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Long-term bowel function and fate of the ileal pouch after restorative proctocolectomy in patients with Crohn's disease. A systematic review with meta-analysis and metaregression.

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ABSTRACT

Background and aims: Debate exists on whether IPAA can be safely offered to patients diagnosed with CD. Aim was to assess the outcome of ileal pouch anal anastomosis (IPAA) for Crohn's disease (CD) vs ulcerative colitis (UC).

Methods: PRISMA/MOOSE-compliant meta-analysis. Studies published between 1993 and 2018 were retrieved. Primary endpoints included complications. Secondary endpoints included functional outcome. The time of CD diagnosis was considered (intentional vs incidental IPAA).

Results: Eleven studies comprising 6770 patients (CD=352, UC=6418) were included, with 44-120 months of follow-up. Pouch fistulae were more common in CD (CD vs UC; OR 6.08; $P=0.0003$, GRADE+++), as were strictures (OR 1.82; $P=0.02$, GRADE+++), and failure (OR 5.27; $P<0.0001$, GRADE++++). Compared with UC, postoperative CD diagnosis was associated with much higher risk of fistulae (OR 6.23; $P=0.006$, GRADE+++), and failure (OR 8.53; $P<0.0001$, GRADE++++), than intentional IPAA in CD (fistula: OR 4.17; $P=0.04$, GRADE+++; failure: OR 2.48; $P=0.009$, GRADE++++). Age at surgery was positively associated with failure in CD ($P=0.007$). Obstruction was more common after intentional IPAA for CD. The risk of pouchitis did not differ between CD and UC (OR 1.07, $P=0.76$, GRADE+++). CD patients were at higher risk of seepage (OR 2.27; $P=0.010$, GRADE++).

Conclusions: Patients with CD have 5-fold higher risk of failure, and 2-fold risk of strictures after IPAA compared with UC. The risk is much higher if diagnosis was performed after IPAA. Function in those who retain the pouch seemed similar to that of patients with UC. CD does not increase the risk of pouchitis. IPAA could be offered to a selected population of CD patients after proper preoperative counselling.

(PROSPERO registry 116811)

Key-words: crohn's disease; IPAA; ileoanal pouch; ulcerative colitis; pouch; restorative proctocolectomy

ABBREVIATIONS

ACPGBI: Association of Coloproctologists of Great Britain and Ireland

ASCA: anti-Saccharomyces cerevisiae antibody

CD: Crohn's disease

CI: Confidence Intervals

ECCO: European Crohn's and Colitis Organisation

ESCP: European Society of Coloproctology

GRADE: Grading of Recommendations Assessment, Development and Evaluation

IPAA: ileal pouch anal anastomosis

MOOSE: Meta-analysis Of Observational Studies in Epidemiology

OR: Odds Ratio

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

UC: ulcerative colitis

AUTHOR CONTRIBUTION

GP: Study conception and design, data interpretation and analysis, drafting of manuscript

DV: Data collection and interpretation, drafting of manuscript

GiS: Study design, data analysis and interpretation

CK: Data interpretation, critical revision of the manuscript

SC: Critical revision of the manuscript for important content

FS: Data interpretation, critical revision of the manuscript for important content

GuS: Study conception, data collection and interpretation, drafting and revision of manuscript

All authors revised and approved the final version of the manuscript.

INTRODUCTION

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is widely accepted as the surgical procedure of choice in ulcerative colitis (UC) and patients with familial adenomatous polyposis^{1,2,3}. Debate exists on whether IPAA can be safely performed in patients diagnosed with Crohn's disease (CD).

Few studies have been published on the topic, and they have always been associated with several complications and poor functional results which, in most cases, led to pouch failure⁴. As a consequence of a perceived suboptimal outcome, patients with a diagnosis of CD have typically not been offered IPAA.

Nevertheless, results from referral centres for CD^{5,6} demonstrated good results after IPAA at long-term follow-up in patients with isolated Crohn's colitis and no anoperineal involvement. The most recent European Crohn's and Colitis Organisation (ECCO) and European Society of Coloproctology (ESCP) guidelines on the surgical treatment of CD, concluded that patients with colonic CD without involvement of the perineum and small bowel may be suitable candidates for restorative proctocolectomy⁷. However, the practical implication has remained controversial, due to the low quality of available data, and due to the variability in pathologic criteria used for the diagnosis of CD¹. An additional confounder is whether the IPAA is performed before or after the diagnosis of CD (incidental vs intentional IPAA). No systematic reviews and meta-analyses have been published in the last decade on the topic.

The aim of the present study is to perform an updated evaluation of the complications and functional results of IPAA in patients with CD compared with UC. Further analyses included comparison of the outcomes of such procedure depending on the time of the diagnosis of CD.

METHODS

This is a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)⁸ and Meta-analysis Of Observational Studies in Epidemiology (MOOSE)-compliant⁹ systematic review with meta-analysis and metaregression. The review has been registered on PROSPERO Registry(<https://www.crd.york.ac.uk/prospero/> - ID 116811).

Data Sources

A systematic review of the literature was performed for articles published between 1993 and 2018. The following databases were searched: MEDLINE (PubMed), EMBASE (OvidSP), Ovid, and Cochrane Database (last search 19 October 2018). The following search terms were used: “Crohn’s colitis”, “Ileal pouch-anal anastomosis”, “Restorative Proctocolectomy”, “Crohn’s disease”, “Crohn colitis”, and “IPAA”. Cross searches were performed for references from retrieved articles. Two screeners independently performed the literature screening and review (GuS and DV). Discrepancies were addressed by agreement with a third screener (GiS).

The following data were independently extracted by the reviewers from included studies: first author, journal, country, year of publication, study type, number of patients (CD and UC), mean age of patients, and median duration of follow-up.

Inclusion and Exclusion Criteria

Only studies comparing the outcome of IPAA in CD and UC and with more than two years of follow-up were included. In the event of studies from the same centre, only the most recent or the study with more complete data was included. Only studies published as full text articles were included. Non-comparative studies, studies with calculable end-points with less than 50

patients, studies with follow-up shorter than 24 months, and those published before 1993 were not included.

Outcome Definitions

Postoperative complications represented the primary outcome measure of the present study. These included pouch failure, pelvic sepsis, pouch fistula, pouchitis, anastomotic stricture and small-bowel obstruction (SBO). The secondary outcomes included functional results, among which incontinence, urgency, seepage and pads use were considered.

Definitions are reported in the **Supplementary Table 1**.

A subset, sensitivity meta-analysis was performed in order to compare the complications in patients with CD that received diagnosis before or after IPAA versus UC.

Quality assessment and risk of bias evaluation

The Newcastle-Ottawa Scale (NOS)¹⁰ was utilized to grade the quality of included studies (nine points maximum, corresponding to highest quality).

The risk of bias was assessed by means of visual inspection of Funnel Plots. This was only considered for outcomes with more than 10 studies.

To evaluate the quality of evidence for the outputs in this study and to grade recommendations, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used¹¹.

Statistical Analysis

The effect measures estimated are reported as odds ratio (OR) with 95 percent confidence intervals (95%CI). The ratio represented the odds of an adverse event occurring in the CD group compared with UC group. **An OR>1 indicated worse results in CD**, and the point

estimate of the OR was considered statistically significant at $P < 0.05$ level if the 95%CI did not include the value “1”. Random effect model was used.

The Haldane correction was applied to studies that contained a zero in one cell for the number of events, whereby a value of 0.5 was added in both groups from that particular study.

Heterogeneity was assessed with I^2 statistic, and heterogeneity was considered significant with values of $>50\%$. The meta-analysis was performed using the Review Manager software (RevMan 5, The Cochrane Collaboration).

Meta-regression analyses were performed using STATA (STATA 15.1; StataCorp, College Station, TX) *metareg* command¹². OR were plotted against the following variables: mean age, mean duration of follow-up, year of publication. Meta-regression was only considered if a minimum of 10 publications was available for the specific aim¹². The point estimates of the log odds ratio were obtained and plotted with the area of the circles proportional to the inverse of the squared standard errors.

RESULTS

Studies Characteristics

A total of sixty studies were retrieved. The process of selecting trials for inclusion is shown in **Figure 1**. Forty-nine of these studies were excluded because of the type of study, study design, absence of primary outcome with the impossibility to calculate it according to the published data, and presence of exclusion criteria.

Finally, eleven studies^{2,5,13-21} comprising 6770 patients (CD = 352, UC = 6418) were included in the quantitative analysis. The characteristics of these studies are shown in **Table 1**.

Follow-up ranged between 44 and 120 months. **A diagnosis of CD was reached only after colectomy in 70% of cases.** GRADE-based recommendations are reported in **Table 2**.

Primary aim

Pouch Failure

All the included studies^{2,5, 13-21} reported pouch failure rates. The overall pouch failure rate was 24.7% (87/352) in the CD group and 5.7% (369/6418) in the UC group. The meta-analysis found that pouch failure was a more common complication in CD patients than in UC patients (CD vs. UC; OR 5.27; 95% CI, 2.58–10.79, $P < 0.0001$) (**Figure 2a**). Heterogeneity was high in the analysis of this primary outcome ($I^2 = 72\%$) and the funnel plot showed asymmetry (**Supplementary Figure 1**).

The pouch failure rate in the CD group with a pre-operative diagnosis was significantly **higher** compared to UC (preop CD vs. UC; OR 2.48; 95% CI, 1.25–4.92, $P = 0.009$; $I^2 = 0\%$), **but lower than** the CD group with postoperative diagnosis **compared to UC** (postop CD vs. UC; OR 8.53; 95% CI, 3.21–22.66, $p < 0.0001$; $I^2 = 80\%$) (**Figure 2b**).

Pouch Fistulae

Pouch fistulae were described in nine studies^{2,5, 13-15, 18-21}. The pouch fistula rate was 23.3% (75/322) in the CD group and 4.5% (273/6047) in the UC group, and the difference was significant (CD vs. UC; OR 6.08; 95% CI, 2.28–16.23, $P=0.0003$; $I^2=83\%$). (**Figure 3a**).

The risk of fistulae was still higher in preoperative diagnosis of CD vs UC, but at lower extent (preop CD vs. UC; OR 4.17; 95% CI, 1.08–16.12, $p=0.04$; $I^2=58\%$), while it increased with postoperative diagnosis of CD (postop CD vs. UC; OR 6.23; 95% CI, 1.67–23.19, $P=0.006$; $I^2=86\%$) (**Figure 3b**).

Anastomotic Strictures

Strictures were described in eight studies^{2, 13-15, 18-21}. The post-operative stricture rate was 19.9% (58/291) in the CD group and 13.3% (803/6047) in the UC group. The risk was higher in CD (CD vs. UC; OR 1.82; 95% CI, 1.12–2.95, $p=0.02$; $I^2=35\%$) (**Supplementary Figure 2a**).

Postoperative CD diagnosis seemed to increase the risk of strictures (preop CD vs. UC; OR 1.12; 95% CI, 0.53–2.36, $p=0.77$; $I^2=0\%$) (postop CD vs. UC; OR 1.78; 95% CI, 0.72–4.40, $P=0.21$; $I^2=77\%$) (**Supplementary Figure 2b**).

Pelvic Sepsis

Only four studies^{2,15,20,21} reported on pelvic sepsis. Pelvic sepsis rate was 15.2% (34/224) in the CD group and 8% (356/4457) in the UC group, but the difference was not statistically significant (CD vs. UC; OR 1.95; 95% CI, 0.78, 4.85, $p=0.15$; $I^2=73\%$) (**Supplementary Figure 3**).

Postoperative diagnosis of CD seemed to be associated with increased risk of pelvic sepsis (preop CD vs. UC; OR 1.09; 95% CI, 0.22–5.47, $P=0.91$; $I^2=25\%$); (postop CD vs. UC; OR 1.20; 95% CI, 0.21–7.00, $P=0.84$; $I^2=88\%$).

Small-bowel obstruction

SBO was reported in seven studies^{2,5,15,18-21}. **SBO rates in CD (19.3%) were somewhat higher than in UC (16.4%), although the difference was not statistically significant (CD vs. UC; Overall OR, 1.27; 95% CI, 0.91, 1.76; P=0.15; I²=0%).**

SBO was more common in patients with preoperative CD diagnosis than in postoperative CD group compared with UC (preop CD vs. UC; OR 2.19; 95% CI, 1.16–4.11, P=0.02; I²=0%) (postop CD vs. UC; OR 1.16; 95% CI, 0.79–1.69, P=0.45; I²=1%) (**Supplementary Figure 4**).

Pouchitis

Pouchitis was reported in nine studies^{2,14-21}, with 33.3% (95/285) and 35.7% (1860/5212) rates in CD and UC, respectively.

There were no significant differences in the incidence of pouchitis between CD and UC (OR 1.07, 95% CI, 0.70, 1.63; P=0.76; I²=32%) (**Supplementary Figure 5**).

Subset metanalysis showed a mildly increased risk in postoperative diagnosis of CD, with no statistical significance (preop CD vs. UC; OR 1.23; 95% CI, 0.58–2.62, P=0.59; I²=42%) (Figure 7.1); (postop CD vs. UC; OR 1.31; 95% CI, 0.69–2.50, P=0.40; I²=51%).

Secondary Aim

Functional Outcomes

There were no differences in terms of incontinence (CD vs. UC; Overall OR, 1.08; 95% CI, 0.78, 1.51; P=0.64; I²=5%^{2,5, 13-16, 19-21}), urgency (CD vs. UC; Overall OR, 1.89; 95% CI, 0.82, 4.35; P=0.13; I²=51%^{2,5,13,14,20}) and use of pads (CD vs. UC; Overall OR, 1.71; 95% CI, 0.72, 4.07; P=0.23; I²=66%^{2,5,13,14}) (**Supplementary Figure 6a-c**); however, patients with CD were at higher risk of seepage (CD vs. UC; OR 2.27; 95% CI, 1.21-4.29; P=0.01, I² = 35%^{2,5,13-15,20}) (**Figure 4**).

Subset analyses were not possible because of the paucity and variability of available data.

Meta-regression

Meta-regression was only performed for pouch failure (eleven studies available). There were no significant trends between age at treatment, year of publication and duration of follow-up overall (**Supplementary Figure 7a-c**). Analyses were stratified for CD and UC subgroups. In patients with CD there was a positive association between age at treatment and failure (**Figure 2c**). The estimated slope equalled 0.234 (standard error 0.065) with $t = 3.58$ and $P = 0.007$. Therefore, the risk of pouch failure increased with increasing age at treatment in patients diagnosed with CD.

DISCUSSION

This is the first PRISMA/MOOSE-compliant systematic review with metanalysis and metaregression to compare the long-term outcomes of IPAA in CD with those of UC, resulting in GRADE-based recommendations. Subsets analyses were run to compare the outcomes of IPAA in UC patients with those of 1) patients with CD who underwent IPAA after receiving diagnosis (intentional IPAA) and 2) patients who underwent IPAA and were later diagnosed with CD (incidental IPAA). CD patients were 5-fold more likely to suffer from failure, but the heterogeneity between studies and risks of bias were high. **The risk of failure was more than doubled** if IPAA was performed after receiving diagnosis of CD (“intentional” IPAA in CD) **compared with UC, but failure rates** reached up to 8 times higher in the event of CD diagnosed after IPAA (“incidental” IPAA in CD). Pelvic sepsis was also higher in CD, but subset analysis again confirmed that this is likely to be observed only for incidental IPAA. Anastomotic strictures were more common in CD, irrespective of the time at which diagnosis was performed, but postoperative diagnosis of CD further increased the risk of fistulae. SBO was twice more commonly observed after intentional IPAA vs UC, which was not the case with incidental IPAA in CD. The incidence of pouchitis was not significantly different between CD and UC, even if postoperative diagnosis of CD seemed to increase the risk. Function was comparable in both CD and UC, with slightly lower performance in CD, especially in terms of seepage. Metaregression suggested that failure is not influenced by the year of treatment and duration of follow-up, but the risk increases with increasing age in patients with CD.

IPAA is regarded as the gold standard for the surgical treatment of UC. This is very complex procedure, which can be associated with significant morbidity^{2,3,20,22}. It should also be considered that it needs a “maturation” or “adaptation” period, during which patients will be

able to adapt to a novel bowel functioning. Eventually, medium- and long-term outcomes are excellent, with good quality of life^{2,3,22-25}; results are stable with time^{2,3,26}. However, pouch-associated symptoms are common among UC patients^{25,27}, and surgical revision of the pouch might be needed, with slightly worse function^{28,29}. Concern exists about the possibility of offering IPAA to patients with CD, due to the different pathophysiology and patterns of disease as compared with UC. Septic complications that occur early after surgery can affect long-term functional results^{2,22,30}, and long-term data on IPAA for CD are sparsely reported. Recent evidence-based guidelines drafted by a panel of gastroenterologists and surgeons with expertise in IPAA, recommended that a subgroup of CD could benefit from IPAA⁷. Unsurprisingly, the quality of evidence was low, resulting in weak recommendation⁷.

Available evidence for IPAA in CD includes case reports, case series, and some comparative studies. Most studies agree that only patients with isolated colonic CD should be considered for IPAA⁵⁻⁷. Many surgeons would not consider IPAA even in this subgroup, because of the non-negligible risk of developing recurrent disease in the pouch, which might lead to pouch excision and significant reduction of bowel length, along with the risks of significant pouch dysfunction and need for long-term medical therapy³¹.

However, there have been significant improvements in the results of IPAA over the last years, which have resulted in rates of early infection and pouch failure decreasing from 22% and 13% in 2002-2009 to 11% and 2% in 2010-2015³². According to the UK pouch registry of the Association of Coloproctologists of Great Britain and Ireland (ACPGBI), pelvic sepsis and pouch failure occurred in 9.4% and 4.7% of 5352 patients over four decades³³. The most important aspect of IPAA surgery is performing the procedure in referral centres, where short- and long-term complications can be promptly detected and addressed. This led to a revived attention to the role of IPAA in CD.

Time of CD diagnosis is an important factor to be taken into account when trying to interpret available data from the literature. Regimbeau et al.⁶ reported that post-operative diagnosis of

CD was the only predictive factor of CD-related complications after IPAA. In their series, 47% of patients with a postoperative diagnosis of CD suffered from adverse events versus 15% of those with pre-operative diagnosis of CD at 10-year follow-up⁶. The need of pouch excision was also affected by the time of CD diagnosis (35% vs 10%, incidental vs intentional IPAA, respectively)⁶. Similar findings were reported by others^{1,34-37}. In our metanalysis, the outcome of IPAA for CD were assessed, but a stratification of patients was also performed, according to whether the procedure was performed intentionally or presuming that the patients suffered from UC, and they were later diagnosed with CD.

Pelvic sepsis is the most dreaded early complication of IPAA^{2, 22}, but it was only assessed in four studies^{2,15,20,21}. In the present analysis, this complication was almost twice as high in CD, although studies showed significant heterogeneity (GRADE++) (**Supplementary Figure 3**). CD patients with incidental IPAA were at increased risk of sepsis, which was not the case with intentional IPAA (GRADE+).

Strictures of the anastomosis are common after IPAA, and they can be usually dealt with by dilatation. Pouch-related fistulas and strictures are long-term complications that often raise suspicion of CD, especially for strictures of the pouch body or fistulas not originating from the staple line^{3,28,29}. Treatment can be challenging and might require repeated surgical approach, with unpredictable functional outcomes^{28, 29}. Along with pelvic sepsis, the risk of pouch-related fistulas (OR 6.08; P=0.0003, GRADE+++) and anastomotic strictures (OR 1.82; P=0.02, GRADE+++) were significantly increased in CD. Interestingly, the risk of fistulae was much higher after incidental IPAA in CD (GRADE+++).

SBO is reported to affect up to 17% of patients after IPAA for UC³². It usually requires bowel rest and hospitalization, with surgical treatment reserved to patients with complications or if obstruction does not resolve spontaneously. Studies suggested an increased rate of SBO in CD^{2,5,15,18-21}. We did not find any significant association overall (GRADE+++), but patients with CD who underwent intentional IPAA showed a significant 2-fold increased risk of SBO

(OR 2.19; P=0.02, GRADE+++) **(Supplementary Figure 4)**. This might result from a higher number of patients retaining their pouch, which could reflect the lower failure rate in this subgroup.

Pouch failure was the most commonly reported outcome of IPAA in the present study. Pouch failure was more common in CD vs. UC (OR 5.27; P<0.0001, GRADE++++) **(Figure 2a)**, but bias could have affected the finding. The subset meta-analysis highlighted the difference in the pouch failure rate for CD according to time of diagnosis. The pouch failure rate after intentional IPAA for CD **was higher than that of UC**, but it was much lower compared to the overall CD failure rate, showing a not excessively higher percentage of failure compared to the UC group (OR 2.48; P= 0.009, GRADE++++). On contrast, incidental IPAA increased the risk of failure almost 9 times (OR 8.53; P<0.0001, GRADE++++) **(Figure 2b)**. **Any attempt should be made to better select patients for IPAA, because this is the main reason underlying the differences in the long-term outcomes between sub-groups. Previous studies suggested the utility of small bowel barium enema^{18,19} for those in whom the diagnosis is questionable. We would suggest that a good policy could be to perform an MRI enterography and/or examination under anaesthesia to assess the anorectum⁵. Such a careful selection of CD patients has been previously associated with a mitigated failure rate³⁸.** However, data on previous history of anorectal disorders and preoperative assessment were lacking in most of the studies. Pouch failure allowed for metaregression analyses. The risk of failure has slightly decreased over time, according to the year of publication, even if this finding was not significant **(Supplementary Figure 7b)**. Importantly, age at surgery was a significant prognosticator of pouch failure in CD **(Figure 2c)**, suggesting that this might be an important factor to consider. Of note, the duration of follow-up was not associated with failure **(Supplementary Figure 7c)**; rather, the risk tended to be lower over time, suggesting that the majority of incidental IPAA in CD might have failed early. This finding would probably need further attention.

Pouchitis is the most common long-term complication of IPAA, occurring in almost 30% of patients^{32,39}. Rates were 33.2% and 35.7% in CD and UC, respectively, with no significant differences (GRADE+++). Time of CD diagnosis did not seem to affect the risk of pouchitis. Of note, the definition of pouchitis and its diagnosis varied among studies, and these factors have been the reason of pouchitis been reported in 7-49% of patients after IPAA³⁹. Authors have proposed that pouchitis should be classified as acute and chronic, and that pouchitis occurring in CD should be considered as secondary pouchitis³⁹. This suggests different aetiology underlying each of them, with different clinical significance and treatment targets. In UC, the presence of anti-Saccharomyces cerevisiae antibody (ASCA) and anti-CBir1 have been associated with the development of pouchitis. ASCA are known to increase the risk of CD⁴⁰. It might be important to assess the immunological status of CD patients that are candidates to IPAA in order to identify those at higher risk of developing complications. Importantly, it has been suggested that mechanical or structural issues of the pouch can underly a chronic inflammation of the mucosa⁴¹, which might sometimes be misdiagnosed as pouchitis. Therefore, the actual incidence of pouchitis in CD is difficult to be estimated, and the different mechanisms causing the condition make it difficult to compare CD with UC. CD itself should not be regarded as a risk factor for pouchitis. Moreover, the present metanalysis included articles from referral centres^{2,14-21}, in which the diagnosis of pouchitis must have been performed according to agreed criteria³, making results reliable. **Lastly, it is difficult to estimate the relative risk of pouchitis after IPAA in CD as compared with UC patients, because some “pouchitis” are in fact recurrence of CD within the pouch. Data on pouchitis should therefore be interpreted with caution.**

IPAA is a procedure aimed at achieving good quality of life. Bowel control and function are - important endpoints. Among the most disturbing symptoms after IPAA, incontinence, urgency, and seepage can cause severe deterioration of quality of life, along with use of pads^{2,3,22}. In patients who preserved their pouch, continence (GRADE+++)³ was not

significantly affected by baseline diagnosis. On the contrary, urgency (GRADE++) and use of pads (GRADE++) were increased, although differences did not reach statistical significance (**Supplementary Figure 6a-c**). Seepage was significantly higher in patients with CD (OR 2.27; $P=0.01$, $I^2 = 35\%$, GRADE++) (**Figure 4**). Notwithstanding the fact that most of the functional endpoints were not significantly different, surgeons counselling CD patients towards IPAA must carefully disclose that function could be not as good as that reported in UC patients. The relatively low level of the quality of evidence for functional outcomes further supports such conduct.

The present study has several limitations, which the reader should take into account. First, medical and surgical treatment of CD and UC are continuously evolving, and our results might have been affected by the different treatment strategies adopted over time. The heterogeneity of findings was low for few outcomes, and the quality of published study was poor overall, with no randomized trials available. However, prospective studies are difficult to plan and deliver, and – without solid data to support them – they could raise ethical concerns. Lastly, systematic reviews on CD and IPAA might not be able to capture a subset of those patients with CD **that were classified as UC**, who underwent IPAA uneventfully and with good function³⁴. They might never be identified **as CD** because of a favourable post-operative course with IPAA³⁴.

The present study has strengths. It represents the largest pooled analysis to date comprising 6770 patients (CD = 352; UC = 6418). Long-term outcome of IPAA was assessed. The grading of evidence according to GRADE system, suggested that data on failure and complications are reliable. This is the first metanalysis to subdivide and analyse patients based on whether IPAA was an incidental or intentional event in CD; we were able to prove that the latter is associated with better outcomes. We also found that failure in CD was higher with increasing age at IPAA. Lastly, we showed that function might not be worse if the pouch

is retained in CD. Taken altogether, these findings offer important points to be discussed with CD patients and their relatives during consultation ahead of an IPAA procedure. Young patients with colonic CD, without anal/perineal manifestations and with no small bowel involvement, should be advised that they might still be at higher risk of failure and repeated surgery for complications compared with UC, and they might have more episodes of SBO. The risk of seepage might be higher. Patients must be highly motivated and accept the risk. At the same time, a relevant proportion of them is likely to achieve good results **Such information could be very important at the time of patient counselling, especially in CD young patients with refractory colitis and proctitis but without anoperineal disease and small bowel disease. The choice between total proctocolectomy with definitive end ileostomy and IPAA should be taken after careful discussion of all the possible advantages and disadvantages, and patients should be offered realistic expectations. However, if considered that IPAA can actually represent an alternative to definitive ileostomy in CD, higher failure rate than UC might not be the most important problem. If because of IPAA it is possible to keep the function even for few years, such option could be interesting in young patients, with no reported impact on life expectancy even if failure occurs.**

Some considerations are also needed, concerning the indications to IPAA in CD, which might increase in a near future, because of the availability of newer medical agents. Medications including TNF inhibitors have been successfully used during recent years in order to salvage the rectum in patients with failed ileorectal anastomosis⁴², and are now well-established agents to treat CD of the pouch^{3,43}. A multicentre study with patients diagnosed with inflammatory disorders of the pouch that were treated with infliximab, suggested that failure in just over half of all patients, but additional medical therapies avoided an ileostomy in almost three-quarters of patients⁴⁴. On the other hand, new

advances in medical treatment might lead to offer IPAA patients with previous (but not current) anoperineal disease, which is currently a contraindication for most authors.

Further studies aimed at specifically addressing the outcome of intentional IPAA in CD in larger samples are desirable. They must include assessment of immunological status, objective measures of bowel function, and patient-reported outcomes, including health-related quality of life.

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LEGENDS FOR ILLUSTRATIONS

Figure 1. PRISMA flow chart of study selection for the current metanalysis.

Figure 2. Forest plots and metaregression for pouch failure. All studies^{2,5,13-21} reported pouch failure rates. **2a: Pouch failure in Crohn's disease (overall) vs ulcerative colitis.** Pouch failure was more common in CD patients than in UC patients (CD vs. UC; OR 5.27; 95% CI, 2.58–10.79, $P < 0.0001$). Heterogeneity was high in the analysis of this primary outcome ($I^2 = 72\%$) and the funnel was asymmetric (Supplementary Figure 1). **2b: Crohn's disease preoperative vs ulcerative colitis (top) - Crohn's disease postoperative vs ulcerative colitis (bottom).** The pouch failure rate in the CD group with a pre-operative diagnosis was significantly lower compared to UC (preop CD vs. UC; OR 2.48; 95% CI, 1.25–4.92, $P = 0.009$; $I^2 = 0\%$), whereas it was higher in the CD group with postoperative diagnosis (postop CD vs. UC; OR 8.53; 95% CI, 3.21–22.66, $p < 0.0001$; $I^2 = 80\%$). **2c: Metaregression for pouch failure according to mean age at surgery.** In patients with CD there was a positive association between age at treatment and failure. Estimated slope: 0.234 (standard error 0.065) $t = 3.58$ $P = 0.007$. The risk of pouch failure increased with increasing age at treatment in patients diagnosed with CD. CD: Crohn's disease UC: Ulcerative colitis M-H: Mantel-Haenszel method Random effect.

Figure 3. Forest plots for pouch fistulae. Pouch fistulae were described in nine studies^{2,5, 13-15, 18-21}. **3a: Pouch fistulae in Crohn's disease (overall) vs ulcerative colitis.** Fistulae were more common in CD vs UC (CD vs. UC; OR 6.08; 95% CI, 2.28–16.23, $P = 0.0003$) but heterogeneity was high ($I^2 = 83\%$). **3b: Crohn's disease preoperative vs ulcerative colitis (top) - Crohn's disease postoperative vs ulcerative colitis (bottom).** The risk of fistulae was less markedly higher in

preoperative diagnosis of CD vs UC, (preop CD vs. UC; OR 4.17; 95% CI, 1.08–16.12, $p = 0.04$; $I^2=58\%$), while it was much higher with postoperative diagnosis of CD (postop CD vs. UC; OR 6.23; 95% CI, 1.67–23.19, $P=0.006$; $I^2=86\%$). *CD: Crohn's disease UC: Ulcerative colitis M-H: Mantel-Haenszel method Random effect.*

Figure 4. Forest plots for seepage. Seepage was described in six studies^{2,5,13-15,20}. Patients with CD were at higher risk of seepage (CD vs. UC; OR 2.27; 95% CI, 1.21-4.29; $P=0.01$, $I^2 = 35\%$). *CD: Crohn's disease UC: Ulcerative colitis M-H: Mantel-Haenszel method Random effect.*

Table 1. Characteristics of included studies

Author [ref]	Country	Year	Study Type	Number of patients		Mean Age (years)		Median follow-up (months)		NOS ¹⁰ score
				CD	UC	CD	UC	CD	UC	
Grobler et al. ¹⁵	UK	1993	<i>Retrospective</i>	10	61	37	32	68	67	9
Panis et al. ⁵	France	1996	<i>Prospective</i>	31	71	36	33	72	72	9
Yu et al. ²¹	USA	2000	<i>Prospective</i>	38	1411	34	34	120	83	8
de Oca et al. ¹⁴	Spain	2002	<i>Retrospective</i>	12	99	35	32	76	83	9
Rudolph et al. ¹⁹	USA	2002	<i>Prospective</i>	14	71	37	38	75	47	9
Pishori et al. ¹⁸	USA	2004	<i>Retrospective</i>	5	285	NA	NA	40	40	7
Brown et al. ¹³	Canada	2005	<i>Prospective</i>	36	1135	31	34	83	98	9
Tekkis et al. ²⁰	UK	2005	<i>Retrospective</i>	26	26	31,6	NA	66	NA	8
Grucela et al. ¹⁶	USA	2009	<i>Prospective</i>	13	39	34	35	44	44	7
Fazio et al. ²	USA	2013	<i>Prospective</i>	150	2959	38,3	38,4	102	84	9
Le et al. ¹⁷	USA	2013	<i>Prospective</i>	17	261	45	38	60	36	7

CD: Crohn's disease

UC: ulcerative colitis

NOS: Newcastle-Ottawa Scale

Table 2. Summary of outcomes and quality of evidence assessed based on the GRADE¹¹ approach

Comparison I: Crohn's disease (overall) vs ulcerative colitis

Outcome	Pooled effect estimates		Pooled relative effect (95% CI)	Number of patients/studies	Heterogeneity I ²	P for overall effect estimate	Quality of evidence (GRADE)
	CD	UC					
Pouch Failure	25%	5.7%	OR 5.27 (2.58 - 10.79)	6770/11	72%	<0.0001	++++
Pouch Fistulae	23.2%	4.5%	OR 6.08 (2.28 - 16.23)	6440/9	83%	0.0003	+++
Strictures	19.9%	13.3%	OR 1.82 (1.12 - 2.95)	6338/8	35%	0.02	+++
Pelvic Sepsis	15.2%	8.2%	OR 1.95 (0.78 - 4.85)	4681/4	73%	0.15	++
Small-bowel obstruction	19.3%	16.4%	OR 1.27 (0.91 - 1.76)	5158/7	0%	0.15	+++
Pouchitis	33.2%	35.7%	OR 1.07 (0.70 - 1.63)	5497/9	32%	0.76	+++
Incontinence	46.4%	44.8%	OR 1.08 (0.78 - 1.51)	6202/9	5%	0.64	+++
Urgency	46.8%	48.7%	OR 1.89 (0.82 - 4.35)	4545/5	51% ⁸	0.13	++
Pads	20.1%	17.2%	OR, 1.71 (0.72 - 4.07)	4493/4	66%	0.23	++
Seepage	35.5%	28.1%	OR 2.27 (1.21 - 4.29)	4616/6	35%	0.01	++

Comparison II: Crohn's disease (preoperative diagnosis or intentional IPAA) vs ulcerative colitis

Outcome	Pooled effect estimates		Pooled relative effect (95% CI)	Number of patients/studies	Heterogeneity I ²	P for overall effect estimate	Quality of evidence (GRADE)
	PRE-CD	UC					
Pouch Failure	12.1%	5.3%	OR 2.48 (1.25 - 4.92)	4829/9	0%	0.0009	++++
Pouch Fistulae	11.6%	4%	OR 4.17 (1.08 - 16.12)	4508/7	58%	0.04	+++
Strictures	11.7%	12.8%	OR 1.12 (0.53 - 2.36)	4419/6	0%	0.77	+++
Pelvic Sepsis	8.1%	9.3%	OR 1.09 (0.22 - 5.47)	3083/3	25%	0.91	+
Small-bowel obstruction	11.7%	12.8%	OR 2.19 (1.16 - 4.11)	4419/6	0%	0.02	+++
Pouchitis	35.3%	34.6%	OR 1.23 (0.58 - 2.62)	3689/8	42%	0.59	+++

Table 2. continued

Comparison III: Crohn's disease (postoperative diagnosis or incidental IPAA) vs ulcerative colitis							
Outcome	Pooled effect estimates		Pooled relative effect (95% CI)	Number of patients/studies	Heterogeneity I ²	P for overall effect estimate	Quality of evidence (GRADE)
	POST-CD	UC					
Pouch Failure	31.6%	5.7%	OR 8.53 (3.21 - 22.6)	6234/8	80%	P<0.0001	++++
Pouch Fistulae	23.5%	4.2%	OR 6.23 (1.67 - 23.19)	6186/7	86%	P=0.006	+++
Strictures	16.7%	13.4%	OR 1.78 (0.72 - 4.40)	6102/6	77%	0.21	++
Pelvic Sepsis	9.5%	7.9%	OR 1.20 (0.21 - 7.00)	4646/4	88%	0.84	+
Small-bowel obstruction	18.8%	16.6%	OR 1.16 (0.79 - 1.69)	5020/6	1%	0.45	+++
Pouchitis	34.7%	35.4%	OR 1.31 (0.69 - 2.50)	5068/7	51%	0.40	+++
CD: Crohn's disease							
IPAA: ileal pouch-anal anastomosis							
OR: odds ratio OR>1 associated with increased risk							
POST-CD: Crohn's disease diagnosed postoperatively (after IPAA)							
PRE-CD: Crohn's disease diagnosed preoperatively (before IPAA)							
UC: ulcerative colitis							
95%CI: 95% confidence intervals							

GRADE score explanation

The quality of evidence for most outcomes varied from very low to high quality. All the studies have been downgraded because they include no randomized clinical trials (RCT). In the specific case of this meta-analysis, the objective of the considered studies makes RCT probably not feasible because of the consequences and amount of time required to carry out such kind of trial.

Heterogeneity has been taken into account into the grading for inconsistency and the I² statistics has been used. In contrast with the group of pre-operative CD diagnosis (PRE-CD), in the post-operative CD diagnosis (POST-CD) heterogeneity was higher. This factor has been taken into account during grading.

The results addressed directly our questions and objectives, suggesting no risk of indirectness. The large sample of patients allowed for calculating a precise effect estimate with no risk of imprecision.

Both the number of patients included in each analysed outcome and the magnitude effect (by means of the resulting OR) were taken into account. In the cases of “pouch failure” and “pouch fistulae” we have applied a 2-level upgrade because of an OR>5 in all cases resulting in high quality outcomes ¹¹.

Figure 1



PRISMA 2009 Flow Diagram

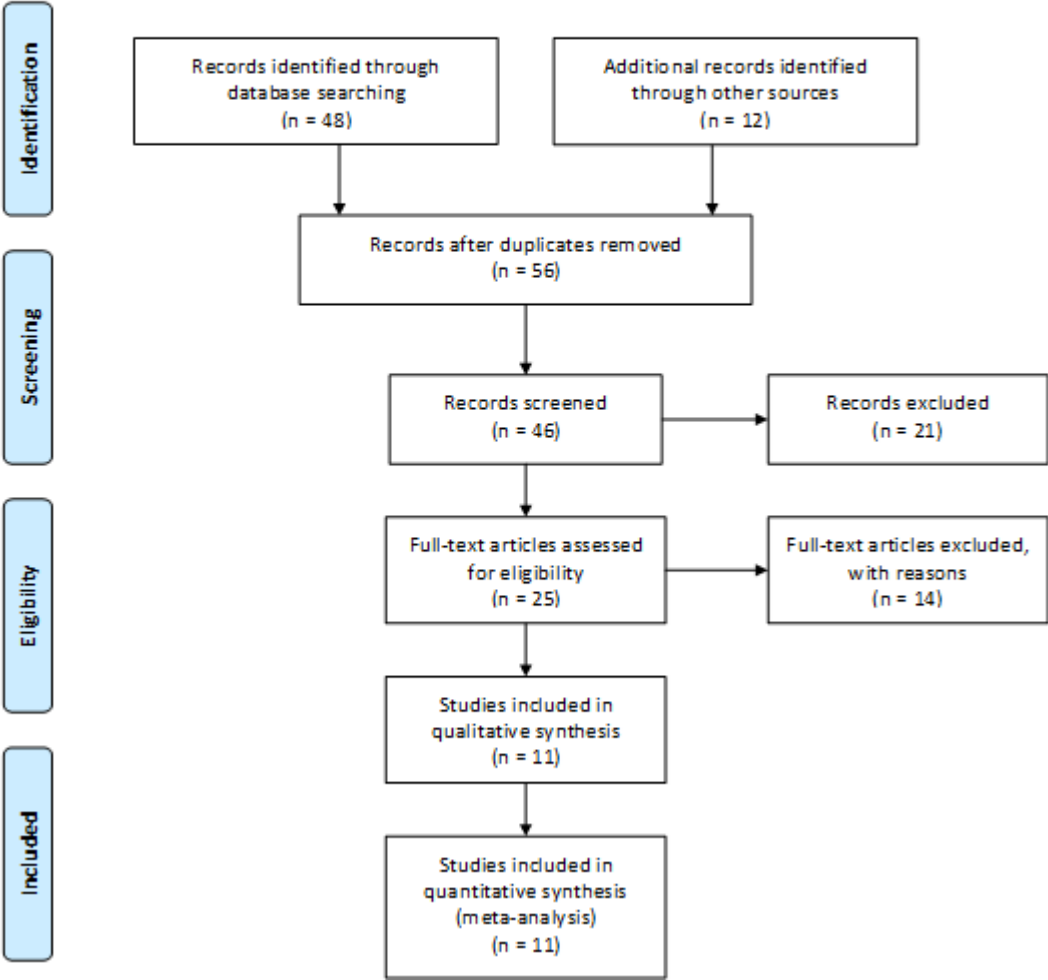


Figure 2

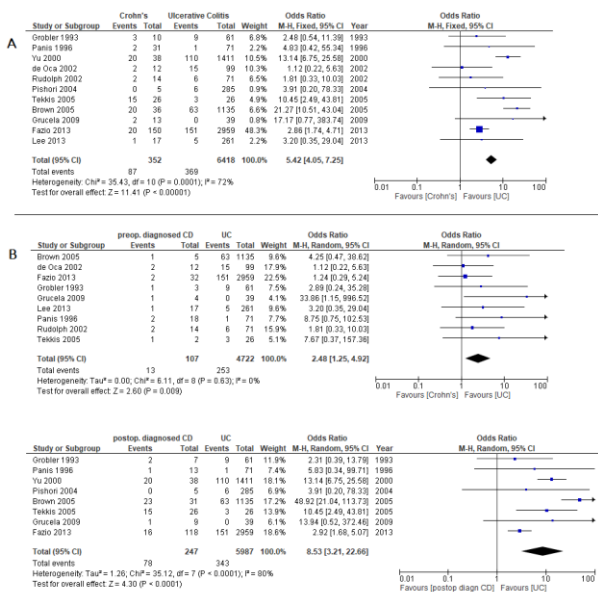
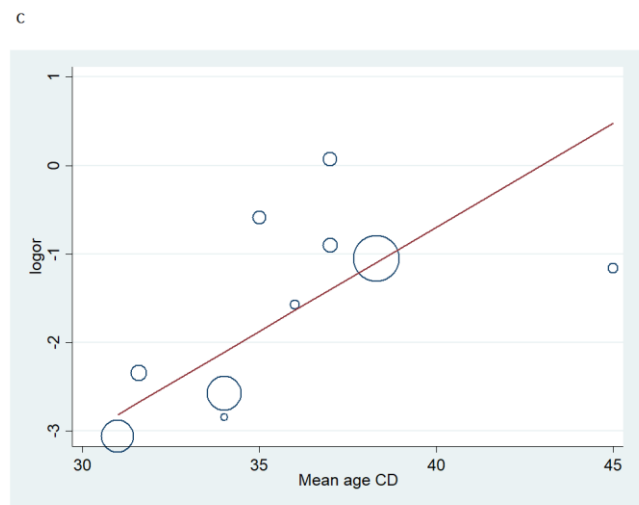


Figure 3

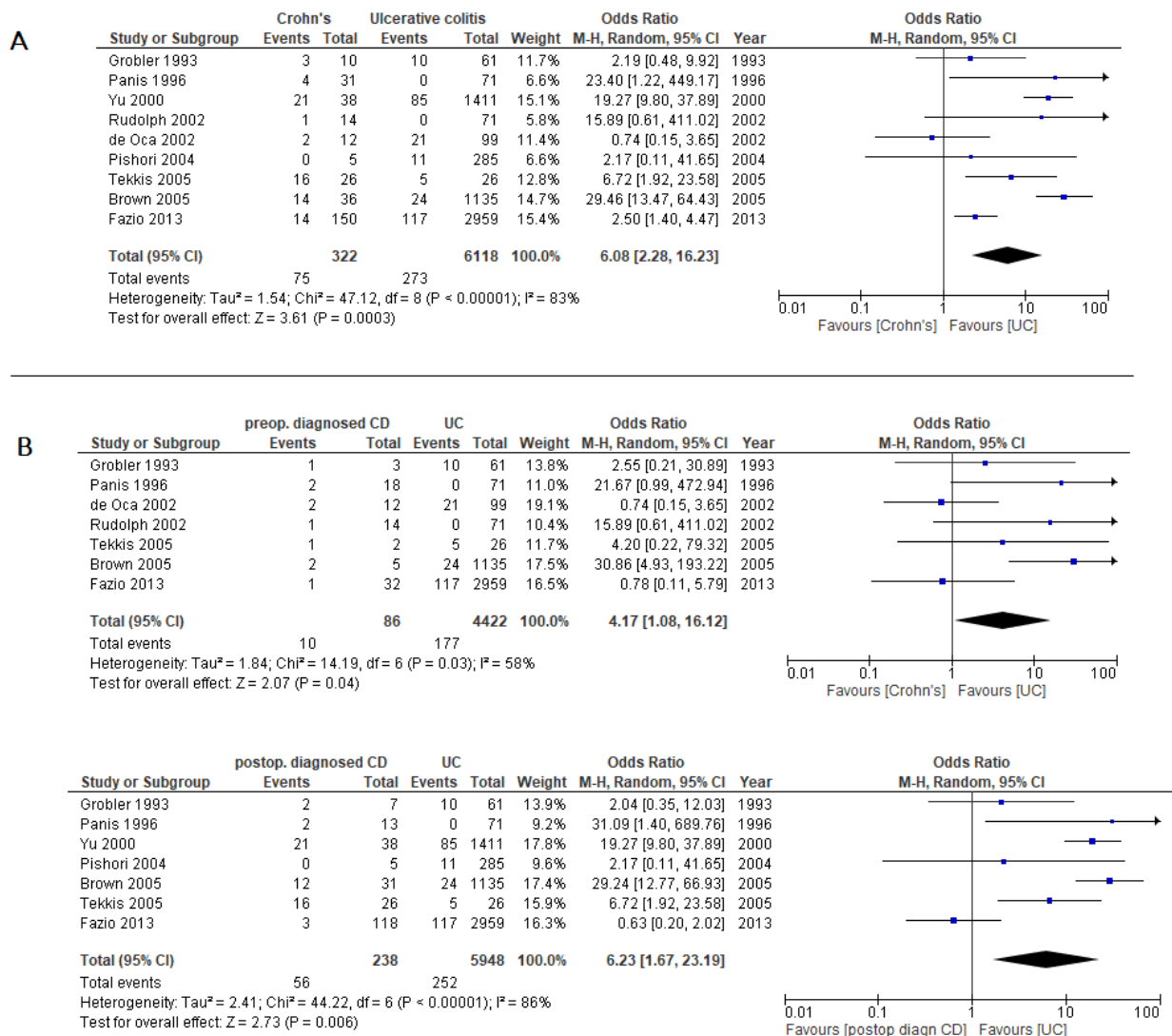
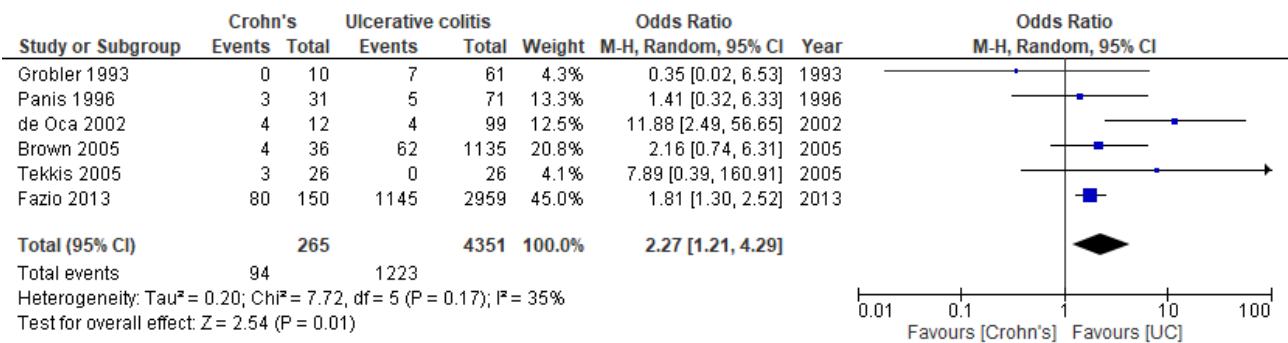


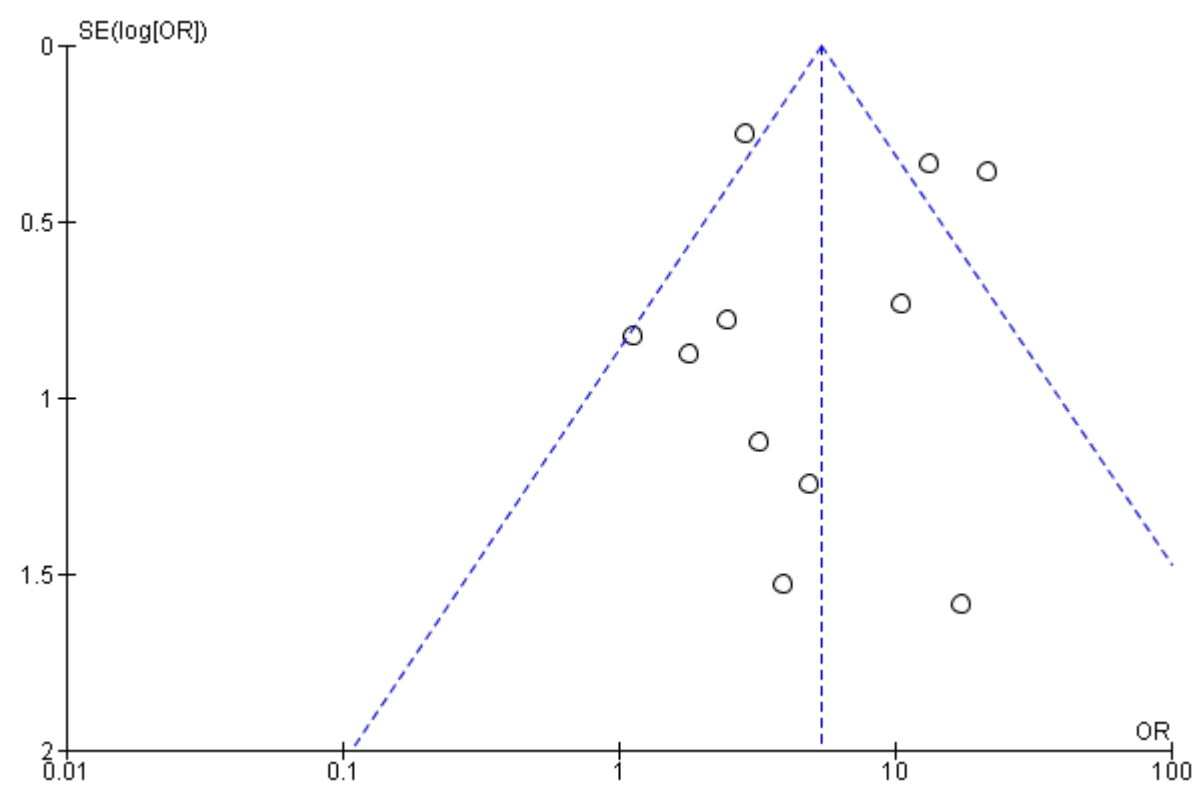
Figure 4



Supplementary Table 1. Definitions and Diagnostic Criteria for Complications and Functional Results Related to IPAA Procedure^{1-3,7,29}

- **Pouch failure:** the need for permanent stoma, with or without excision of the pouch,
- **Pelvic sepsis:** any infective process in the peripouch area: abscess with or without anastomotic leak and/or further development of chronic sinus with cavity, or fistulae detected by clinical or radiological means.
- **Pouch fistula:** an abnormal tract from the pouch to another organ, surface or skin.
- **Pouchitis:** clinical presentation with typical symptoms of pouchitis (increased number of bowel movements, rectal bleeding, urgency, incontinence, and/or abdominal or pelvic cramps). Diagnosis requires abnormal endoscopy and biopsies, which were not consistently reported.
- **Anastomotic Stricture:** narrowing at the anastomosis that required dilation
- **Small-bowel obstruction:** nausea, abdominal pain, vomiting, abdominal distension, often requiring readmission with or without subsequent surgery.
- **Incontinence:** accidental loss of stool or gas through the anal canal in previously continent patients
- **Urgency:** inability to postpone defecation for more than 15/20 minutes
- **Seepage:** leakage of fecal content with the presence of a physiological fecal continence and evacuation
- **Pads:** a thick piece of soft material used to protect the perianal skin or to absorb liquid

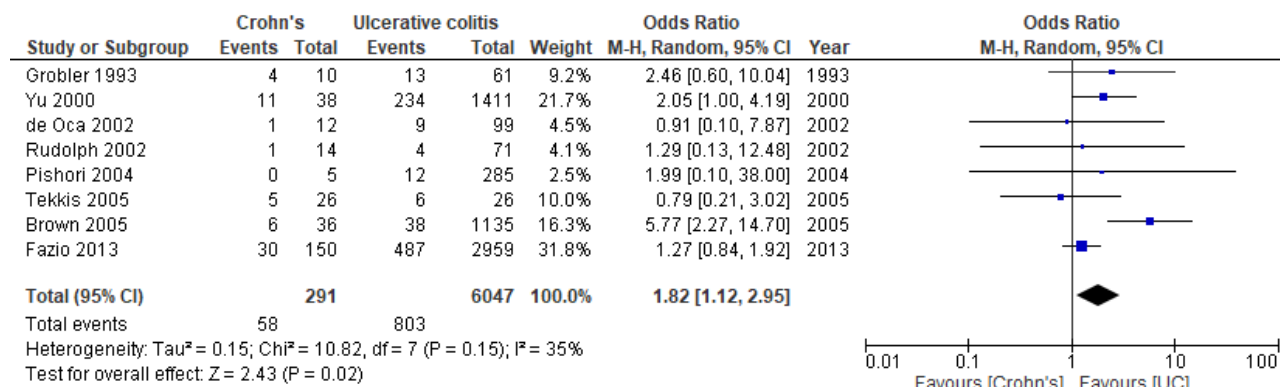
Supplementary Figure 1



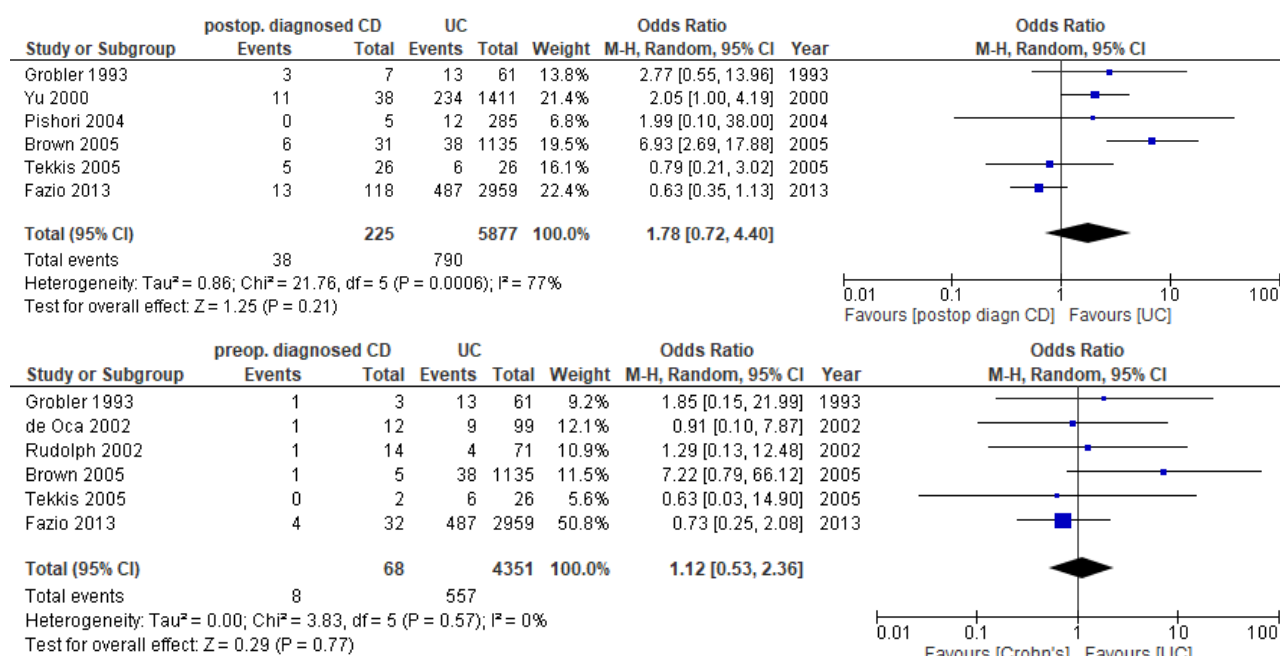
Funnel plot for pouch failure. A certain degree of asymmetry can be observed within included study, suggesting the potential risk for bias.

Supplementary Figure 2. Anastomotic Strictures

2a Crohn's disease (overall) vs ulcerative colitis



2b Crohn's disease preoperative vs ulcerative colitis (top) - Crohn's disease postoperative vs ulcerative colitis (bottom)

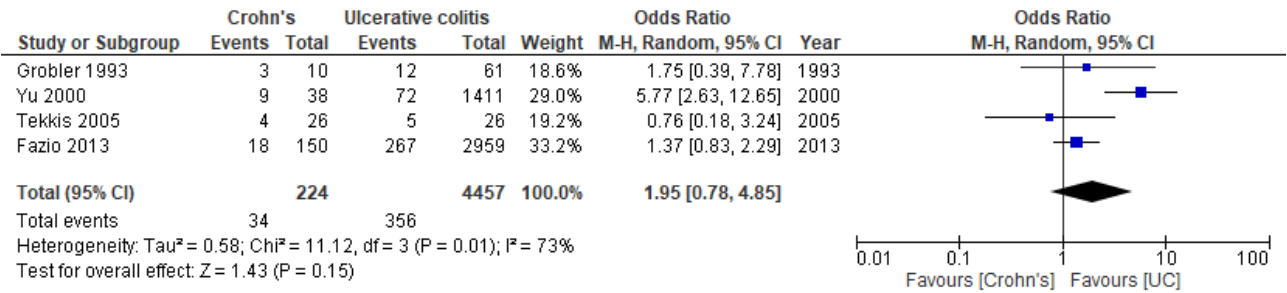


CD: Crohn's disease UC: Ulcerative colitis M-H: Mantel-Haenszel method Random effect

The risk of anastomotic stricture was higher in Crohn's disease (CD vs. UC; OR 1.82; 95% CI, 1.12–2.95, $p = 0.02$), with acceptable heterogeneity ($I^2 = 35\%$).

Postoperative diagnosis of Crohn's disease seemed to increase the risk of strictures (preop CD vs. UC; OR 1.12; 95% CI, 0.53–2.36, $p = 0.77$; $I^2 = 0\%$) (postop CD vs. UC; OR 1.78; 95% CI, 0.72–4.40, $P = 0.21$; $I^2 = 77\%$).

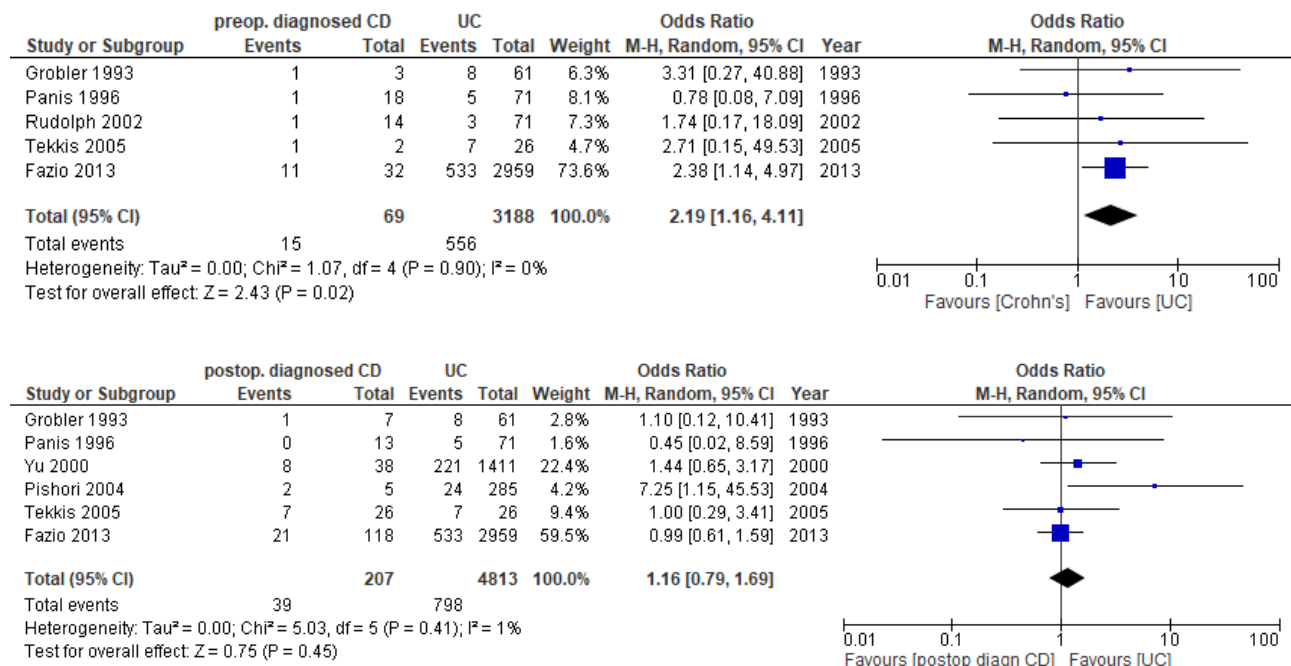
Supplementary Figure 3. Pelvic sepsis



CD: Crohn's disease UC: Ulcerative colitis M-H: Mantel-Haenszel method Random effect

There were no statistically significant differences in pelvic sepsis overall. (CD vs. UC; OR 1.95; 95% CI, 0.78, 4.85, p = 0.15; I²=73%)

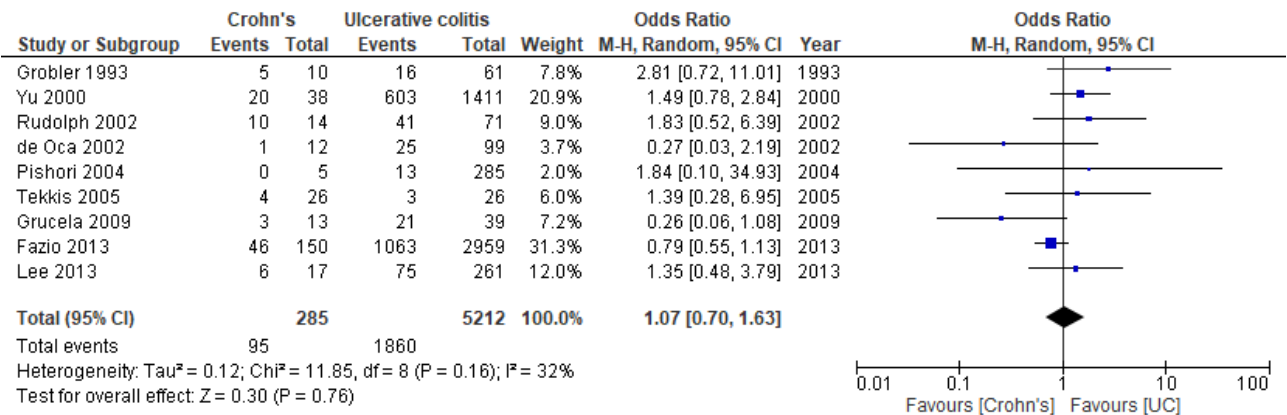
**Supplementary Figure 4. Small bowel obstruction in Crohn's disease preoperative vs ulcerative colitis (top)
- Crohn's disease postoperative vs ulcerative colitis (bottom)**



CD: Crohn's disease UC: Ulcerative colitis M-H: Mantel-Haenszel method Random effect

Small bowel obstruction (SBO) was more common in patients with preoperative CD diagnosis than in postoperative CD group compared with UC (preop CD vs. UC; OR 2.19; 95% CI, 1.16–4.11, P=0.02; I²=0%) (postop CD vs. UC; OR 1.16; 95% CI, 0.79–1.69, P=0.45; I²=1%)

Supplementary Figure 5. Pouchitis

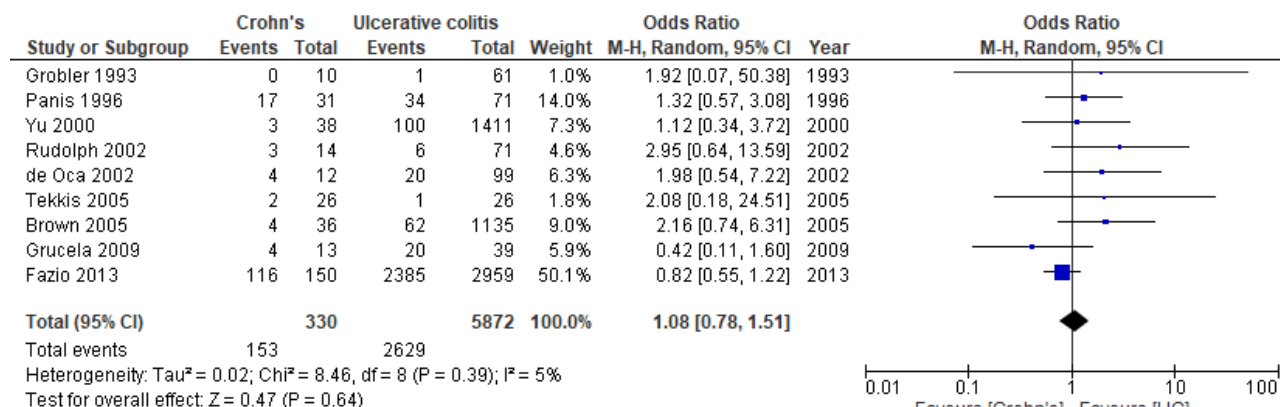


CD: Crohn's disease UC: Ulcerative colitis M-H: Mantel-Haenszel method Random effect

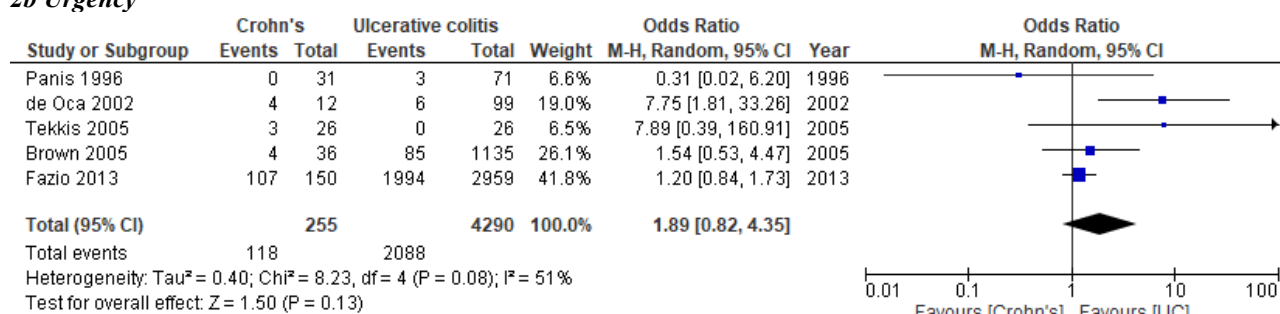
There were no significant differences in the incidence of pouchitis between CD and UC (OR 1.07, 95% CI, 0.70, 1.63; P=0.76; I²=32%)

Supplementary Figure 6. Functional outcomes

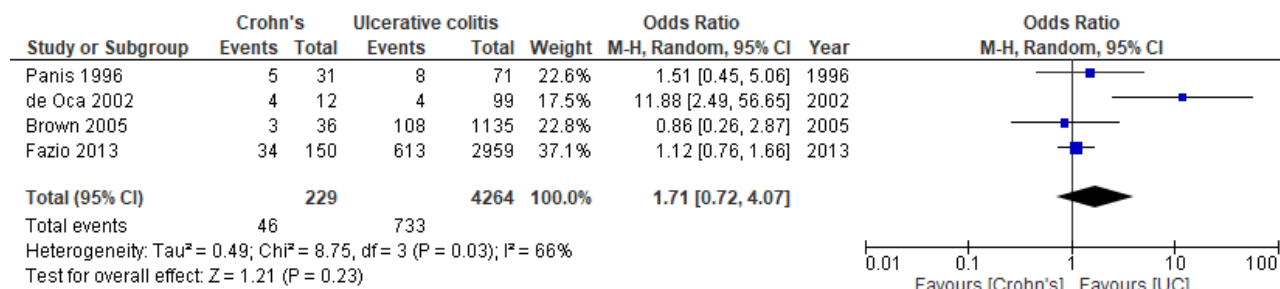
2a Incontinence



2b Urgency



2c Use of pads

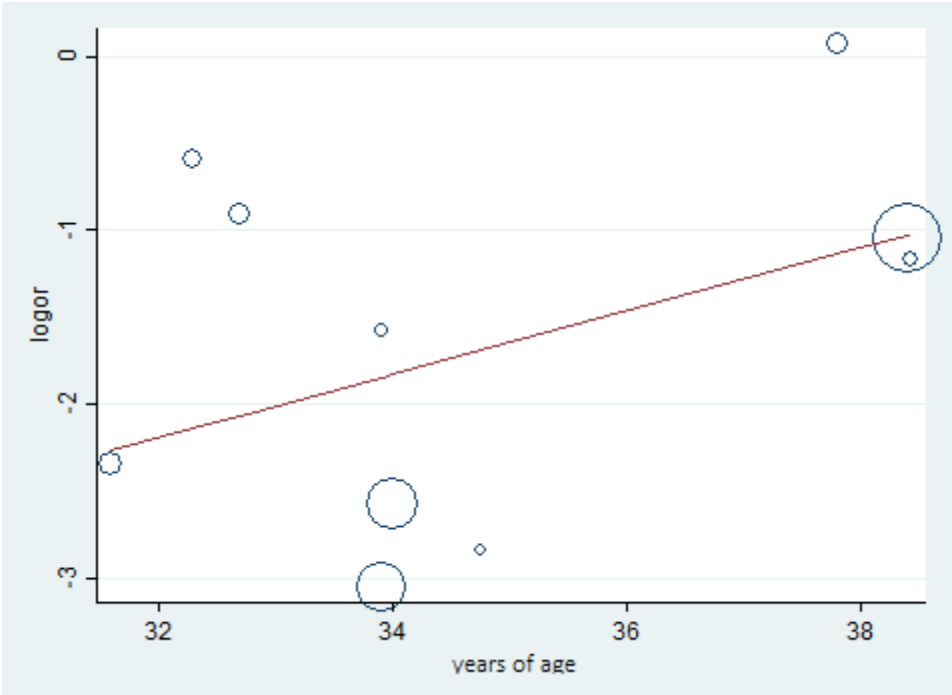


CD: Crohn's disease UC: Ulcerative colitis M-H: Mantel-Haenszel method Random effect

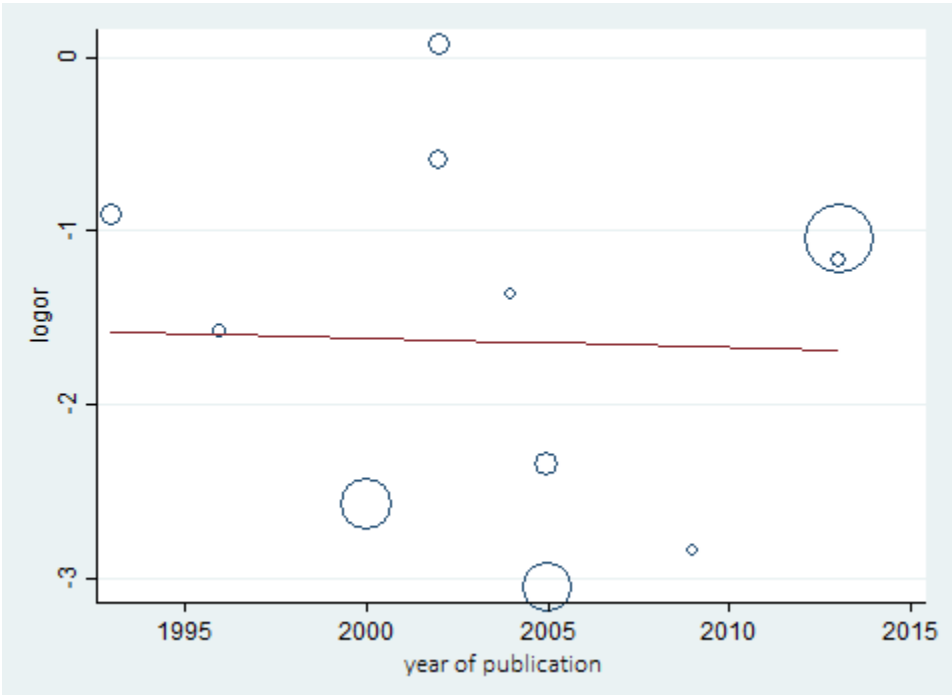
There were no significant differences in incontinence (CD vs. UC; Overall OR, 1.08; 95% CI, 0.78, 1.51; $P=0.64$; $I^2=5\%$; [2,5, 13-16, 19-21]), urgency (CD vs. UC; Overall OR, 1.89; 95% CI, 0.82, 4.35; $P=0.13$; $I^2=51\%$, [2,5,13,14,20]) and use of pads (CD vs. UC; Overall OR, 1.71; 95% CI, 0.72, 4.07; $P=0.23$; $I^2=66\%$, [2,5,13,14]) between CD and UC in the long term.

Supplementary Figure 7. Metaregression analysis (pouch failure)

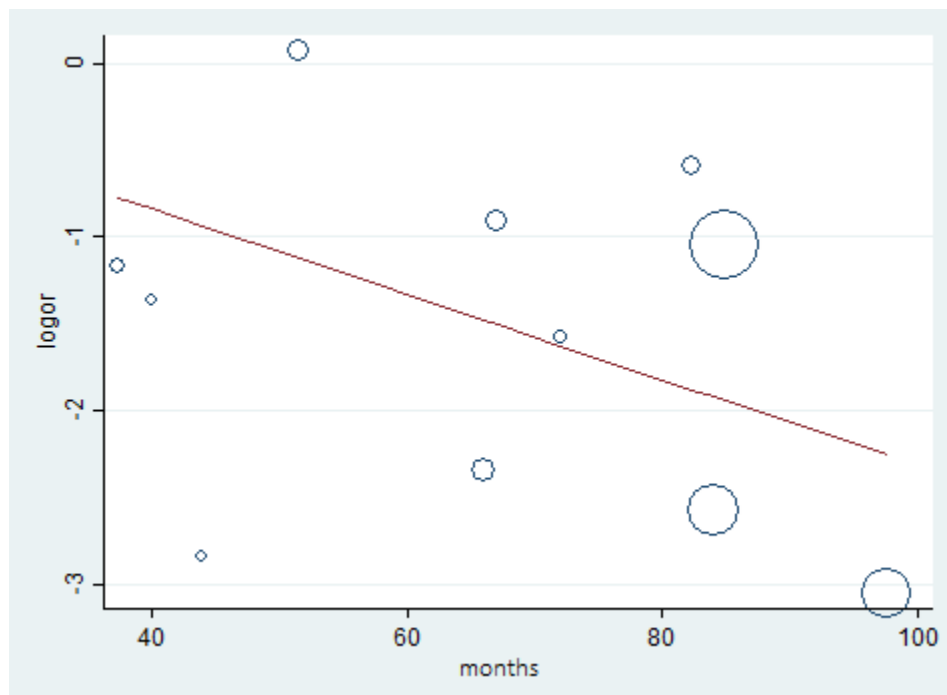
7a Age at treatment, all patients



7b Year of publication, all patients



7c Duration of follow-up



The minimum required numbers of studies for meta-regression in ten¹² Meta-regression was only performed for pouch failure (eleven studies available)^{2,5, 13-21}.

The number of y axis indicates the risk expressed as logOR, whereas numbers on the x indicates age in years (7a), year of publication (7b), follow-up duration in months (7c).

There were no significant trends between age at treatment, year of publication and duration of follow-up overall.

The risk of pouch failure seemed to increase with increasing age at surgery (7a). Estimated slope: 0.182 (standard error 0.140) with $t = 1.30$ and $P = 0.230$.

The risk seemed stable over time (7b).

Longer follow-ups were not associated with increased risk of failure (7c). Estimated slope: 0.025 (standard error 0.0179) with $t = -1.38$ and $P = 0.202$.