our review of literature findings of inconsistent results with selective COX-2 use and IBD exacerbation are in keeping with conclusion from earlier systematic

review by Miao et. al.[51], with our work encompassing more articles. Interestingly, we did observe an association between acetaminophen use and risk of IBD exacerbation, although only two studies have previously examined such an association.

Our study has several strengths that are worth noting. First, this study followed the recommendations for rigorous systematic review and had a pre-defined and published protocol.[10, 11, 15] Secondly, to our knowledge, our study represents the most comprehensive evaluation to date of the association between acetaminophen, NSAIDs or COX-2 inhibitor use and risk of IBD exacerbation. Lastly, two independent reviewers undertook all stages of the data review process and we used an objective assessment to define low risk of bias studies.

We acknowledge several limitations. First, definitions of disease exacerbation varied widely across the studies, introducing significant heterogeneity. Second, confounding by indication may have biased the results of some of the included studies that did not routinely document information on the reason for acetaminophen, NSAIDs or COX-2 inhibitor use. Third, we acknowledge that our meta-analysis may have not been powered to detect modest associations. However, assuming that the prevalence of NSAIDs use is 40% among IBD patients,[9] and there is a 40% rate of IBD exacerbation among non-NSAIDs users,[52, 53] we estimated that our meta-analysis had over 80% power to detect a minimum RR of 1.1 at a significance level of 0.05. We recognize that IBD is a heterogeneous disease and therefore, there may be subgroups of patients particularly at risk of disease exacerbations with use of NSAIDs. Therefore, future studies focused on examining predictors of disease exacerbations/progression with use of NSAIDs are needed. Lastly, our work was based on studies reported in English language and though we did not find any non-English reported studies, we acknowledge this may limit generalizability of our findings to populations in geographic regions not well represented by English language literature.

Conclusion

Contrary to generally accepted belief, we did not find a consistent association between acetaminophen, NSAIDs, or COX-2 inhibitor use and risk of CD and UC exacerbation. Nevertheless, analysis limited to studies with low risk of bias showed a positive association between NSAIDs use and CD exacerbation but not UC. Our meta-analysis confirms the need for larger well-designed studies examining the relationship between acetaminophen and NSAIDs, and disease activity among patients with established IBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hirschowitz BI. Nonsteroidal antiinflammatory drugs and the gastrointestinal tract. *Gastroenterologist*. 1994; 2(3):207–23. [PubMed: 7987619]
2. Sostres C, Gargallo CJ, Lanás A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Research & Therapy*. 2013; 15(Suppl 3):S3–S3.
3. Laine L. Nonsteroidal anti-inflammatory drug gastropathy. *Gastrointest Endosc Clin N Am*. 1996; 6(3):489–504. [PubMed: 8803564]
4. Ananthakrishnan AN, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. *Ann Intern Med*. 2012; 156(5):350–9. [PubMed: 22393130]
5. Gleeson MH, Davis AJ. Non-steroidal anti-inflammatory drugs, aspirin and newly diagnosed colitis: a case-control study. *Aliment Pharmacol Ther*. 2003; 17(6):817–25. [PubMed: 12641504]
6. Evans JM, et al. Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut*. 1997; 40(5):619–22. [PubMed: 9203940]
7. Niu J, et al. Identification of Environmental Factors Associated with Inflammatory Bowel Disease in a Southwestern Highland Region of China: A Nested Case-Control Study. *PLoS One*. 2016; 11(4):e0153524. [PubMed: 27070313]
8. Hensley A I, Beales L. Use of Cyclo-Oxygenase Inhibitors Is Not Associated with Clinical Relapse in Inflammatory Bowel Disease: A Case-Control Study. *Pharmaceuticals (Basel)*. 2015; 8(3):512–24. [PubMed: 26371009]
9. Long MD, et al. Role of Nonsteroidal Anti-Inflammatory Drugs in Exacerbations of Inflammatory Bowel Disease. *J Clin Gastroenterol*. 2016; 50(2):152–6. [PubMed: 26485106]
10. Moher D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009; 151(4):264–9. w64. [PubMed: 19622511]
11. Oluwatoba Moninuola, HK. Impact of Non-steroidal Anti-inflammatory Drugs (NSAIDs) on Crohn's disease progression after diagnosis: systematic review and meta-analysis; PROSPERO. 2016. p. CRD42016051808 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016051808
12. McHugh ML. Interrater reliability: the kappa statistic. *Biochemia Medica*. 2012; 22(3):276–282. [PubMed: 23092060]
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7(3):177–88. [PubMed: 3802833]
14. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. *Am J Epidemiol*. 1982; 116(3):547–53. [PubMed: 7124721]
15. Higgins, JPT., GS, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011. Available from www.handbook.cochrane.org
16. Sterne, JA., et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. p. 1756-1833.(Electronic)
17. Lo CKL, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Medical Research Methodology*. 2014; 14(1):45. [PubMed: 24690082]
18. Bae JM. A suggestion for quality assessment in systematic reviews of observational studies in nutritional epidemiology. *Epidemiology and Health*. 2016; 38:e2016014. [PubMed: 27156344]
19. Vadada D, et al. Inflammatory bowel disease exacerbations after the initiation of aspirin and clopidogrel (Plavix®) - A retrospective case control study. *American Journal of Gastroenterology*. 2010; 105:S472–S473.
20. Felder JB, et al. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: a case-control study. *Am J Gastroenterol*. 2000; 95(8):1949–54. [PubMed: 10950041]
21. Rampton DS, McNeil NI, Sarner M. Analgesic ingestion and other factors preceding relapse in ulcerative colitis. *Gut*. 1983; 24(3):187–9. [PubMed: 6826100]

22. Riley SA, et al. Why do patients with ulcerative colitis relapse? *Gut*. 1990; 31(2):179–83. [PubMed: 2311975]
23. Dhingra R, et al. Higher intake of vitamin A and use of NSAIDs are risk factors for relapse of ulcerative colitis in deep remission. *Journal of Gastroenterology and Hepatology*. 2012; 27:203.
24. Feagins LA, Spechler SJ. A prospective, case-control study of factors that trigger flares of inflammatory bowel disease. *Gastroenterology*. 2011; 140(5):S793.
25. Aalykke C, et al. Role of NSAID use in inflammatory bowel disease. A 5-year follow-up study. *Gastroenterology*. 118(4):A869.
26. Bunney R, et al. NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND THE BOWEL. *The Lancet*. 1989; 334(8670):1047–1048.
27. Dominitz JA, Koepsell TD, Boyko EJ. Association between analgesic use and inflammatory bowel disease (IBD) flares: A retrospective cohort study. *Gastroenterology*. 118(4):A581.
28. Bonner GF, et al. Tolerance of nonsteroidal antiinflammatory drugs in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2000; 95(8):1946–8. [PubMed: 10950040]
29. Bernstein CN, et al. A prospective population-based study of triggers of symptomatic flares in IBD. *Am J Gastroenterol*. 2010; 105(9):1994–2002. [PubMed: 20372115]
30. Bonner GF, Fakhri A, Vennamaneni SR. A long-term cohort study of nonsteroidal anti-inflammatory drug use and disease activity in outpatients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2004; 10(6):751–7. [PubMed: 15626893]
31. Feagins LA, Iqbal R, Spechler SJ. Case-control study of factors that trigger inflammatory bowel disease flares. *World J Gastroenterol*. 2014; 20(15):4329–34. [PubMed: 24764669]
32. Meyer AM, et al. Relapse of inflammatory bowel disease associated with use of nonsteroidal anti-inflammatory drugs. *Dig Dis Sci*. 2006; 51(1):168–72. [PubMed: 16416231]
33. Takeuchi K, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2006; 4(2):196–202. [PubMed: 16469680]
34. Juneja M, et al. NSAIDs and hormone replacement therapy in geriatric crohn's disease. *American Journal of Gastroenterology*. 2010; 105:S463.
35. Mahadevan U, et al. Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease. *Am J Gastroenterol*. 2002; 97(4):910–4. [PubMed: 12008668]
36. Matuk R, et al. The spectrum of gastrointestinal toxicity and effect on disease activity of selective cyclooxygenase-2 inhibitors in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2004; 10(4):352–6. [PubMed: 15475742]
37. Biancone L, et al. Rofecoxib and early relapse of inflammatory bowel disease: an open-label trial. *Aliment Pharmacol Ther*. 2004; 19(7):755–64. [PubMed: 15043516]
38. Reinisch W, et al. An open-label trial of the selective cyclo-oxygenase-2 inhibitor, rofecoxib, in inflammatory bowel disease-associated peripheral arthritis and arthralgia. *Aliment Pharmacol Ther*. 2003; 17(11):1371–80. [PubMed: 12786631]
39. El Miedany Y, et al. The gastrointestinal safety and effect on disease activity of etoricoxib, a selective cox-2 inhibitor in inflammatory bowel diseases. *Am J Gastroenterol*. 2006; 101(2):311–7. [PubMed: 16454836]
40. Sandborn WJ, et al. Safety of celecoxib in patients with ulcerative colitis in remission: a randomized, placebo-controlled, pilot study. *Clin Gastroenterol Hepatol*. 2006; 4(2):203–11. [PubMed: 16469681]
41. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2010; 105(3):501–23. quiz 524. [PubMed: 20068560]
42. Bjarnason I, et al. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. *Gastroenterology*. 1993; 104(6):1832–47. [PubMed: 8500743]
43. Hawkey CJ. Non-steroidal anti-inflammatory drug gastropathy: causes and treatment. *Scand J Gastroenterol Suppl*. 1996; 220:124–7. [PubMed: 8898449]

44. Musumba C, Pritchard DM, Pirmohamed M. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. *Aliment Pharmacol Ther.* 2009; 30(6):517–31. [PubMed: 19575764]
45. Matsui H, et al. The pathophysiology of non-steroidal anti-inflammatory drug (NSAID)-induced mucosal injuries in stomach and small intestine. *Journal of Clinical Biochemistry and Nutrition.* 2011; 48(2):107–111. [PubMed: 21373261]
46. Wallace JL. Nonsteroidal anti-inflammatory drugs and gastroenteropathy: the second hundred years. *Gastroenterology.* 1997; 112(3):1000–16. [PubMed: 9041264]
47. Bonner GF. Using COX-2 inhibitors in IBD: anti-inflammatories inflame a controversy. *Am J Gastroenterol.* 2002; 97(4):783–5. [PubMed: 12003408]
48. Kvasnovsky CL, Aujla U, Bjarnason I. Nonsteroidal anti-inflammatory drugs and exacerbations of inflammatory bowel disease. *Scand J Gastroenterol.* 2015; 50(3):255–63. [PubMed: 25314574]
49. Forrest K, Symmons D, Foster P. Systematic review: is ingestion of paracetamol or non-steroidal anti-inflammatory drugs associated with exacerbations of inflammatory bowel disease? *Aliment Pharmacol Ther.* 2004; 20(10):1035–43. [PubMed: 15569105]
50. Kefalakes H, et al. Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality? *Eur J Clin Pharmacol.* 2009; 65(10):963–70. [PubMed: 19711064]
51. Miao XP, et al. Selective cyclooxygenase 2 inhibitors for the treatment of rheumatological manifestations of inflammatory bowel disease. *Journal of Digestive Diseases.* 2014; 15:84.
52. Samuel S, et al. CUMULATIVE INCIDENCE AND RISK FACTORS FOR HOSPITALIZATION AND SURGERY IN A POPULATION-BASED COHORT OF ULCERATIVE COLITIS. *Inflammatory bowel diseases.* 2013; 19(9):1858–1866. [PubMed: 23660997]
53. Solberg IC, et al. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Hepatol.* 2007; 5(12):1430–8. [PubMed: 18054751]

** Multiple entries

Figure 1.
Flow Diagram of Eligible Studies

Figure 2.
Meta-Analysis of NSAIDs Use and Risk of IBD Exacerbation

Figure 3.
Meta-Analysis of Acetaminophen Use and Risk of IBD Exacerbation

Figure 4.
Meta-Analysis of NSAIDs Use and Risk of IBD Exacerbation Among Studies with Low Risk of Bias

Figure 5.
Meta-Analysis of NSAIDs Use and Risk of IBD Exacerbation Among Cohort Studies

Characteristics of Studies Included in the Meta-analysis of NSAIDs Use and Risk of IBD Exacerbation

Table 1

Author	Year	Disease	Study design	Sample size	Exposure definition	Exposure duration	Outcome definition	Newcastle Ottawa score
Rampton [21]	1983	UC	Case-control	83	NSAIDs	4 weeks	Clinical relapse, confirmed by the presence of mucosal inflammation with contact or spontaneous bleeding on sigmoidoscopy	4
Foster [26]	1989	UC	Case-control	82	NSAIDs	1 month	Clinical relapse confirmed on sigmoidoscopy	4
Evans [6]	1997	CD	Case-control	791	NSAIDs	<45 days	Emergency admission due to symptoms flare	7
		UC	✓	607	✓	✓		
		IBD	✓	1398	✓	✓		
Bonner [28]	2000	CD	Case-control	112	NSAIDs	N/A	Active vs inactive disease (by a gastroenterologist)	6
		UC	✓	80	✓	✓		
Felder [20]	2000	IBD	Case-Control	122	NSAIDs	<1 month	IBD exacerbation determined by a combination of history, physical examination, blood tests, GI x-rays, and endoscopy.	3
Aalykke [25]	2000	IBD	Retrospective cohort	669	NSAIDs	N/A	N/A(Relapse)	8
Dominicz [27]	2000	IBD	Retrospective cohort	1940	NSAIDs	6 months	Disease flare requiring steroids or hospitalization	8
Meyer [32]	2006	IBD	Case-Control	60	NSAIDs + Selective COX	1 month	Active vs inactive disease (by 3 gastroenterologists)	6
Bernstein [29]	2010	IBD	Prospective Cohort	552	NSAIDs	3 months	Manitoba IBD index>4-level symptoms	9
Dhingra [23]	2012	UC	Prospective cohort	95	NSAIDs	15 days	Clinical relapse	5
Feagin [31]	2014	IBD	Case-Control	134	NSAIDs	3 months	Mayo>2 UC, CDAI>150 CD	8
Hensley [8]	2015	CD	Case-control	46	NSAIDs	3 months	Endoscopic Mayo score 2 in any ileocolonic segment.	7
		UC	✓	110	✓	✓	Simple colitis activity index >3.	
		IBD	✓	158	✓	✓	Harvey-Bradshaw or simple colitis activity index >3.	

Author	Year	Disease	Study design	Sample size	Exposure definition	Exposure duration	Outcome definition	Newcastle Ottawa score
Long[9]	2016	CD	Prospective Cohort	572	NSAIDs	6 months	Short CD activity(sCDAD)	150.
		UC	✓	219	✓	✓	Simple clinical colitis activity index >2.	
		IBD	✓	791	✓	✓	Manitoba disease index	

CD= crohn's disease, IBD= inflammatory bowel disease, UC= ulcerative colitis, N/A= not available.

Characteristics of Studies Included in the Systematic Review of NSAIDs Use and Risk of IBD Exacerbation

Table 2

Author	Year	Disease	Study design	Sample size	Exposure definition	Exposure duration	Results
Riley [22]	1990	UC	Prospective cohort	92	NSAIDs	48 weeks	35 patients (38%) relapsed. Relapsers and non-relapsers show no significant differences in the reporting of analgesic use. Clinical relapse confirmed on sigmoidoscopy
Bonner [30]	2004	UC & CD	Prospective cohort	629	Any NSAIDs (low dose vs. high dose for at least 3 days prior to clinic visit)	N/A	For CD patients, average MHB score of 4.07 for the no-NSAIDs group, 4.24 for low-dose NSAIDs (P = 0.46), and 4.78 for high-dose (P = 0.0072 versus no NSAIDs). UC patients corresponding scores were 5.64, 5.46, and 6.20, respectively (P = not significant)
Takeuchi [33]	2006	IBD	Non-randomized clinical trial	143	Naproxen Indomethacin Diclofenac Nabumetone	1 months	Trial one: Naproxen use associated with relapse in 9 (28%) patients. Relapse occurred in 5 (24%) patients with Indomethacin use and 5 (17%) patients who used Diclofenac. Trial two: 4 (20%) patients each in the naproxen and nabumetone treated groups had relapse.
Jejuma [34]	2010	CD	Retrospective cohort	90	NSAIDs	18 months	Among patients with active CD, 9.4% were on NSAIDs while the inactive CD cohort had 15.5% receiving NSAIDs. This study of geriatric CD patients suggests that use of NSAIDs did not correlate with increased rates of disease activity.
Feagin [24]	2011	IBD	Case-control	56	NSAIDs	6 months	Fisher's exact test revealed that the only significant difference in the frequency of potential triggers between the two groups was for medication non-compliance

CD= crohn's disease, IBD= inflammatory bowel disease, UC= ulcerative colitis, NSAIDs= non-steroidal anti-inflammatory drug, MHB= modified Harvey Bradshaw, N/A= not available.

Table 3
 Characteristics of Studies Examining Use of COX-2 Inhibitors and Risk of IBD Exacerbation

Author	Year	Disease	Study design	Sample size	Exposure definition	Exposure duration	Results
Mahadevan [35]	2002	UC, CD, Pouchitis	Retrospective cohort	27	Celecoxib 200mg/day or rofecoxib 25mg/day	Median 9 months	2 (7.4%) patients, 95% CI (2–23%), experienced exacerbation of their IBD from baseline after initiating therapy.
Reinisch [38]	2003	UC & CD	Prospective open-label trial	32	Rofecoxib 12.5–25 mg/day	20 days	In 2 (10%) CD patients, rofecoxib (12.5 mg/day) was discontinued after 1 and 3 days, respectively, due to diarrhea and bleeding from a perianal fistula. No flare of IBD occurred.
Matuk [36]	2004	UC & CD	Retrospective cohort	33	Celecoxib or rofecoxib	<1 week – 6 weeks	13 (39%) patients experienced IBD exacerbation; 8 (61%) had CD, 4 (31%) had UC and 1 had indeterminate colitis
Biancone [37]	2004	UC & CD	Prospective open-label trial	51	Rofecoxib 12.5 mg/day	2 days – 1 month	Rofecoxib use was associated with increased GI symptoms inducing clinical relapse in 5 (20%) CD and 4 (20%) UC patients. IBD vs. controls (dyspeptic patients), $p < 0.001$.
Takeuchi [33]	2006	IBD	Non-randomized clinical trial	20	Nimesulide	1 months	Trial two: 1 (5%) patient had relapse with nimesulide use.
Sandborn [40]	2006	UC	Multicenter RCT	222	Celecoxib 200mg BID	14 days	No significant difference in rate of UC exacerbation between treatment and placebo groups. $RR=0.73$ (0.17,3.18)
El Miedany [39]	2006	UC & CD	Multicenter RCT	146	Etoricoxib 60–120 mg/day	3 months	No difference between treatment and control groups in disease activity index of IBD. ($p > 0.05$). $RR=0.92$ (0.37, 2.32)
Hensley [8]	2015	IBD	Case-control	7	Celecoxib or Etoricoxib	3 months	Only 1 patient out of total 7 had an IBD relapse. Unadjusted OR = 0.27 (0.03–2.28)

CD= crohn's disease, IBD= inflammatory bowel disease, UC= ulcerative colitis, GI= gastrointestinal, RR= relative risk, OR= odds ratio

Table 4
 Characteristics of Studies Examining Use of Acetaminophen and Risk of IBD Exacerbation

Author	Year	Disease	Study design	Sample size	Exposure definition	Exposure duration	Results
Rampton [21]	1983	UC	Case-control	83	Acetaminophen	4 weeks	Acetaminophen was significantly related to relapse (48% (10/21) vs 21% (13/62), chi-square 4.33, p<0.05). Crude RR 2.27 (1.17, 4.39)
Foster [26]	1989	UC	Case-control	82	Acetaminophen	1 month	Proportion of patients in relapse using acetaminophen was 56% compared with 40% of patients in remission. These differences are not statistically significant. Crude RR 1.39 (0.87, 2.23)
Dominitz [27]	2000	IBD	Retrospective cohort	1940	Acetaminophen	6 months	67% of all patients had exposure to acetaminophen. Hazard ratio of IBD flare with acetaminophen use was 1.57 (1.21, 2.03)
Takeuchi [33]	2006	IBD	Non-randomized clinical trial	46	Acetaminophen	1 months	Trial one: No relapse among 26 patients. Trial two: 1 relapse among 20 patients.
Hensley [8]	2015	IBD	Case-control	65	Acetaminophen	3 months	Acetaminophen use was associated with non-significant increase in IBD relapse rates (adjusted OR 1.43 (0.65, 3.14).
Long [9]	2016	UC & CD	Prospective cohort	791	Acetaminophen	6 months	Acetaminophen use at baseline among individuals with CD was independently associated with active disease at follow-up (adjusted RR, 1.72 (1.11, 2.68). Unadjusted RR for UC 1.06 (0.82, 1.35).

CD= crohn's disease, IBD= inflammatory bowel disease, UC= ulcerative colitis, NSAIDs= non-steroidal anti-inflammatory drug, RR= relative risk, OR= odds ratio