

Systematic Review

# New Onset Inflammatory Bowel Disease Risk Following Bariatric Surgery: A Systematic Review and Meta-Analysis of Observational Studies

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**Abstract:** Background: While bariatric surgery may reduce obesity-associated inflammation, alterations in gut microbiome and nutrition could impact inflammatory bowel disease (IBD) risk. This study aimed to investigate the association between bariatric surgery and new onset IBD. Methods: A systematic review and meta-analysis of observational studies was conducted from inception to 31 January 2024. Risk estimates were pooled using a DerSimonian and Laird random-effects model, and adjusted hazards ratios (HRs) with corresponding 95% confidence interval (CI) were reported. The modified Newcastle-Ottawa Quality Assessment Scale (NOS) was used to examine the risk of bias. Results: Of 98 articles screened, four studies comprising 4,727,600 participants were included in the systematic review and two studies in the meta-analysis. Included studies had high quality and low risk of bias according to NOS. The pooled analysis revealed a significant risk of new onset IBD (HR: 1.28, 95% CI: 1.04–1.53,  $I^2 = 74.9\%$ ), particularly Crohn's disease (HR: 1.75, 1.59–1.92,  $I^2 = 0$ ), following bariatric surgery, but no significant risk of ulcerative colitis (HR: 0.93, 0.75–1.11,  $I^2 = 11.5\%$ ). Conclusions: This meta-analysis found that bariatric surgery was associated with a higher risk of developing Crohn's disease. Patients should be counseled on IBD risk pre-surgery, and symptomatic patients should be evaluated post-surgery to enable early diagnosis and management.

**Keywords:** Crohn's disease; ulcerative colitis; Roux-en-Y; sleeve gastrectomy



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## 1. Introduction

Bariatric surgery has long been recognized as the most efficacious and enduring surgical intervention for obesity and its correlated metabolic conditions, including metabolic syndrome, metabolic-dysfunction-associated steatotic liver disease and possibly liver cancer [1,2]. In 2022, over 250,000 bariatric surgeries were performed in the United States, illustrating its increasing importance in combatting the obesity epidemic [3]. Notably, surgical interventions such as sleeve gastrectomy followed by Roux-en-Y gastric bypass (RYGB) are the leading bariatric procedures performed in the United States, as compared to endoscopic procedures such as endoscopic sleeve gastropasty and intragastric balloon [1,3].

After bariatric surgery, it is not uncommon for patients to develop gastrointestinal (GI) manifestations due to a myriad of factors [4]. These manifestations encompass symptoms such as nausea, vomiting and abdominal pain, often attributable to the anatomical modifications leading to gastric restriction, alterations in gastric motility, particularly notable in procedures such as sleeve gastrectomy and changes in the microbiome [4]. Furthermore, patients may present with symptoms stemming from the anatomical changes post-RYGB,

including diarrhea, dumping syndrome, malabsorption and nutritional deficiencies [5]. Additionally, uncommon adverse events post bariatric surgery encompass strictures, fistulas and GI bleeding [4,5].

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder predominantly affecting the GI tract, encompassing mainly two conditions: Crohn's disease (CD) and ulcerative colitis (UC) [6]. Despite extensive research efforts, the pathogenesis of IBD is still unclear, with the current understanding implicating a multifaceted interplay involving genetic predisposition, immune system dysregulation, environmental factors and lifestyle influences [7]. Emerging data underscore a substantial correlation between obesity and IBD, purportedly influenced by the inflammatory milieu and alterations in gut microbiota observed in individuals with obesity [6,7]. Additionally, data suggest that IBD and diabetes mellitus type I—which is a common comorbidity that might impact the choice of bariatric surgery—share parallel immune-mediated pathogenesis that might impact the disease association, risk and clinical outcomes [8].

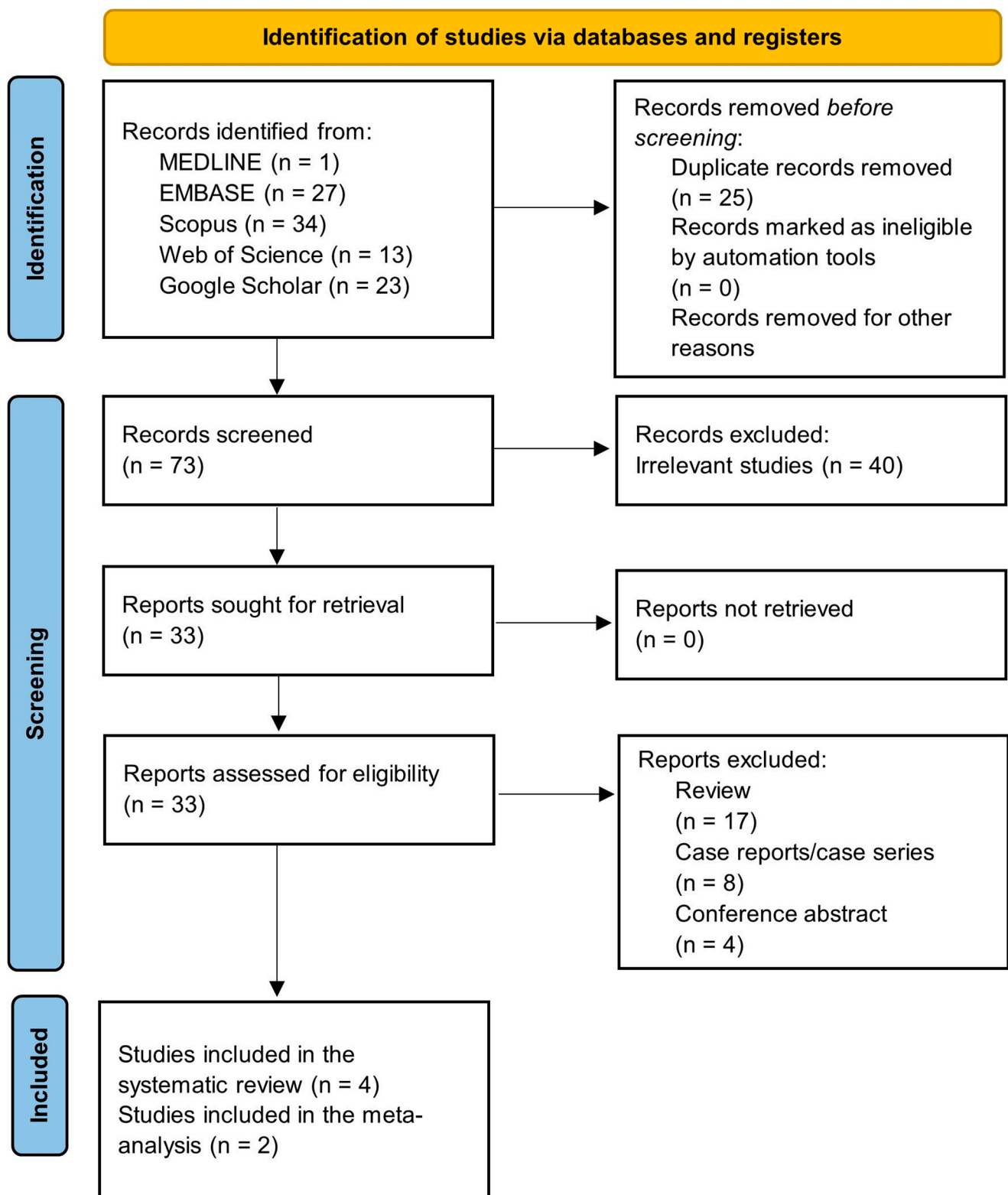
Furthermore, evidence suggests that surgical interventions targeting weight reduction, such as bariatric surgery, may confer beneficial effects in alleviating symptoms and enhancing outcomes in patients suffering from IBD [6,7,9]. Nonetheless, the association between bariatric surgery and the development of new onset IBD is controversial [9,10]. Some studies have reported an increased risk of the development of new onset IBD following bariatric surgery [11]. Conversely, other studies have indicated that the bariatric surgery might decrease the risk of new onset IBD [12].

The association between new onset IBD, CD and UC and bariatric surgery remains an area warranting further investigation. Although previous studies have been published on this topic, this is the most up-to-date study to provide a precise estimate of new onset IBD, CD and UC, which was not achieved in previous studies [9,10,13]. Therefore, the aim of this study is to systematically search the literature for observational studies evaluating the risk of new onset IBD following bariatric surgery and to provide a point risk estimate when prior study results are mixed.

## 2. Materials and Methods

### 2.1. Literature Search

A systematic review and meta-analysis were conducted according to the updated PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines [14], as illustrated in Figure 1. An experienced medical librarian performed searches between 1 and 5 February 2024 of the electronic databases MEDLINE, EMBASE, Scopus, Web of Science and Google Scholar (hand-searched the first 10 pages) for articles of observational studies assessing the risk of new onset IBD following bariatric surgery. The combination of free text and medical subject heading (MeSH) terms of “human”, “clinical studies”, “new onset”, “de novo”, “inflammatory bowel disease”, “Crohn's disease”, “ulcerative colitis”, “bariatric surgery”, “gastric banding”, “sleeve gastrectomy”, “laparoscopic sleeve gastrectomy”, “gastric bypass”, “Roux-en-Y”, “gastroplasty”, “observational study”, “cohort analysis”, “retrospective studies”, “prospective studies”, “outcome assessment” and “disease association” was used. All studies published from inception up to 31 January 2024 and in English language were considered in the study. A manual check of references of selected studies and previously published systematic reviews and meta-analysis was also conducted. The study was registered in PROSPERO, registration ID: 569410.



**Figure 1.** PRISMA flow chart of the included studies.

## 2.2. Study Selection

The systematic review included studies if they (1) used a cohort or case-control design; and (2) evaluated the risk of new onset IBD following bariatric surgery among adult population by reporting the hazards ratio (HR). Excluded studies were case reports, case series, editorials, reviews, conference abstracts, randomized controlled trials, in vitro and

nonhuman studies. For analysis, a history of bariatric surgery including sleeve gastrectomy and RYGB is considered the exposure, while the development of new onset IBD, CD or UC is considered the outcome.

### 2.3. Data Extraction

A total of 98 articles were exported from EndNote into Covidence. Of these, 25 duplicates were removed leaving an initial count of 73 articles for screening. Two independent authors (WAA and NB) screened titles and/or abstracts followed by full-text screening according to the prespecified inclusion criteria. Conflicts that arose during the screening process were resolved by consensus. The following information was collected: first author, journal, year, study design, study location, study population, sample size, sex, bariatric surgery type, number of CD and UC cases, follow-up, confounding factors and the HR estimates with their 95% confidence interval (CI).

Two authors (WAA and ASB) independently assessed the risk of bias using the modified Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control and cohort studies [15]. The maximum score for NOS is nine points: (0–4) for selection, (0–2) for comparability and (0–3) for exposure/outcome of the study. The quality of the study is classified according to the total points to low (0–3), moderate (4–6) and high (7–9).

### 2.4. Statistical Analysis

All statistical analyses were conducted using STATA 18 MP (StataCorp, College Station, TX, USA). The combined outcome results were reported as adjusted HR and 95% CI using the DerSimonian and Laird random-effects models. Heterogeneity among the included studies were evaluated using the Cochran Q test ( $P_{\text{heterogeneity}}$ ) and  $I^2$  statistics and were classified as low (25%), moderate (50%) or high (75%).

## 3. Results

### 3.1. Studies' Characteristics

Figure 1 shows the database search strategy used to identify the included studies. A total of 98 studies were identified, of which 25 duplicates and 40 irrelevant studies were removed. Thirty-three records were assessed for eligibility, of which 17 reviews, 8 case reports/case series and 4 conferences abstracts were removed, leaving 4 studies for full-text review. Four studies were included in the systematic review [16–19] and two studies in the meta-analysis [16,17]. Kochhar et al. reported the prevalence odds ratio which could not be approximated to HR [18], while Ungaro et al. provided the odds ratios of CD and UC after recent and past history of bariatric surgery [19]; given the inconsistent reporting of those two studies, it was decided to exclude them from the meta-analysis.

Table 1 summarizes the characteristics of the included studies. Overall, two studies were retrospective cohort [16,18], one prospective cohort [17] and one had both case series and a matched case-control design [19], published between 2018 and 2022. Two studies were conducted in the United States [18,19], one in Sweden [16] and one in Denmark [17]. The total sample size was 4,727,600 participants. No participants with previous diagnosis of IBD at baseline were included in the cohort studies. According to the modified NOS, all the included studies were of high quality (Table 2).

Table 1. Characteristics of the included studies.

| Author              | Journal                                  | Year | Study Design         | Country | Study Population                                                       | Sample Size | Sex (M:F)                      | Surgery Type                       | IBD                                                  | CD                                                 | UC                                                  | Follow-Up                                                           | Factors Adjusted for                                                          |
|---------------------|------------------------------------------|------|----------------------|---------|------------------------------------------------------------------------|-------------|--------------------------------|------------------------------------|------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Kiasat et al. [16]  | Surgery for Obesity and Related Diseases | 2022 | Retrospective cohort | Sweden  | Scandinavian Obesity Surgery Registry (SOREg)                          | 698,718     | 165,067 (M)<br>533,651 (F)     | RYGB: 54,465<br>SG: 9723           | Controls: 2006<br><br>BS: 285<br>RYGB: 264<br>SG: 21 | Controls: 701<br><br>BS: 123<br>RYGB: 119<br>SG: 4 | Controls: 1116<br><br>BS: 111<br>RYGB: 97<br>SG: 14 | Controls: 3,444,186 person-years<br><br>Cases: 346,860 person-years | Sex, age and preoperative BMI, for SG                                         |
| Allin et al. [17]   | Journal of Crohn's and Colitis           | 2021 | Prospective cohort   | Denmark | Danish Civil Registration System                                       | 3,917,843   | 2,001,473 (M)<br>1,916,370 (F) | RYGB: 13,827<br>SG: 937<br>GB: 583 | Controls: 35,294<br><br>BS: 100                      | Controls: 11,199<br><br>BS: 51                     | Controls: 23,955<br><br>BS: 49                      | 14.8 years (median)                                                 | Age, sex, birth cohort, education and number of obesity-related comorbidities |
| Kochhar et al. [18] | Alimentary Pharmacology & Therapeutics   | 2020 | Retrospective cohort | USA     | Health Insurance Portability and Accountability Act compliant database | 59,000      | 22,078 (M)<br>36,922 (F)       | RYGB<br>SG<br>GB                   | Controls: 58,530<br><br>BS: 470                      | Controls: 31,110<br><br>BS: 260                    | Controls: 27,420<br><br>BS: 210                     | -                                                                   | -                                                                             |
| Ungaro et al. [19]  | Alimentary Pharmacology & Therapeutics   | 2018 | Matched case-control | USA     | Symphony Health Solutions LLC (SHA) Integrated Dataverse (IDV)         | 52,039      | 19,934 (M)<br>32,105 (F)       | RYGB<br>SG<br>GB                   | -                                                    | -                                                  | -                                                   | 4.3 years (mean)                                                    | Age, obesity and medications exposure                                         |

BMI: body mass index, BS: bariatric surgery, CD: Crohn's disease, F: female, GB: gastric banding, IBD: inflammatory bowel disease, M: male, RYGB: Roux-en-Y gastric bypass, SG: sleeve gastrectomy, UC: ulcerative colitis, USA: United States of America.

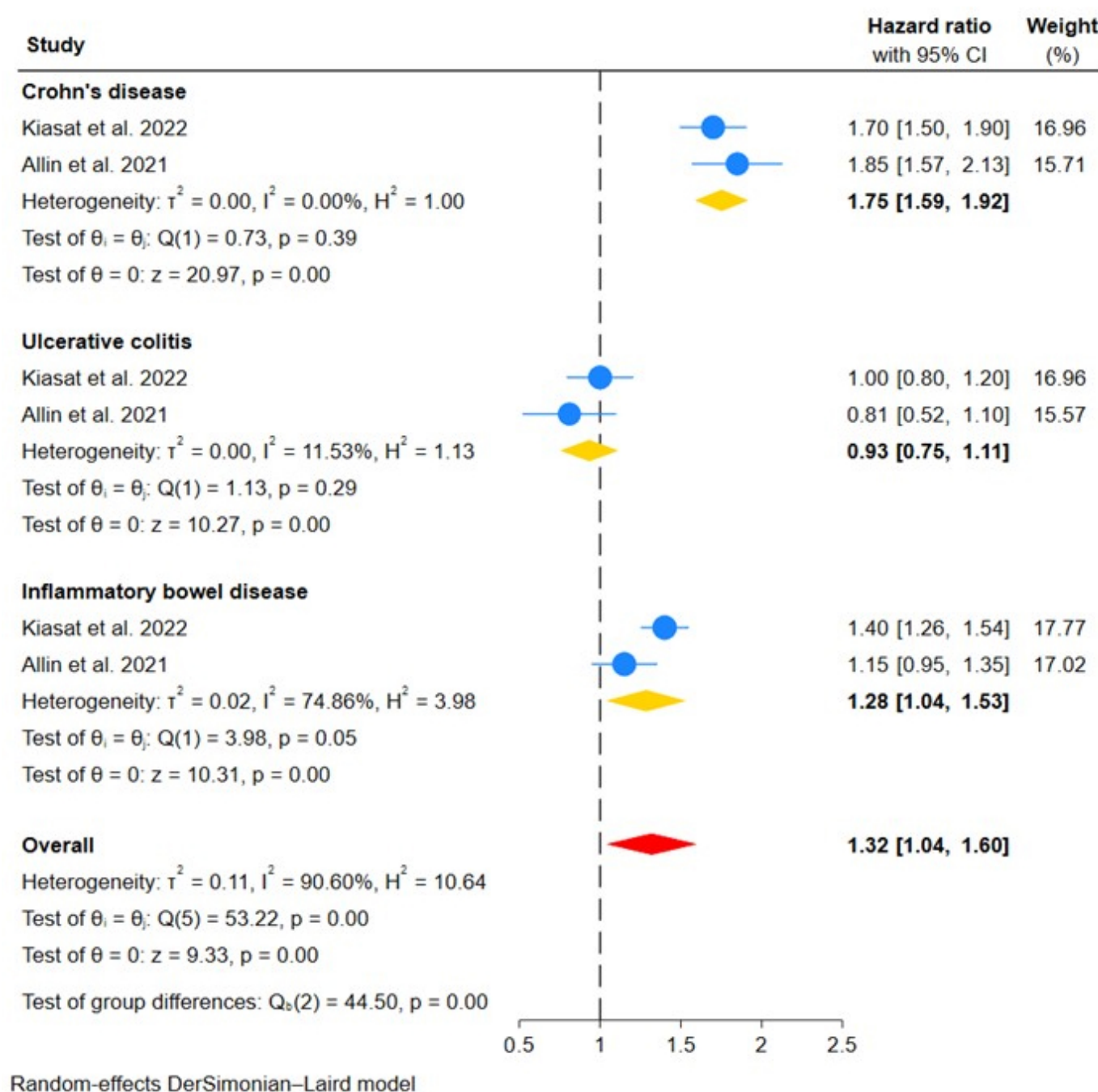
**Table 2.** Quality assessment of the included studies.

| Cohort Studies       |                          |                          |                        |                                                           |                    |                               |                        |                         |                    |         |
|----------------------|--------------------------|--------------------------|------------------------|-----------------------------------------------------------|--------------------|-------------------------------|------------------------|-------------------------|--------------------|---------|
| Selection            |                          |                          |                        |                                                           | Comparability      |                               |                        | Outcome                 |                    |         |
| Studies              | Representativeness       | Selection of non-exposed | Exposure ascertainment | The outcome of interest was not present at start of study | Age                | Controlled factors            | Outcome assessment     | Follow-up period        | Follow-up adequacy | Total * |
| Kiasat et al. [16]   | 1                        | 1                        | 1                      | 1                                                         | 1                  | 1                             | 1                      | 1                       | 1                  | 9       |
| Allin et al. [17]    | 1                        | 1                        | 1                      | 1                                                         | 1                  | 1                             | 1                      | 1                       | 1                  | 9       |
| Kochhar et al. [18]  | 1                        | 1                        | 1                      | 1                                                         | 1                  | 1                             | 1                      | 0                       | 0                  | 7       |
| Case-control studies |                          |                          |                        |                                                           |                    |                               |                        |                         |                    |         |
| Selection            |                          |                          |                        |                                                           | Comparability      |                               |                        | Exposure                |                    |         |
| Studies              | Case definition adequacy | Representativeness       | Controls selection     | Controls definition                                       | Controlled factors | Controlled additional factors | Exposure ascertainment | Method of ascertainment | Non-response rate  | Total * |
| Ungaro et al. [19]   | 1                        | 1                        | 1                      | 1                                                         | 1                  | 1                             | 1                      | 1                       | 1                  | 9       |

\* A total score of (0–3) indicates low quality, (4–6) indicates moderate quality, and (7–9) indicates high quality.

### 3.2. The Risk of New Onset IBD Development Following Bariatric Surgery

Figure 2 shows the meta-analysis of two studies evaluating the risk of new onset IBD following bariatric surgery [16,17]. The overall pooled adjusted HR of the new onset IBD following bariatric surgery versus the non-exposed groups was 1.32 (95% CI: 1.04–1.60). Our pooled analysis found a significant risk of new onset IBD (HR: 1.28, 95% CI: 1.04–1.53,  $I^2 = 74.9\%$ ) and CD (HR: 1.75, 95% CI: 1.59–1.92,  $I^2 = 0$ ) following bariatric surgery. However, no significant UC risk (HR: 0.93, 95% CI: 0.75–1.11,  $I^2 = 11.5\%$ ) was found. The overall heterogeneity of the included studies was high ( $I^2 = 90.6\%$ ).



**Figure 2.** Risk of new onset inflammatory bowel disease following bariatric surgery. Kiasat et al. [16], Allin et al. [17].

#### 4. Discussion

In this study, we performed a systematic review and meta-analysis to explore the risk of new onset IBD after bariatric surgery. Initially, we meticulously reviewed the existing literature, identifying four relevant articles for inclusion in our systematic review [16–19]. Among these, a study by Kiasat et al. stands out—a population-based retrospective investigation conducted in Sweden utilizing data from patients enrolled in the Scandinavian Obesity Surgery Registry who underwent either RYGB or sleeve gastrectomy between 2007 and 2018 [16]. They compared these cohorts with a control group matched for age, sex and geographic location and found that patients who underwent bariatric surgery exhibited increased risks for IBD (HR 1.4) and CD (HR 1.7), but no significant elevation in the risk of developing UC (HR 1.0); similar patterns were observed for patients undergoing RYGB, with increased risks for IBD (HR 1.4) and CD (HR 1.8), but not UC (HR 0.9), compared to the control group. However, in patients undergoing sleeve gastrectomy, although an increased risk for UC (HR 1.8) was observed, the risks for IBD (HR 1.5) and CD (HR 0.8) did not reach statistical significance. This could potentially be attributed to the smaller size of the sleeve gastrectomy cohort (9730 compared to 54,465 in the RYGB group) and their shorter follow-up duration, thereby contributing to the ambiguity of the results in this subgroup. One significant constraint of this study is its omission of patient assessment based on their body mass index (BMI).

Another population-based study, conducted prospectively by Allin et al., involved Danish citizens from 1996 to 2018, with bariatric surgery as the exposure and IBD, UC or CD as outcomes, utilizing the Danish National Patient Register [17]. The register's outcomes were deemed complete and valid upon comparison with pathology register information. Utilizing Cox proportional hazards regression models, they found a statistically significant adjusted HR of 1.85 for developing new onset CD after bariatric surgery, adjusting for age, sex, birth cohort, education and number of obesity-related comorbidities, while the HRs were not statistically significant for UC at 0.81. Notably, 90% of patients undergoing bariatric surgery in this study opted for RYGB. Additionally, a sensitivity analysis was performed, restricting it to individuals diagnosed with overweight/obesity, yielding results consistent with the main study findings.

Meanwhile, Kochhar et al. conducted a population-based study using a U.S. based-health insurance database to assess the prevalence of new onset IBD among patients undergoing bariatric surgery, comparing them with obese controls with a BMI above 30 from 1999 to 2018 [18]. The study found a statistically significant lower prevalence of new onset UC or CD after bariatric surgery compared to obese controls, across all types of bariatric surgery except for CD after RYGB, which did not reach statistical significance. However, the study did not account for the duration of follow-up, instead recording prevalence rather than incidence rates, and calculated prevalence odds ratios. It is important to note that the control group consisted of obese patients, and there was no adjustment for confounders. Additionally, they did not include patients as new onset IBD if they were only exposed to 5-ASA therapy, potentially leading to the omission of mild IBD cases. The authors suggested that the persistence of obesity after bariatric surgery might be a crucial factor in the development of IBD.

One additional study incorporated into our systematic review is a matched case-control investigation conducted by Ungaro et al. [19]. The study utilized a U.S.-based medical and pharmacy claims database spanning from 2008 to 2012 to compare patients diagnosed with IBD to controls. Logistic regression was used to derive odds ratios, presenting the results. The finding showed that individuals with new onset IBD had significantly higher odds of having undergone bariatric surgery in the past (occurring more than four years prior) but not recently, compared to matched controls, with this association being significant even after adjusting for age, obesity and medication exposure. In the study, they categorized new onset IBD based on a criterion of at least three separate encounters with an associated ICD-9-CM code for CD or UC in 2012. Patients were excluded if they had any ICD-9-CM codes or prescriptions for IBD-related medication prior to the first ICD-9-CM

code in 2012. However, due to their inability to verify whether patients identified as having new onset IBD were truly new cases, limitations exist in this regard.

In our study, we conducted a meta-analysis to assess the likelihood of developing new onset IBD subsequent to bariatric surgery, revealing a notable correlation with a statistically significant HR of 1.28, indicating a 28% increased risk among individuals with a history of bariatric surgery. Moreover, upon analyzing the data for subtypes of IBD, it became evident that there is a statistically significant HR of 1.75 for CD, suggesting a 75% heightened risk for CD following bariatric surgery. However, the HR of 0.93 for UC, not statistically significant, does not suggest a connection between bariatric surgery and new onset UC. In the meta-analysis, we restricted our inclusion to studies conducted by Kiasat et al. and Allin et al. [16,17], as both utilized Cox proportional hazards regression models, yielding results in HRs rather than other effect measures. This decision was made to avoid potential bias and enhance interpretability, considering the different assumptions associated with each effect measure. Furthermore, we excluded the study by Kochhar et al. from the meta-analysis because they utilized controls with BMI above 30, did not account for follow-up duration and excluded cases solely exposed to 5-ASA, potentially resulting in the exclusion of mild IBD cases, all factors that could complicate comparisons with other studies [18]. Meanwhile, the study by Ungaro et al. was a case-control study rather than a cohort study, and although they identified 253 patients with prior bariatric surgery, they did not specify the proportion of these patients who developed new onset IBD, CD or UC [19].

The precise pathogenesis of IBD remains unclear, much like the understanding of why bariatric surgery is linked with CD. One proposed explanation is that bariatric surgery may alter the composition of the gut microbiome, similar to the dysbiosis observed in IBD, with this dysbiosis potentially being more pronounced in CD than in UC [12,20–25]. This alteration might be implicated in a decrease in firmicutes and an increase in *Faecalibacterium prausnitzii*. Gut microbiome changes are more pronounced in anatomy-altering surgeries like RYGB compared to purely restrictive procedures such as sleeve gastrectomy. This observation might explain why certain studies show an association between IBD and RYGB but not with sleeve gastrectomy, although this could be due to the relatively smaller number of sleeve gastrectomy patients in the existing literature, along with insufficient follow-up time to evaluate IBD development [16]. Furthermore, the influence of the gut microbiome on IBD remains poorly understood and requires further evaluation. It is important to highlight that studies included in our systematic review have demonstrated that the duration from bariatric surgery to IBD diagnosis can span several years [16,17,19]. One study suggests that a history of bariatric surgery more than four years ago [18], rather than recent surgery, is associated with new onset IBD, with another study reporting a mean duration of 3.6 years [16] and another showing a median of four years [17].

Previous studies reported a dose-response relationship between obesity and the incidence of CD regardless of surgical history [26,27]. Similarly, research by Holt et al. suggests that visceral adiposity may independently contribute to post-operative CD recurrence [28], potentially explaining the association of bariatric surgery with CD rather than UC in our meta-analysis. In the studies included in our meta-analysis, Kiasat et al. did not provide information on the weight of the control cohort, and weight was not matched between groups [16]. Meanwhile, the study by Allin et al. found that both obesity and underweight were associated with CD but not UC [17]. However, it did not provide data on weight loss changes following bariatric surgery, leaving it unclear whether alterations in adipose tissue contributed to the development of CD. Additionally, Allin et al. adjusted for obesity-related comorbidities such as diabetes, hypertension and sleep apnea, reducing the likelihood that these conditions significantly influenced the development of IBD [17]. Moreover, vitamin D deficiency, common in obesity and following bariatric surgery, is associated with IBD, particularly CD, potentially contributing to the development of new onset IBD after bariatric surgery [29,30].

Furthermore, it is common practice for patients to quit smoking before elective major surgeries including bariatric surgeries. Considering smoking's impact on IBD—increasing

the risk of CD and decreasing the risk of UC—quitting smoking might be expected to have an inverse effect. However, our study revealed a contrary outcome, showing an increased risk of new onset CD but not UC. Additionally, post bariatric surgery, individuals typically experience gastrointestinal symptoms, including malabsorption, which can resemble IBD, particularly CD. This similarity could lead to misdiagnosis. However, the studies incorporated in our meta-analysis employed rigorous methodologies to ensure accurate diagnosis of new onset IBD.

Despite the aforementioned considerations, the association between bariatric surgery and new onset IBD should not sway the decision regarding whether an eligible patient undergoes bariatric surgery or not, especially since studies by Aminian et al. and Mabeza et al. demonstrated positive outcomes in IBD patients [31,32]. Furthermore, it is crucial to thoroughly evaluate patients before bariatric surgery to detect any potential latent IBD and to monitor for any incidence of IBD in the years following the procedure.

This is the most up-to-date systematic review and meta-analysis of observational studies investigating the risk of the development of new onset IBD, CD and UC following bariatric surgery. The collective sample size across included studies was 4,727,600 participants. All the included studies were of high quality according to the modified NOS. Despite this, there is a scarcity of observational studies addressing this topic, compounded by inconsistent and insufficiently informative data reporting among the included studies, which curtailed the number of studies eligible for meta-analysis. The limited number of studies and differences in study design, geography and patient characteristics contributed to this study's high heterogeneity. Moreover, due to the limited number of included studies, publication bias using funnel plot was not evaluated. Additionally, both studies included in the meta-analysis involved Scandinavian patients, highlighting the importance of investigating the generalizability of our study results through other prospective studies. The included studies did not account for healthcare access and utilization as a confounder in this population leading to detection bias; those with close follow-up after bariatric surgery may be more likely to have a disease detected than similar patients without access to care but who still have CD. In our view, this risk is low given the lack of association with ulcerative colitis; however, future studies should assess overall new onset GI conditions after bariatric surgery and compare them with other non-GI-specific elective surgeries. Moreover, a baseline endoscopic examination was not performed to rule out quiescent disease before bariatric surgery which could worsen following the procedure, thereby making bariatric surgery a risk factor for exacerbating rather than initiating IBD. Further studies are warranted to establish the risk of new onset IBD in disease-free proven population following bariatric surgery.

## 5. Conclusions

This systematic review and meta-analysis of observational studies evaluating the risk of IBD following bariatric surgery found an increased risk of new onset CD but not UC following bariatric surgery. However, the result should be interpreted with caution given this study's high heterogeneity. Patient counseling on IBD risk prior to bariatric surgery and prompt assessment of symptomatic patients post bariatric surgery may allow early detection and management. Further longitudinal studies are warranted to accurately evaluate the risk of new onset IBD following bariatric surgery.

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