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# The risk of colectomy and colorectal cancer after appendectomy in patients with ulcerative colitis: a systematic review and meta-analysis

*Short title: Colectomy and colorectal cancer after appendectomy in UC*

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**Potential competing interests:** none

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52 **Abstract**

53 *Background:* Appendectomy decreases the risk of developing ulcerative colitis (UC), and is suggested  
54 to have a beneficial effect on the clinical course of established UC. However, recent studies showed  
55 no significantly decreased colectomy rate, and moreover an apparently increased risk of colorectal  
56 cancer (CRC). We aimed to investigate the suggested correlation in a meta-analysis, and analyze  
57 possible confounding factors.

58 *Methods:* A systematic review and meta-analysis were performed using MEDLINE, EMBASE and the  
59 Cochrane library. Data from studies describing the influence of appendectomy on colectomy and CRC  
60 were extracted from published reports. Exclusion criteria were patients <18 years, non-UC, and  
61 animal studies.

62 *Results:* From 891 studies, 13 studies evaluating 73323 UC patients (appendectomy n=2859) were  
63 included. All studies, except one, were rated as poor quality. Overall, colectomy rate in  
64 appendectomized and non-appendectomized patients was not significantly different (OR 1.25, 95%CI  
65 0.88-1.77,  $I^2=53\%$ ). The proportion of colectomies undertaken for CRC or high grade dysplasia (HGD)  
66 was significantly higher after appendectomy (OR 2.85, 95%CI 1.40-5.78,  $I^2=32\%$ ), with 50% of the  
67 colectomies indicated for CRC/HGD compared to 9.4% in non-appendectomized patients. Possible  
68 additional confounding factors were a longer UC disease duration, less medication use and a higher  
69 prevalence of PSC in appendectomized patients.

70 *Conclusions:* Appendectomy in established UC is associated with apparently higher rates of  
71 subsequent CRC/HGD, but this appears to be due to inequalities in at-risk exposure between groups,  
72 presumably secondary to positive clinical effects of appendectomy on disease symptoms. This finding  
73 emphasizes the importance of regular endoscopic surveillance in this patient group.

74

75 **Keywords:** Ulcerative Colitis, Appendectomy, Colorectal Cancer, High Grade Dysplasia

## 76 **Introduction**

77 An appendectomy is a protective factor against the development of ulcerative colitis (UC), and is also  
78 suggested to confer beneficial effects on the clinical course of established disease.<sup>1</sup> As early as in  
79 1987, Gilat et al<sup>2</sup> evaluated childhood factors associated with inflammatory bowel disease and  
80 reported an inverse relationship between appendectomy and subsequent diagnosis of UC. This  
81 observation was regarded as an incidental finding for many years, until another study found an  
82 appendectomy prevalence of 0.6% in UC patients compared to 25.4% in controls.<sup>3</sup> Thereafter, more  
83 epidemiological and case-control studies reported similar results, and led to an increase in interest  
84 over the last decade of the potential therapeutic benefits of an appendectomy in established UC.  
85 Various studies exploring this intervention reported lower relapse rates and a decreased risk of  
86 colectomy, making this relatively cheap procedure an attractive treatment option for UC patients.<sup>4</sup>

87 However, more recently published data show contradictory findings after appendectomy in  
88 UC patients with an apparently increased colectomy rate, and moreover an increased risk of  
89 colorectal cancer (CRC). The retrospective database analysis of Parian et al<sup>5</sup> including 2714 UC  
90 patients found a higher risk of colectomy in 48 patients who underwent appendectomy after UC  
91 diagnosis and concluded that an appendectomy should not be recommended as a therapy for  
92 ulcerative colitis. Harnoy et al<sup>6</sup> also reported an increased risk of colorectal cancer and high grade  
93 dysplasia (HGD) in UC patients after appendectomy with an odds ratio of 16.88, although this study  
94 only included 15 patients undergoing appendectomy and the timing of appendectomy in relation to  
95 their UC diagnosis was unknown. If an appendectomy is indeed associated with the an increased risk  
96 of the subsequent development of CRC, this would have considerable implications for ongoing  
97 clinical studies and daily clinical practice.

98 We systematically reviewed the literature and performed a meta-analysis to investigate if an  
99 appendectomy is associated with an increased risk of colectomy, and CRC/HGD in UC patients.  
100 Additionally, possible confounding factors for the development of CRC or HGD were evaluated

101 including disease duration, extent and severity of disease, primary sclerosing cholangitis (PSC), and  
102 family history for CRC.<sup>7</sup>

103 Our research questions were: (1) Is an appendectomy in UC patients associated with an  
104 increased risk of colectomy and CRC/HGD? (2) Is there a change in the colectomy indication after  
105 appendectomy? (3) What possible patient-level confounding factors should be taken into account  
106 when interpreting current data?

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## 122 **Methods**

### 123 *Search strategy and selection criteria*

124 A systematic review and meta-analysis were performed according to the Preferred Reporting Items  
125 for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.<sup>8</sup> All randomized controlled trials,  
126 cohort studies, case-control studies and case series describing the influence of an appendectomy on  
127 the colectomy rate or risk of CRC or HGD in UC patients were included. Patients with any extent of  
128 the disease, and both active and non-active disease, were eligible. There were no limitations  
129 concerning timing and reason of appendectomy, nor limitations concerning use of medication.  
130 Exclusion criteria were patients <18 years, appendectomy performed in non-UC patients, and animal  
131 studies.

132 An electronic search was performed in MEDLINE (PubMed), EMBASE (Ovid), and the  
133 Cochrane library, with the last update on 10 July 2017. The search contained both MeSH and free  
134 text terms and was composed with a clinical librarian. Search terms used were 'ulcerative colitis' or  
135 'colitis' or 'proctitis' or 'proctocolitis' or 'UC' or 'pancolitis' and 'appendectomy' or 'appendicectomy'.  
136 No restrictions considering the date or type of publication, language, or other methodological filters  
137 were used. Further details of the search are provided in Supplementary 1.

138 Two reviewers (MS and MK) independently screened the titles and abstracts of the studies  
139 obtained from the search. Cases of disagreement about inclusion were resolved by joint discussion  
140 and when needed the opinion of a third researcher (CB) was sought. The remaining articles were  
141 separately reviewed by reading the full-text version (by MS and MK). The reference lists of relevant  
142 articles were cross-checked to find any additional studies of interest. Included articles were  
143 translated if they were not published in English or Dutch. We used data extracted from published  
144 reports and contacted the study authors in cases where data was missing.

145

### 146 *Data analysis*

147 The co-primary outcomes of this study were colectomy rate and risk of CRC or HGD after

148 appendectomy in UC patients. To investigate possible confounding factors for developing CRC or  
149 HGD, we specifically looked at UC duration, disease extent and severity, PSC and family history for  
150 CRC. Patient characteristics and outcome data were obtained separately for appendectomized and  
151 non-appendectomized patients. The collected patient characteristics were: gender, age, age at UC  
152 diagnosis, age and timing of appendectomy, UC disease duration, extent and severity of disease  
153 (including symptoms, endoscopy results and medication use), PSC, family history of CRC, and  
154 duration of follow-up. Outcome data contained: the percentage of colectomies including the age at  
155 colectomy, the percentage of CRC and HGD and age at diagnosis, and the indication for colectomy.

156 Two investigators (MS and MK) independently assessed the risk of bias of the included  
157 studies according to The Newcastle Ottawa Quality Assessment Scale.<sup>9</sup> The quality items were  
158 adjusted for cohort studies and case-control studies. Studies with less than 5% loss to follow-up and  
159 a minimal follow-up duration of eight years were considered acceptable since an increased colorectal  
160 cancer risk is only seen after a longer period of time.<sup>10</sup> The Newcastle-Ottawa scale scores were rated  
161 following the AHRQ standard as good, fair or poor depending on the number of assigned stars.<sup>11</sup>

162 A meta-analysis was performed comparing the risk of colectomy, and of CRC and/or HGD in  
163 appendectomized and non-appendectomized patients. The influence of timing of appendectomy,  
164 before or after the diagnosis of UC, was evaluated in subgroup analyses. A random-effects model was  
165 applied and an  $I^2 \geq 60\%$  was considered as a substantial heterogeneity. A p-value of  $<0.05$  was  
166 statistically significant and the odds ratios and 95% confidence intervals were reported. The  
167 statistical analyses were done using Review Manager (version 5.3).

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## 172 Results

173 The systematic literature search resulted in 891 studies: 285 in PubMed, 592 in EMBASE and 14 from  
174 the Cochrane library. After removal of the duplicates, 573 records were screened on title and  
175 abstract. Main reasons for exclusion were: no patients with UC or appendectomy, no data about  
176 colectomy or CRC/HGD provided and wrong study designs such as reviews and conference abstracts.  
177 In total 81 full-text articles were assessed for eligibility. A further 13 articles were excluded because  
178 there was no full text available (most were old and therefore not retrievable), and 55 articles had  
179 different outcome parameters, including disease severity, hospitalization or requirement of medical  
180 therapy. Qualitative synthesis was done in 13 studies and of these studies, 12 were eligible for the  
181 quantitative synthesis. More details can be obtained from figure 1.

182 There were two prospective cohort studies, ten retrospective cohort studies, and one case-  
183 control study. Table 1 shows the study and patient characteristics of the included studies. A total of  
184 73323 UC patients was evaluated of whom 2859 (3.9%) previously had an appendectomy. Patients  
185 who had an appendectomy were subdivided in three groups: appendectomy before UC diagnosis  
186 (n=1879), appendectomy after UC diagnosis (n=927) and appendectomy with timing unknown  
187 (n=53). Of the 13 included studies, two studies did not make a distinction between appendectomy  
188 before or after UC diagnosis.<sup>6, 12</sup> The follow-up ranged from a median of 14 months to 193 months,  
189 however, 6 studies did not report the follow-up time. All of the included studies, except one, were  
190 rated as poor quality studies. The retrospective study of Hallas et al<sup>13</sup> was the only study meeting the  
191 criteria of a good quality study (supplementary table 1).

192

### 193 *Appendectomy and the risk of colectomy*

194 The risk of colectomy was investigated in 11 studies in 72453 UC patients. Two studies observed a  
195 significantly higher colectomy risk in the appendectomy group, and two studies in the non-  
196 appendectomy group (table 2). The prospective study of Bolin et al<sup>14</sup> was not included in the final



197 meta-analyses due to the lack of a control group.

198           The forest plot of the 10 resulting studies showed no significant difference in colectomy rate  
199 between the group with appendectomy and the group without appendectomy (OR 1.25, 95% CI 0.88  
200 to 1.77,  $I^2=53\%$ ; figure 2). Interestingly, patients who underwent an appendectomy after UC  
201 diagnosis seemed to have a slightly higher risk of colectomy (OR 1.37, 95% CI 0.61 to 3.07,  $I^2=63\%$ ;  
202 supplementary figure 1) compared to an appendectomy before diagnosis (OR 0.99, 95% CI 0.62 to  
203 1.58,  $I^2=39\%$ ; supplementary figure 2), however, this difference was not statistically significant.

204

#### 205 *Appendectomy and the risk of CRC or HGD*

206 A total of seven studies evaluated the risk of CRC or HGD in 5064 UC patients. Two studies<sup>12, 15</sup>  
207 reported cases of CRC including HGD, the other five studies<sup>6, 16-19</sup> separated CRC from HGD (table 2).

208           Meta-analysis of the risk of having a colectomy for CRC or HGD showed a significant increase  
209 after appendectomy (OR 2.85, 95% CI 1.40 to 5.78,  $I^2=32\%$ ; figure 3). Subgroup analysis of the five  
210 studies looking at colorectal cancer risk specifically also showed a significant increase after  
211 appendectomy with an OR of 3.97 (95% CI 1.35 to 11.70,  $I^2=48\%$ ; figure 4). Five of the studies  
212 evaluated the effect of appendectomy before diagnosis and only one of the studies after diagnosis,  
213 therefore no subgroup analysis on timing of appendectomy and the risk of CRC or HGD was  
214 performed.

215

#### 216 *Confounding factors*

217 The indication for colectomy was described in four of the studies, and the pooled weighted  
218 percentage of colectomies indicated for (therapy refractory) UC was 40.9% in appendectomized  
219 patients, versus 86.3% in non-appendectomized patients. In appendectomized patients, 50% of the  
220 colectomies were performed for an indication of CRC or HGD, compared to 9.4% in non-  
221 appendectomized patients.

222           When looking at the patient and disease characteristics, there are some possible  
223 confounding factors that might influence the risk of developing CRC or HGD in our included studies.  
224 UC disease duration was significantly increased in the appendectomy group in four of seven studies<sup>5</sup>,  
225 <sup>6, 16, 20</sup>(table 3). Furthermore, the average weighted disease duration across the included studies was  
226 133.0 months in the appendectomy group versus 112.3 months in the non-appendectomy group.  
227 Also the age at colectomy was significantly higher in the appendectomy group compared to the non-  
228 appendectomy group in one out of three studies (median 49.0 versus 38.5 years respectively)(table  
229 2). This same study<sup>6</sup> also reported the age at colectomy for patients with CRC specifically, and the  
230 median age was three years older in the appendectomy group (44 versus 41 years), but this  
231 difference was not statistically significant. None of the studies reported the exact age at diagnosis of  
232 CRC or HGD in appendectomized and non-appendectomized patients separately.

233           As time to colectomy is related to disease severity, we also scored clinical symptoms,  
234 endoscopic severity, and need for medication. Unfortunately, symptoms and endoscopic severity  
235 were only reported in the uncontrolled study of Bolin et al.<sup>14</sup> Medication use was presented in seven  
236 studies, with a lower pooled weighted percentage of immunomodulators and/or biologicals in the  
237 appendectomy group (18.0% versus 28.5%).

238           When looking at other well-known predictors for the development of CRC we found a  
239 significantly higher percentage of patients with PSC in the appendectomy group in three out of seven  
240 studies, with a pooled weighted percentage of 12.1% versus 3.9% in the non-appendectomy group.  
241 Interestingly, the incidence tended to be higher in patients undergoing appendectomy before UC  
242 diagnosis (13.8%) compared to after diagnosis (6.8%). In contrast, there was no significant difference  
243 in extent of disease across studies, with extensive colitis in 44.5% of appendectomized patients  
244 versus 43.0% in the non-appendectomized patients. One study<sup>17</sup> looked at the extent of disease in  
245 CRC patients separately and in this study all patients had extensive colitis irrespective of a previous  
246 appendectomy or not. Another study<sup>6</sup> described the location of CRC and interestingly this was more

247 often in the right hemicolon in appendectomized patients compared to non-appendectomized  
248 patients (P=0.004). Finally no difference in a positive family history for sporadic colorectal neoplastic  
249 changes was found between the appendectomy and non-appendectomy group, although this was  
250 only reported in two studies.<sup>6 19</sup>

251

## 252 **Discussion**

253 We have identified that the previously reported higher rates of CRC and/or HGD after appendectomy  
254 in established UC persist in meta-analysis, but are likely to be a result of a marked change in  
255 indication for colectomy, alongside unequal risk exposure due to delayed colectomy in those  
256 undergoing appendectomy. Significantly less colectomy operations were performed for colitis  
257 symptoms in the appendectomy group (40.9%), compared to the non-appendectomy group (86.3%).  
258 This has resulted in a denominator shift which produces the aberrant impression of higher rates of  
259 malignant transformation in the appendectomy group – when in fact there are just less operations  
260 being performed for colitis. This must be interpreted alongside other positive findings which suggest  
261 a clinical benefit from appendectomy in terms of both decreasing relapse rates and postponing  
262 colectomy.

263 We demonstrated a significantly longer duration of UC in the appendectomy group in four  
264 out of seven studies, accompanied by a decreased use of immunomodulators and/or biologicals. If an  
265 appendectomy results in decreased disease activity but does not lead to mucosal healing, this might  
266 result in a situation where the need for colectomy can be postponed or avoided on the grounds of  
267 clinical symptoms. However, leaving a (subclinical) inflammatory colon in situ might promote tumor  
268 development as the production of chemokines and cytokines facilitate tumor growth, genomic  
269 instability and angiogenesis.<sup>21</sup> Therefore, a postponed colectomy might produce an apparently  
270 increased CRC risk over the long term, due to a disparity in at-risk exposure for appendectomized  
271 patients compared to the normal UC population.

272 This hypothesis is further supported by results of the only two prospective series so far  
273 describing clinical results in therapy-refractory UC patients undergoing appendectomy. The study of  
274 Bolin et al<sup>14</sup> showed an improvement in the clinical activity index score in 27/30 (90%) patients, but  
275 after one year only 12 (40%) patients had a complete resolution of symptoms. There was no  
276 description of the number of patients in endoscopic remission in this study. The long-term results of  
277 28 patients reported in the abstract of another prospective cohort series showed clinical response in  
278 12 (46%) patients and remission in 5 (18%) patients 12 months after appendectomy for therapy  
279 refractory UC.<sup>22</sup> After a median of 4 years, 13 (46%) had lasting clinical response and 6 (21%) were in  
280 endoscopic remission. Although the results were considered to be promising as this patient group  
281 was originally referred for colectomy, it also demonstrates that only a minority of patients achieve  
282 complete remission.

283 These studies do suggest that an appendectomy can result in a beneficial clinical effect; a  
284 substantial proportion of patients appear to experience a reduction in inflammation and disease  
285 activity , thereby waiving the need for colectomy. In contrast, in our study we found no overall  
286 significant decrease in the risk of colectomy in appendectomized patients although we identified a  
287 shift in the indication for colectomy from (therapy refractory) disease activity to (pre)malignant  
288 degeneration. In the study of Harnoy et al<sup>6</sup>, the prevalence of CRC in appendectomized UC patients  
289 was 33%, while the overall prevalence of CRC in any UC patient is estimated to be around 4%.<sup>23</sup> The  
290 shift in indication might, over time, result in comparable colectomy rates in both groups.

291 Another well-known risk factor which is associated with the development of CRC in UC  
292 patients is PSC. The prevalence of PSC was significantly higher in the appendectomy group in three  
293 out of seven studies. The relation between appendectomy and the development of PSC has been  
294 analyzed previously in several studies and a recently published meta-analysis found a significant  
295 association with an OR of 1.37.<sup>24</sup> However, this meta-analysis included both PSC (without UC) and  
296 PSC-UC patients, and perhaps only the UC patients are at risk after appendectomy due to a distinct

297 IBD phenotype with more frequent involvement of the right hemicolon.<sup>25</sup> In addition to this, the only  
298 study in our meta-analysis describing the location of CRC found significantly more cancers located in  
299 the right hemicolon in appendectomized patients. A Swiss nationwide cohort study including 2744  
300 patients (which was not included in the aforementioned meta-analysis) builds upon this hypothesis  
301 as the authors indicated an appendectomy as independent risk factor for developing PSC in UC  
302 patients (OR 4.11, P = 0.019).<sup>26</sup> Further research is required to investigate this possible association  
303 and possible underlying immunological mechanisms.

304           Unfortunately, we cannot comment on other important risk factors for CRC like severity and  
305 a history of CRC in the family.<sup>7</sup> Due to the retrospective character of most of the included studies in  
306 this systematic review, data on these variables was often lacking.

307           There are several limitations to this study. As only two prospective studies could be included,  
308 the conclusions of our meta-analysis are merely based on retrospective data with its inherent  
309 shortcomings. Pooling data of these different study designs is generally not preferred as this poses  
310 substantial heterogeneity. Even though the heterogeneity in our main analyses was low, it should be  
311 kept in mind that this might be due to simplification of the analytical model (from adjusted  
312 regression to non-adjusted regression). Also, several studies did not present all relevant outcome  
313 parameters, which could lead to bias. An attempt was made to collect these data from the original  
314 author groups, but this was not completely successful. Lastly, it is difficult to clearly extrapolate these  
315 findings to clinical practice because in the majority of the studies describing appendectomy and the  
316 risk of CRC/HGD the appendectomy was performed prior to the diagnosis of UC. This impacts on the  
317 relevance to current UC sufferers. . Compounding this, since we know that appendectomy protects  
318 against the development of UC in the first place, if a patient goes on to develop the condition having  
319 already had an appendectomy, this may perhaps be viewed as a special high-risk subset of a  
320 particularly virulent version of UC – hence the higher subsequent risk of CRC/HGD. If an  
321 appendectomy performed after the diagnosis of UC postpones colectomy, when do we call this

322 clinically relevant? Obviously, if this difference is 10 years, like the data presented by Harnoy et al<sup>6</sup>,  
323 an appendectomy will be interesting for this generally young patient group (e.g. with respect to  
324 fertility), but in our pooled data (including both appendectomies prior to and after the UC diagnosis)  
325 the difference was less compelling (112.3 versus 133.0 months). The clinical relevance of postponing  
326 colectomy is dependent on the years gained with colon in situ and good quality of life. Unfortunately,  
327 it is impossible to comment on this with these retrospective data. A recently published abstract of  
328 prospective data demonstrated that quality of life measured by the disease specific (IBDQ)  
329 significantly improve after appendectomy, but it should be emphasized that this is a therapy-  
330 refractory patient group who were referred for colectomy.<sup>22</sup>

331  
332 In conclusion, this systematic review and meta-analysis shows that when the data is pooled from  
333 previously published reports, the apparently significantly increased risk of CRC and HGD after  
334 appendectomy in UC patients persists. The increased risk of CRC and HGD is likely to be secondary to  
335 the fact that the colon is longer in situ because of the suggested positive effect of appendectomy on  
336 disease severity. With the current findings, discontinuation of ongoing studies on appendectomy in  
337 UC is not recommended. In contrast, we feel that this review confirms the clinical interest in the role  
338 of an appendectomy as therapy for UC. However, it is clear that there remains an ongoing risk of CRC  
339 or HGD in patients who may have clinically improved after appendectomy, and as such this study  
340 emphasizes the importance of ongoing regular endoscopic surveillance in appendectomized UC  
341 patients. Future studies should aim to address possible confounding factors when analyzing the  
342 effect of an appendectomy on UC and CRC related outcomes.

343

344

345

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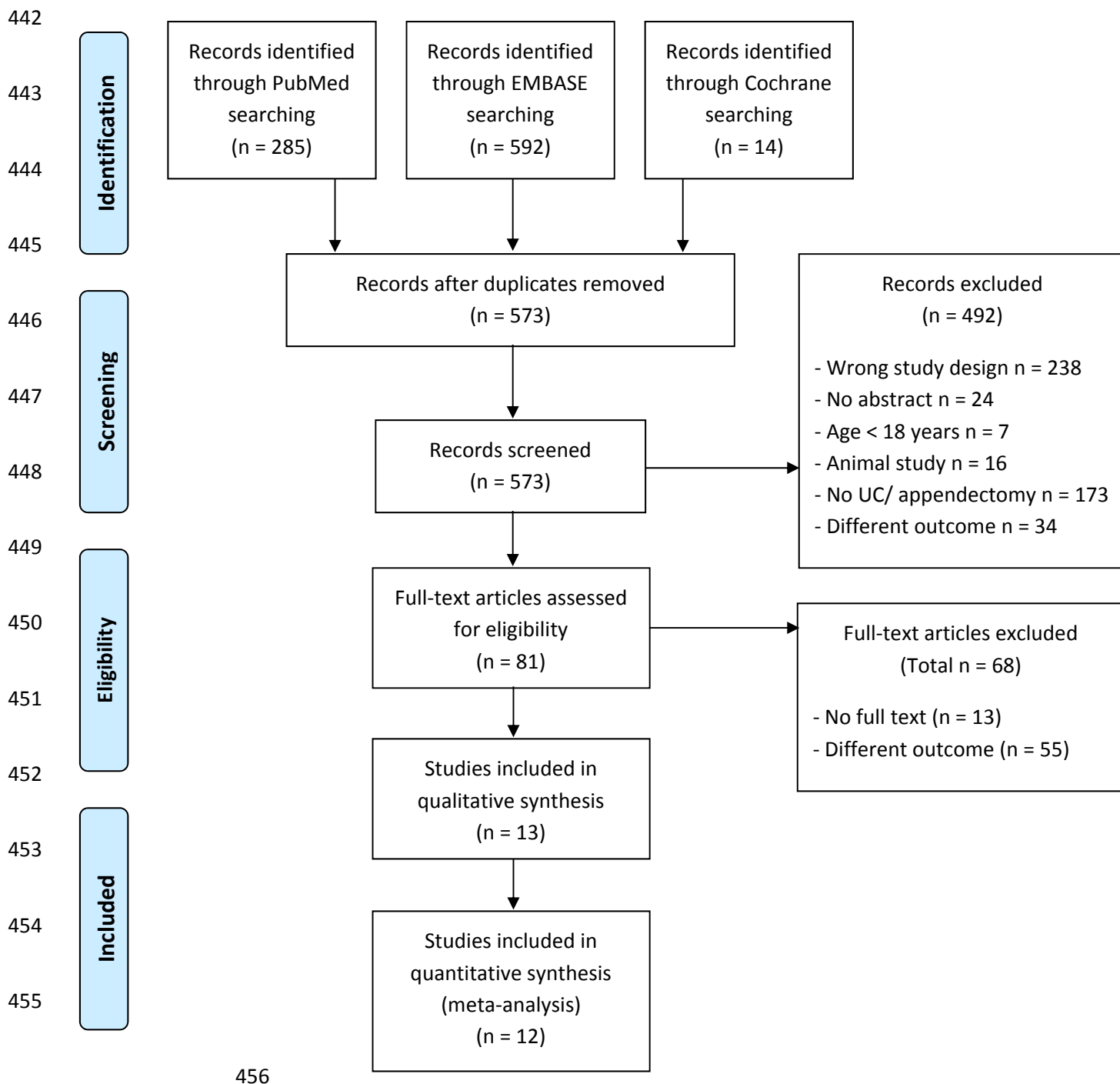


Figure 1: Study selection

Author	Journal	Country	Study design	Inclusion period	Intervention	No. of patients	Female	Age (yrs)	Age at UC diagnosis	Age at appendectomy (yrs)	Fami ly	PSC	Subtotal/pan-colitis	Corticosteroid use	Immunomodulators/ biologicals	Follow-up (mo) until study
Cosnes et al (2002) <sup>16</sup>	Gut	France	R	Jan 1997 -	A-	589 (92.3%)	51.6%	-	Mean 32.9	-	-	-	40.6%	412 (70%)	112 (19%)	-
				Dec 2000	A+ (< UC)	49 (7.7%)	73.5%	-	Mean 35.7	<20: 35	-	-	-	38.8%	33 (67%)	13 (27%)
Selby et al (2002) <sup>20</sup>	The American Journal of Gastroenterology	Australia	R	-	A-	239 (92.3%)	48.6%	Mean 41.8	Mean 32.1	-	-	7.5%*	37.7%	-	43 (18.0%)	-
					A+ (< UC)	12 (4.6%)	-	Mean 62.6	Mean 42.5	Mean 26.6	-	25%*	50%	-	4 (33.3%)	-
					A+ (> UC)	8 (3.1%)	-	Mean 53.8	Mean 24.6	Mean 31.8	-	25%*	25%	-	1 (12.5%)	-
Radford-Smith et al (2002) <sup>15</sup>	Gut	Australia	R	1995-1999	A-	286 (93.2%)	48.9%	Mean 32.7	Mean 31.3	-	-	-	42.1%	-	71 (24.8%)*	-
					A+ (< UC)	21 (6.8%)	-	(0.85)	Mean 37.8	<20: 10, >20:	-	-	61.9%	-	1 (4.8%)*	-
Florin et al (2004) <sup>17</sup>	Gut	Australia	R	1995-2002	A-	275 (93.5%)	48.2%	Mean 32.7	Mean 32.4	-	-	17.4*	40%	-	74 (27%)*	-
					A+ (< UC)	19 (6.9%)	-	(0.86)	Mean 37.9	<20: 8, >20:	-	50*	58%	-	1 (5.6%)*	-
Hallas et al (2004) <sup>13</sup>	Gut	Denmark	R	Jan 1977 -	A-	808	-	-	Mean 38.7	-	-	-	-	-	-	Mean 131.9 (61.2)
				Dec 1999	A+ (> UC)	202 (1.7%)	58.4%	-	Mean 38.6	Mean 43.3	-	-	-	-	-	-
Manguso et al (2004) <sup>27</sup>	The American Journal of	Italy	P	Jan 1984 -	A-	485 (90.7%)	37.5%*	-	Median 28	-	-	1%	44%	-	-	Median 132 (96)
				Jan 2002	A+ (< UC)	50 (9.4%)	68%*	-	Median 31	-	-	8%	36%	-	-	-
Bolin et al (2004) <sup>27</sup>	The American Journal of	Australia	P	Jul 2006 -	A+ (> UC)	30 (100%)	63.3%	Median 35	-	Median 35	-	-	0%	1 (3.3%)	7 (23.3%)	Median 14 (9-32)
				Jul 2006 -	A+ (> UC)	30 (100%)	63.3%	Median 35	-	Median 35	-	-	-	0%	1 (3.3%)	7 (23.3%)
Picazo-Ferrera et al (2011) <sup>12</sup>	Revista de gastroenterologia	Mexico	R	Jan 2007 -	A-	76 (66.7%)	43.7%	-	<40: 71%	-	-	1.3%*	48.6%	-	-	-
				Jun 2010	A+	38 (33.35)	47.3%	-	<40: 63.2%	25.1	-	10.5%*	50%	-	-	-
Lee et al (2014) <sup>18</sup>	Journal of gastroenterology and hepatology	South Korea	R	Jul 1989 -	A-	2544 (96.1%)	45.7%*	Mean 45.3	Mean 37.0	-	-	1.1%	22%	1427	646 (25.4%)	Mean 100.4 (73.4)
				Dec 2013	A+ (< UC)	68 (2.6)	66.2%*	Mean 49.1	Mean 40.7	Mean 31.1	-	1.5%	27.9%	40 (58.8%)	15 (22.1%)	Mean 100.3 (84)
		Dec 2013	A+ (> UC)	36 (1.4%)	47.2%*	Mean 49.9	Mean 36.3	Mean 42.5	-	2.8%	16.7%	4 (26.7%)	8 (24.4%)	Mean 162.6 (98)		
Gordillo et al (2015) <sup>19</sup>	Journal of Crohn's and Colitis	Spain	CC	Jan 2006 -	A-	771 (92.8%)	46%	Mean 56.1	Mean 37.6	-	15%	3%	6.6%	555 (72%)	393 (51%)	Mean 188 (103.1)
				Jan 2010	A+ (< UC)	60 (7.2%)	55%	Mean 58.9	Mean 40.1	-	18%	5%	6.7%	41 (68%)	6 (10%)	Mean 193 (119.1)
Harnoy et al (2016) <sup>6</sup>	British Journal of Surgery	France	R	Jan 2001 -	A-	217 (93.5%)	49.8%	Median 38.5	-	-	4.6%	21.7%	87.1%	204 (94%)	-	Median 41 (14-107)*
				Dec 2011	A+	15 (6.5%)	40%	Median 49.0	-	-	0%	6.7%	86.7%	11 (73.3%)	-	Median 151 (113-242)*
Parian et al (2016) <sup>5</sup>	Gut	USA	R	Jan 2003 -	A-	2603 (95.9)	49.3%	-	Mean 30.8	-	-	-	64.9%	-	-	-
				Nov 2013	A+ (< UC)	63 (2.4%)	55.9%	-	Mean 41.8	<20: 28	-	-	63.4%	-	-	-
				Nov 2013	A+ (> UC)	48 (1.8%)	-	-	-	-	-	-	-	-	-	-
Myreliid et al (2017) <sup>28</sup>	The American Journal of Gastroenterology	Sweden	R	Jan 1964 -	A- (< UC)	62174	47.6%	-	Mean 44.6	-	-	-	-	-	-	603462 person years
				Dec 2010	A+ (< UC)	1537 (2.4%)	48.2%	-	Mean 45.9	Mean 32.2	-	-	-	-	-	15047 person years
				Dec 2010	A+ (> UC)	603 (1.0%)	50.2%	-	Mean 33.6	Mean 40.6	-	-	-	-	-	7598 person years

**Table 1: Study and patient characteristics**

\*significantly different. Mean values are accompanied by SDs and medians by IQRs. R=retrospective. P=prospective. CC=case-control. A=no appendectomy.

A+=appendectomy. <UC=before the diagnosis of UC. >UC=after the diagnosis of UC.

Author	Intervention	No. of patients	Colectomy	Colectomy indicated for UC	Duration of UC (mo)	Age at colectomy	CRC	HGD
Cosnes et al (2002) <sup>16</sup>	A-	589	-	-	Mean 86.4 (99.6)*	-	11 (1.9%)	-
	A+ (< UC)	49	-	-	Mean 121.2 (97.2)*	-	0 (0%)	-
Selby et al (2002) <sup>20</sup>	A-	239	21 (8.8%)	-	Mean 9.7 (1.2)*	-	-	-
	A+ (< UC)	12*	2 (16.7%)	1 (8.3%)	Mean 20.1 (7.9)*	-	1 (8.3%)	-
	A+ (> UC)	8*	1 (12.5%)	0 (0%)	Mean 29.2 (8.0)*	-	0 (0%)	-
Radford-Smith et al (2002) <sup>15</sup>	A-	286	65 (22.7%)*	60 (21.0%)	-	-	5 (1.8%) (+HGD)	-
	A+ (< UC)	21	1 (4.8%)*	0 (0%)	-	-	1 (4.8%) (+HGD)	-
Florin et al (2004) <sup>17</sup>	A-	275	68 (24.7%)	67 (24.4%)	-	-	2 (0.7%)	5 (1.8%)
	A+ (< UC)	19	3 (16%)	1 (5.3%)	-	-	2 (10.5%)	0 (0%)
Hallas et al (2004) <sup>13</sup>	A-	808	42 (5.2%)	-	Mean 131.9 (61.2)	-	-	-
	A+ (> UC)	202	9 (4.5%)	-	Mean 129.2 (62.4)	-	-	-
Manguso et al (2004) <sup>27</sup>	A-	485	6 (1.2%)	-	-	-	-	-
	A+ (< UC)	50	2 (4%)	-	-	-	-	-
Bolin et al (2009) <sup>14</sup>	A+ (> UC)	30	0 (0%)	-	Median 60 (8-360)	-	-	-
Picazo-Ferrera et al (2011) <sup>12</sup>	A-	76	12 (15.7%)*	-	-	-	3 (4.0%) (+HGD)	-
	A+	38	16 (42.1%)*	-	-	-	3 (7.9%) (+HGD)	-
Lee et al (2014) <sup>18</sup>	A-	2544	207 (8.1%)	-	Mean 100.4 (73.4)	Mean 42.3 (14.8)	19 (0.7%)	21 (0.8%)
	A+ (< UC)	68	6 (8.8%)	-	Mean 100.3 (84)	Mean 45.5 (17.9)	0 (0%)	0 (0%)
	A+ (> UC)	36	0 (0%)	-	Mean 162.6 (98)	-	0 (0%)	1 (2.8%)
Gordillo et al (2015) <sup>19</sup>	A-	771	3.7%	-	Mean 223.2	-	19 (2.5%)*	19 (2.5%)
	A+ (< UC)	60	6.7%	-	Mean 224.4	-	5 (8.3%)*	2 (3.3%)
Harnoy et al (2016) <sup>6</sup>	A-	217	(217 (100%))	175 (80.7%)	Median 41 (14-107)*	Median 38.5 (27-50)*	12 (5.5%)*	18 (8.3%)*
	A+	15	(15 (100%))	7 (46.7%)	Median 151 (113-242)*	Median 49.0 (35-64)*	5 (33.3%)*	4 (26.7%)*
Parian et al (2016) <sup>5</sup>	A-	2603	424 (16.4%)*	-	Mean 104.5 (109.2)*	-	-	-
	A+ (< UC)	63	26 (23.6%)*	-	Mean 128.9 (116.4)*	-	-	-
	A+ (> UC)	48	-	-	-	-	-	-
Myrelid et al (2017) <sup>28</sup>	A- (< UC)	62174	7541 (12.1%)*	-	-	Mean 43.5 (17.2)	-	-
	A+ (< UC)	1537	149 (9.7%)*	-	-	Mean 44.1 (14.7)	-	-
	A+ (> UC)	603	70 (11.6%)*	-	-	Mean 38.4 (14.1)	-	-

**Table 2: Outcome data of the included studies**

\*significantly different. Mean values are accompanied by SDs and medians by IQRs. A-=no appendicectomy.

A+=appendicectomy. <UC=before the diagnosis of UC. >UC=after the diagnosis of UC. PSC=primary sclerosing cholangitis

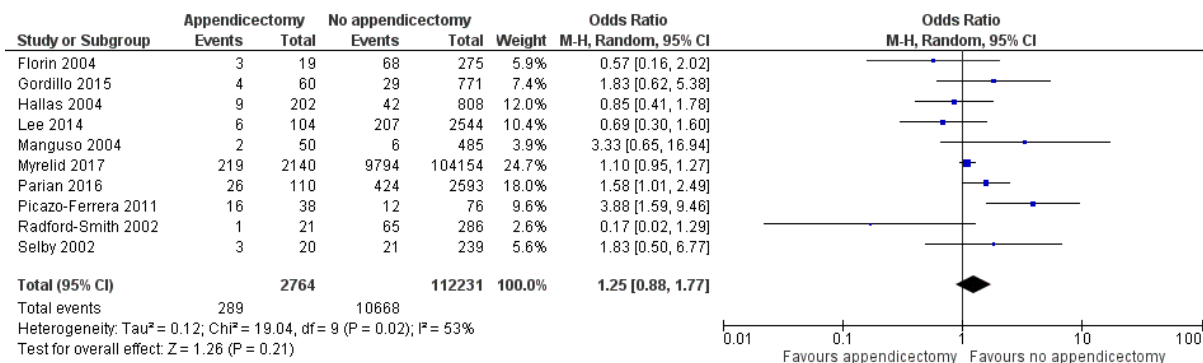


Figure 2: Forest plot of appendectomy and risk of colectomy

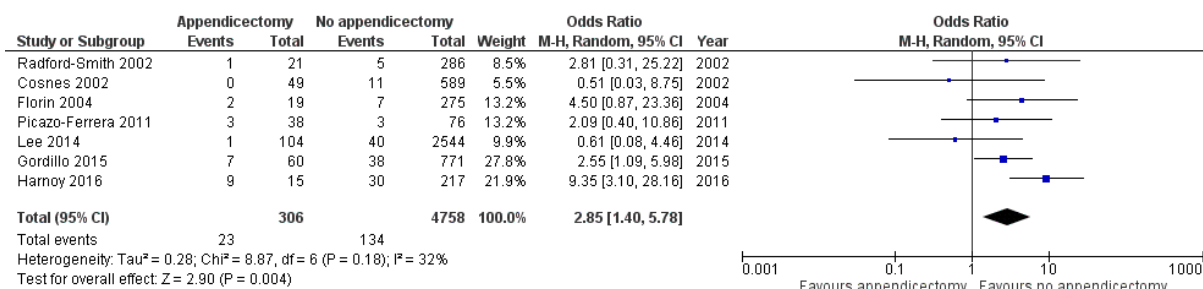


Figure 3: Forest plot of appendectomy and CRC or HGD

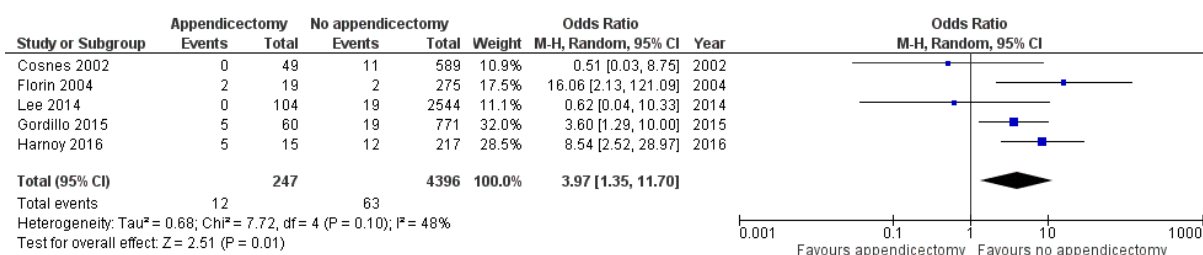


Figure 4: Forest plot of appendectomy and CRC

Author	Disease duration			Extensive disease spread (%)			PSC (%)		
	A-	A+ (< UC)	A+ (> UC)	A-	A+ (< UC)	A+ (> UC)	A-	A+ (< UC)	A+ (> UC)
Cosnes et al <sup>14</sup>	Mean 86.4 (99.6)*	Mean 121.2 (97.2)*		239/589 (40.6)	19/49 (38.8)				
Selby et al <sup>15</sup>	Mean 9.7 (1.2)*	Mean 20.1 (7.9)*	Mean 29.2 (8.0)*	90/239 (37.7)	6/12 (50)	2/8 (25)	18/239 (7.5)*	3/12 (25)*	2/8 (25)*
Radford-Smith et al <sup>16</sup>				120/286 (42.0)	13/21 (61.9)				
Florin et al <sup>17</sup>				110/275 (40.0)	11/19 (57.9)		58/333 (17.4)*	19/28 (50)*	
Hallas et al <sup>13</sup>	Mean 131.9 (61.2)		Mean 129.2 (62.4)						
Manguso et al <sup>18</sup>				213/485 (44.0)	18/50 (36)		5/485 (1)	4/50 (8)	
Picazo-Ferrera et al <sup>12</sup>				37/76 (48.6)	19/38 (50)		1/76 (1.3)*	4/38 (10.5)*	
Lee et al <sup>20</sup>	Mean 100.4 (73.4)	Mean 100.3 (84.0)	Mean 162.6 (98.0)	560/2544 (22.0)	19/68 (27.9)	6/36 (16.7)	29/2544 (1.1)	1/68 (1.5)	1/36 (2.8)
Gordillo et al <sup>21</sup>	Mean 223.3	Mean 224.4					23/771 (3)	3/60 (5)	
Harnov et al <sup>5</sup>	Median 41 (14-107)*	Median 151 (113-242)*		189/217 (87.1)	13/15 (86.7)		47/217 (21.7)	1/15 (6.7)	
Parian et al <sup>5</sup>	Mean 104.5 (109.2)*	Mean 128.9 (116.4)*		1584/2603 (60.9)	64/111 (57.7)				
Mvrelid et al <sup>22</sup>									
<b>Weighted total</b>	112.3 mths	93.2 mths	150.7 mths	3142/7314 = 43.0%	86/219 = 39.3%	8/44 = 18.2%	181/4665 = 3.9%	30/218 = 13.8%	3/44 = 6.8%
		133.0 mths			190/427 = 44.5%			38/315 = 12.1%	

**Table 3: Confounding factors**

\*significantly different. Mean values are accompanied by SDs and medians by IQRs. A-=no appendectomy.

A+=appendectomy. <UC=before the diagnosis of UC. >UC=after the diagnosis of UC. PSC=primary sclerosing cholangitis

