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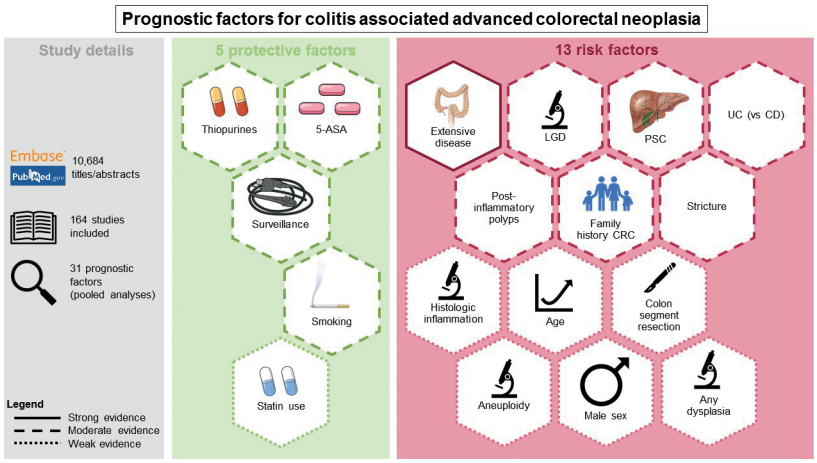

Prognostic factors for advanced colorectal neoplasia in inflammatory bowel disease: systematic review and meta-analysis

Short title: Prognostic factors for aCRN in IBD

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List of abbreviations

5-ASA	5-aminosalicylic acid
aCRN	advanced colorectal neoplasia
CD	Crohn's disease
CI	confidence interval
CRC	colorectal cancer
CRN	colorectal neoplasia
HGD	high-grade dysplasia

HR	hazard ratio
IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease unclassified
IND	indefinite dysplasia
IQR	interquartile range
LGD	low-grade dysplasia
NSAIDs	non-steroidal anti-inflammatory drugs
n	number
OR	odds ratio
PIPs	post-inflammatory polyps
PSC	primary sclerosing cholangitis
QUIPS	quality in prognostic studies
RoB	risk of bias
S	supplementary file
TNF	tumor necrosis factor
UC	ulcerative colitis

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Disclosures

All authors declare no conflicts of interest

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ABSTRACT

Background and aims: Patients with inflammatory bowel disease (IBD) have an increased risk of colorectal cancer (CRC). We performed a systematic review and meta-analysis to identify all prognostic factors for advanced colorectal neoplasia (aCRN, high-grade dysplasia or CRC) in patients with IBD.

Methods: A systematic literature search was conducted according to the MOOSE guidelines. Risk of bias was assessed using the Quality in Prognostic Studies tool. Random-effects models were created separately for odds and hazard ratios, different study designs, and univariable or multivariable data. The evidence for all prognostic factors was categorized as 'weak', 'moderate', or 'strong', based on estimate of effect sizes, heterogeneity, and risk of bias.

Results: A total of 164 studies were included allowing pooled analysis of 31 potential prognostic factors. In the univariable analysis, the evidence for extensive disease was classified as strong while evidence for low-grade dysplasia, strictures, primary sclerosing cholangitis, post-inflammatory polyps, family history of CRC, and ulcerative colitis versus Crohn's disease was considered moderate. Evidence for any dysplasia, colon segment resection, aneuploidy, male sex and age was classified as weak. In addition, histologic inflammation was identified as a risk factor in multivariable analysis (weak evidence). The evidence for the protective factors colonoscopic surveillance, 5-ASA, thiopurines, and smoking was moderate in univariable analysis. Multivariable analysis provided weak evidence for statin use.

Conclusion: In this systematic review and meta-analysis we identified 13 risk factors and 5 protective factors for aCRN in IBD patients, based on univariable and/or

multivariable pooled analyses. These findings might lay the groundwork for an improved CRC risk stratification-based surveillance in IBD.

Keywords: Risk factor, protective factor, ulcerative colitis, colorectal cancer.

INTRODUCTION

Patients with colonic inflammatory bowel disease (IBD) have a 1.7 fold increased risk of colorectal cancer (CRC).[1] Therefore, international guidelines recommend enrollment of patients with ulcerative or Crohn's colitis in surveillance programs to detect and remove dysplastic lesions before progression to advanced colorectal neoplasia (aCRN, high-grade dysplasia (HGD) and CRC) occurs.[2-5] Indirect evidence indicates that endoscopic surveillance is effective in terms of a reduced CRC incidence and CRC-associated mortality.[6] However, effect sizes and levels of evidence of individual prognostic factors have not been incorporated into the stratification algorithms of current surveillance guidelines.

American guidelines recommend surveillance colonoscopies every 1-3 years, without stratifying the individual surveillance interval except for concomitant primary sclerosing cholangitis (PSC).[4, 5] In contrast, European guidelines assign patients to a low, moderate, or high-risk category based on the presence of a number of clinical and histological risk factors[2, 3] including concomitant PSC,[7] a history of low-grade dysplasia (LGD),[8] and extensive disease.[9] However, most recommendations in current guidelines are based on studies of diverse quality.

To provide an up-to-date overview of literature, with a focus on the overall strength of association of prognostic factors for aCRN, we performed a systematic review and meta-analysis.

METHODS

We followed the guidelines for reporting developed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. The study was registered on PROSPERO (CRD42019141345) prior to the literature search (checklist MOOSE provided in supplementary file 1 (S1)).[10]

Search strategy

A comprehensive literature search using broad search criteria was conducted in the PubMed and EMBASE databases (date: July 10th, 2019) with aid of an experienced librarian. In short, the search terms included all key terms for IBD in combination with all terms for (a)CRN and terms for location in the colon. There were no language restrictions. Animal studies were excluded. Details on the search strategy are provided in S2. All reference lists of included studies and previous meta-analyses on prognostic factors were screened for additional eligible articles.

Study selection

First, all titles and abstracts of identified studies were independently screened by two researchers (M.J. and A.W.) to exclude studies irrelevant for our aim. Discrepancies were resolved through a consensus discussion with the senior authors (F.H., M.L., S.E., B.O.). Case reports, conference abstracts, letters, and review articles were excluded. Next, we assessed the full-text of all potentially relevant studies for the following inclusion criteria: 1) cohort study or case-control study; 2) data on prognostic factors for aCRN in IBD, with at least one event of aCRN; 3) reporting an odds ratio (OR) or a hazard ratio (HR) (with a 95% confidence interval (CI)) or

providing data (number of events and patients in exposed and non-exposed group) that allowed for calculation of an OR and its standard error. Studies that reported prognostic factors for LGD and aCRN combined in a composite outcome or that only enrolled patients who had undergone a proctocolectomy were excluded. If more than one article assessed the impact of the same prognostic factor in identical or overlapping cohorts, we included the study that particularly focused on this prognostic factor (if not applicable, the most recent study was selected).

Data extraction and quality assessment

The following data were collected from all eligible studies using an electronic data-entry sheet: first author, publication year, country, study design, inclusion and exclusion criteria, cohort size, duration of follow-up, IBD type, duration of IBD, number of patients with aCRN per prognostic factor, and univariable and multivariable estimates of effect (OR or HR). Details of all included studies are provided in S3. If relative risks (RR) were reported and additional data were provided we calculated the OR because only 6 studies reported a RR for our outcome. Adjusted estimates of effect were documented as multivariable results. The set of covariates that was adjusted for in each study is specified in S4. Data from all studies were extracted separately by M.J. and A.W. and discrepancies were resolved through discussion. The quality of included studies was assessed using the Quality In Prognosis Studies (QUIPS) tool (S5).[11] The criteria of the QUIPS tool were expanded to enable grading of all included studies (S6). The overall quality of included studies was graded according to the methods previously described by Grooten et al.[12] If all QUIPS domains were rated as low risk of bias (RoB), or if all domains were rated as low RoB with one scoring moderate RoB, studies were categorized as low RoB.

Studies were graded as high RoB if one or more domains were scored as high RoB or if ≥3 domains were scored as moderate RoB. Remaining studies were graded as moderate RoB. Domain five, 'study confounding', was not considered in grading the overall quality since few studies reported multivariable models.

Prognostic factors

All potential prognostic factors reported in literature were included without any pre-selection. All prognostic factors that were reported in ≥1 study are discussed in the results section while related forest plots are shown in S7-S39. In addition, the factors endoscopic inflammation and p53 mutations were included, even though pooled analysis was not possible. The remaining factors are reported in S40.

The definitions of the identified prognostic factors are specified in the supplementary files of each prognostic factor.

Statistical analysis

A random-effects model was applied to pool the overall effect of a potential prognostic factor. We performed separate analyses to calculate the pooled univariable and multivariable ORs and HRs of potential prognostic factors. In addition, we performed secondary analyses by study design (cohort and case-control studies separately). I^2 statistics were used to assess the heterogeneity among studies. These were only reported in the manuscript if ≥10 studies were included, because I^2 results in small meta-analyses tend to be inaccurate.[13] An I^2 ≥ 50% indicates substantial (50% to 90%) to considerable (75% to 100%) heterogeneity.[14] These analyses were provided in the supplementary files of the prognostic factor. Meta-analyses were performed using Review Manager, version 5.3 (Cochrane

Collaboration, Copenhagen, Denmark). R statistical software, version 3.5.1 (Metafor package), was used to create funnel plots, to perform Egger's regression test for assessing publication bias, and to run meta-regression analyses.[15] Funnel plots were visually assessed for asymmetry. Egger's regression test was performed if ≥10 studies were available.[14] A p-value < .05 indicated substantial asymmetry of funnel plots, thereby implying publication bias.[16] Meta-regression analysis was performed for prognostic factors that might have changed over time and if ≥10 studies reporting on these prognostic factors were available.[14] Year of cohort was used as a covariate in meta-regression analysis, defined as mean from start to end of the study period (if missing, publication year was used)."

Good quality synthesis

A separate pooled analysis was performed with inclusion of only 'good quality studies'. These studies had to meet the following criteria: 1) the overall quality of the study was graded as 'low RoB', 2) only UC patients with at least left-sided disease or CD patients with colonic involvement were included in the study.

Summary of all identified prognostic factors

The quality of evidence for all identified prognostic factors was graded separately for univariable and multivariable analysis. Prognostic factors had to meet all criteria in the corresponding level of evidence (thus, all four criteria to be graded as 'strong evidence').

- *Strong evidence*: OR/HR ≥2 (risk factor) or ≤0.50 (protective factor) *and* P-value < .05 *and* heterogeneity ≤50% *and* ≥5 studies in pooled analysis *and* P-value < .05 in pooled good quality synthesis

- *Moderate evidence*: OR/HR ≥1.5 (risk factor) or ≤0.67 (protective factor) *and* P-value < .05 *and* ≥5 studies in pooled analysis
- *Weak evidence*: OR/HR >1 (risk factor) or <1 (protective factor) *and* P-value < .05 in pooled analysis

Prognostic factors were only included in the summary table if ≥2 studies were included in the pooled analysis. The pooled subgroup analysis (univariable HR or OR and multivariable OR or HR) including the largest number of studies was selected. If the number of included studies within both sub-analyses was equal, grading of the level of evidence was based on the sub-analysis with the lowest heterogeneity.

RESULTS

Search results

The initial search identified 10,674 unique articles from PubMed and Embase libraries. An additional 6 articles were identified through manual screening of references. A total of 10,291 articles were excluded after screening of titles and abstracts. After full-text screening of the remaining 393 articles, 164 articles remained eligible for inclusion. The main reasons for exclusion were: no evaluation of prognostic factors for aCRN (number (n) =76), not reporting the exact number of aCRN (n=38), and lack of a control group (n=31). In addition, 12 studies were excluded based on overlapping cohorts. The flow diagram of the inclusion process is shown in figure 1.

Study characteristics and quality assessment

A total of 164 studies were included (120 cohort studies, 44 case-control studies). The characteristics of all included studies are shown in S3. A total of 83 studies were

conducted in Europe, 44 in North America, 29 in Asia, 4 in Australia or New Zealand, 2 in Africa and 2 in South America.

The overall quality of the included studies, as assessed using the QUIPS tool, was graded as 'low RoB' in 83 studies, 'moderate RoB' in 32 studies and 'high RoB' in 49 studies (S5).

Prognostic factors

Figure 2 and figure 3 depict the pooled results from the univariable and the multivariable analyses (OR and HR). Meta-analysis was feasible for 31 prognostic factors.

Disease characteristics (and demographics)

Disease extent

The pooled univariable OR comparing extensive UC with left-sided UC was 2.43 (95%CI 2.01-2.93, I^2=0%), based on 40 studies. The pooled HR from 3 studies in UC was 3.48 (95%CI 1.58-7.65). No study assessed the risk of >50% colonic involvement in patients with CD, but in one study, extensive CD, defined as involvement of >2/3rd of the colon was not associated with a higher risk as compared to partial CD (less than 1/3rd of the colon) (calculated OR 0.35, 95%CI 0.01-11.08) (S7A-G).[17]

IBD type

The pooled univariable OR from 7 cohort studies comparing UC versus CD (ileocolonic or colonic disease) was 1.50 (95%CI 1.09-2.06. No difference in aCRN

risk between UC versus CD was found if UC patients who only had proctitis were included in the analysis (OR 1.14 (95%CI 0.79-1.64) (S8A-F).

History of LGD

All analyses showed an increased risk of aCRN in IBD patients with a history of LGD (S9A-E). The pooled univariable OR from 8 studies was 10.85 (95%CI 5.13-22.97). Although all studies reported an increased risk, the magnitude of this risk ranged widely with ORs varying from 1.25 to 86.0. The multivariable HR of 4 studies was 3.67 (95%CI 2.23-6.06).

History of indefinite for dysplasia

Four studies reported on the risk of aCRN in patients with a history of indefinite for dysplasia (IND) lesions (S10A-C). The pooled univariable OR from 3 studies did not show a significantly increased risk (OR 2.42, 95%CI 0.75-7.81), but one cohort study with a multivariable model found a HR of 6.85 (95%CI 1.78-26.36).[18]

Any dysplasia (grade not specified)

This analysis includes only studies that did not specify the grade of dysplasia. If grades of dysplasia were specified, the results were exclusively included in the analysis of IND or LGD. Four studies assessed the impact of any dysplasia on the risk of aCRN (S11A-D). Pooled univariable data of 2 cohort studies resulted in an OR of 10.70 (95%CI 4.60-24.87).

Post-inflammatory polyps

The aCRN risk in patients with post-inflammatory polyps (PIPs) was reported in 8 studies (S12A-D). The pooled univariable OR indicated that patients with PIPs were at higher risk (OR 3.29, 95%CI 2.41-4.48) but this association was not confirmed in the pooled HR analyses (univariable HR 1.67, 95%CI 0.99-2.82; multivariable HR 1.73, 95%CI 0.88-3.40).

Endoscopic inflammation

Two studies evaluated the association of endoscopic inflammation with aCRN (S13A-D). One large cohort study reported a univariable HR of 2.14 (95%CI 1.48-3.09) and a multivariable HR of 2.39 (95%CI 1.63-3.50).[7] One case-control study calculated the mean score of endoscopic inflammation and found a higher risk of aCRN in patients with a higher score (OR 2.62, 95%CI 0.84-8.17 per 1-unit increase in score), although this did not reach statistical significance.[19]

Histologic inflammation

Six studies assessed the impact of histologic inflammation on aCRN using different definitions (described in S14D). Three case-control studies provided data for calculation of a pooled univariable OR (1.98, 95%CI 0.68-5.73). The pooled multivariable HR of 2 cohort studies and one case-control study was 2.51 (95%CI 1.75-3.61) (S14A-D).

Strictures

Four studies were identified in which the impact of colonic strictures on development of aCRN was evaluated. One of these studies provided data for analyzing UC and CD separately (UC: univariable OR 12.74, 95%CI 5.81-27.94; CD: univariable OR

4.14, 95%CI 1.49-11.51).[20] Pooled analysis of all data on strictures in UC patients resulted in a pooled OR of 4.68 (95%CI 0.45-48.25). Combining all data on strictures in CD patients resulted in a pooled OR of 8.03 (95%CI 3.50-18.45). The pooled univariable analysis combining data from CD and UC patients resulted in an OR of 7.78 (95%CI 3.74-16.18, shown in figure 2). One study provided data on strictures and risk of CRC in IBD patients in a multivariable model (OR 8.42, 95%CI 3.85-18.42) (S15A-C).[20]

Perianal disease

Five studies provided risk estimates of rectal aCRN in patients with perianal disease (3 in CD[21-23] and 2 in CD and UC[23, 24]). The pooled OR of 4 studies reporting univariable data was 2.57 (95%CI 0.92-7.15) (S16A-B).

Disease duration

Four studies evaluated the association of disease duration on the development of aCRN in predefined groups using different definitions (S17A-B). Both univariable and multivariable pooled analyses did not show a statistically significant difference.

Aneuploidy

Five studies evaluated the potential of DNA aneuploidy as a premalignant marker (S18A-C). The pooled univariable OR of 4 studies was 5.17 (95%CI 2.28-11.71). Multivariable analysis showed a HR of 4.30 (95%CI 2.50-7.40) in one case-control study.[25]

P53 mutation

Two studies examined whether p53 mutations can serve as biomarkers for development of aCRN (S19A-C). In a cohort of 95 patients with longstanding UC, p53 mutations were not predictive for aCRN (OR 2.47, 95%CI 0.72-8.48).[26] In a case-control study, the presence of p53 mutations in random surveillance biopsies was not associated with the development of CRC (multivariable HR of 1.70, 95%CI 0.93-3.10).[25]

Primary sclerosing cholangitis

A concomitant diagnosis of PSC in IBD patients was associated with an increased aCRN risk, with a pooled univariable OR of 4.14 (95%CI 2.85-6.01, I^2=60%) based on 33 studies. There was substantial heterogeneity due to the wide range in ORs, yet almost all studies showed (a trend towards) an increased risk. The multivariable HR of 4 studies was 2.77 (95%CI 1.76-4.38). Almost all separate analyses per study type demonstrated an increased risk in IBD patients with PSC (S20A-D).

Sex

Pooled results from 60 studies showed that the aCRN risk was higher in male patients (OR 1.27, 95%CI 1.12-1.44, I^2 30%). Male sex remained a significant risk factor for aCRN in the pooled multivariable HR and OR analyses (S21A-D).

Age

Age as a risk factor for aCRN was evaluated in 8 studies, using different definitions (S22A-D). Four studies used the definition 'age per year increase' resulting in a pooled univariable HR of 1.031 per year (95%CI 1.017-1.046). Three studies provided multivariable data, yielding a pooled multivariable HR of 1.036 per year (95%CI 1.012-1.061).

Family history of colorectal carcinoma

Data from 15 studies showed that a positive family history of CRC was associated with a higher aCRN risk (OR 2.62, 95%CI 1.93-3.57, I^2=0%) (S23A-E). Six studies restricted family history of CRC to first-degree relatives (pooled OR 2.48, 95%CI 1.49-4.14). Combination of the remaining 9 studies using different definitions ('any relative', 'second-degree relative') or not providing one, resulted in a pooled OR of 2.59 (95%CI 1.59-4.21).

Family history of IBD

Four studies evaluating the impact of a positive family history of IBD on the aCRN risk did not report a significant association (univariable OR 1.13, 95%CI 0.53-2.39, S24A).

Smoking

Patients with a history of smoking had a lower risk of developing aCRN in univariable, but not in multivariable analysis. The pooled univariable OR in 14 studies was 0.66 (95%CI 0.49-0.88, I^2=28%). All studies but two[27, 28] included only UC patients. The pooled multivariable OR of 3 studies was 1.27 (95%CI 0.75-2.13), based on one study providing data from a UC cohort[29] and 2 studies from IBD cohorts (S25A-C).

Appendectomy

Seven studies evaluated the impact of appendectomy on the aCRN risk (S26A-B). The pooled univariable OR was 1.57 (95%CI 0.72-3.41). All data were derived from UC cohorts except for one study consisting of a CD cohort.[27] One study reporting a multivariable OR did show a higher risk of aCRN in patients with an appendectomy before UC diagnosis (OR 2.66, 95%CI 1.06-6.67).[30]

Age at IBD diagnosis

Studies that compared the impact of young versus old age at IBD diagnosis (n=12) on aCRN development used a wide range of cut-off ages, ranging from 25 to 60 years (S27A-G). Therefore, only a few studies could be pooled. The pooled univariable OR from 3 cohort studies comparing age <30 years versus ≥30 years was 1.00 (95%CI 0.59-1.70). The pooled univariable HR of 2 studies was 1.69 (95%CI 0.83-3.45), while data from 2 studies in a multivariable model reported a pooled HR of 0.76 (95%CI 0.23-2.55).

Colon segment resection

Four studies evaluated the impact of colon segment resection on the development of aCRN. Three of these studies did not specify the indication for resection (S28D). The pooled univariable HR of 2 cohort studies (one study including IBD patients and one study including UC and IBD-U patients) showed an increased risk of aCRN in patients with a history of a colon segment resection 6.46 (95%CI 1.32-31.61). In contrast, one case-control study in CD patients did not find an association (univariable OR 0.63, 95%CI 0.16-2.48).[31] The pooled multivariable analysis of two studies including IBD patients did not find an association as well (HR 0.81, 95%CI 0.06-10.71). One of these studies, in which patients were excluded who received colon segment resection because of a diagnosis of neoplasia, reported a lower risk of aCRN (HR 0.25, 95%CI 0.07-0.89) (S28A-D).[32]

Surveillance colonoscopies

The definition of 'surveillance colonoscopies' varied widely between studies. Pooling of studies in which overlapping definitions were used (as specified in S29E and S29F) yielded conflicting results in subgroup analyses. Pooled univariable and multivariable OR analyses showed a lower risk of aCRN in patients enrolled in surveillance programs (univariable OR 0.39 (95%CI 0.23-0.66); multivariable OR 0.43 (95%CI 0.26-0.70)). However, this protective effect was not observed in the pooled univariable and multivariable HR analyses. Of note, there was considerable heterogeneity between studies.

Race

Three studies evaluated the role of race as a risk factor for aCRN (S30A-D). No differences were found in studies comparing Caucasian race versus 'other race' or 'African-American race' in all sub-analyses (univariable OR of two studies 1.11, 95%CI 0.85-1.45).

Medication

Thiopurines

Thiopurine use was associated with a lower aCRN risk (pooled univariable OR 0.55, 95%CI 0.37-0.82, I^2=66%). This pooled analysis included 19 studies. The pooled univariable HR from 5 studies was 0.55 (95%CI 0.33-0.90). In contrast, the pooled multivariable OR and HR did not show a statistically significant protective effect (S31A-E).

5-Aminosalicylic acid

Patients who ever received 5-Aminosalicylic acid (5-ASA) had a lower risk of aCRN, with a pooled univariable OR of 0.53 (95%CI 0.39-0.72, I^2=67%). Six studies that provided multivariable ORs showed a lower risk as well (pooled OR 0.51, 95%CI 0.39-0.66) (S32A-E).

Tumor necrosis factor (TNF)-alpha inhibitors

Six studies evaluated the use of TNF-alpha inhibitors in relation to aCRN. Our pooled univariable analysis of 4 studies did not show a protective effect (OR 0.71, 95%CI

0.14-3.67). One cohort study did not report a protective effect of anti-TNF in a multivariable model (OR 1.01, 95%CI 0.62-1.65).[33] One case-control study showed a protective effect of anti-TNF in a multivariable hazard model (HR 0.22, 95%CI 0.10-0.50) (S33A-E).[34]

Non-Steroidal Anti-Inflammatory Drugs

No significant effect of the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) on aCRN risk was found in 3 case-control studies. The pooled OR was 0.70 (95%CI 0.22-2.22) (S34A-C). In contrast, the only study reporting on NSAID use in a multivariable model did report a lower risk (OR 0.10, 95%CI 0.03-0.33).[35]

Folic acid

Of 9 studies reporting on the effect of folic acid use, only one found a significant protective effect (S35A-D).[36] The pooled univariable OR of 6 studies was 0.86 (95%CI 0.57-1.29). The pooled multivariable HR from 2 cohort studies was 0.44 (95%CI 0.02-7.93).

Corticosteroids

The impact of corticosteroids on the risk of aCRN was studied in 10 studies. The pooled univariable analysis of 9 studies resulted in an OR of 0.98 (95%CI 0.54-1.78, S36A-D).

Statins

One cohort study found no lower risk in patients who used statins in a univariable model (HR 1.09, 95%CI 0.25-4.74).[37] In contrast, the pooled multivariable OR from 2 studies was 0.39 (95%CI 0.22-0.70, S37A-E).

Calcium supplements

Use of calcium supplements was associated with a non-significant decreased risk of aCRN in 2 studies (OR 0.43, 95%CI 0.18-1.02) (S38A-D).

Acetylsalicylic acid

There was no association between the use of acetylsalicylic acid and aCRN. The pooled univariable OR from 3 studies was 0.62 (95%CI 0.15-2.59). A multivariable analysis suggested a protective effect of acetylsalicylic acid in one other study (OR 0.30, 95%CI 0.10-0.90) (S39A-C).[29]

Other factors

Potential prognostic factors reported in only one study are shown in S40A-L.

Good quality synthesis

Forty studies fulfilled the criteria for ‘good quality’ using the previously defined terms. The results of (pooled) analysis of these studies are shown in figure 4 and 5. Extensive disease, LGD, UC (versus CD), aneuploidy, PSC and male sex remained

risk factors for aCRN in this analysis. Thiopurine use remained a protective factor for aCRN (S41A-F).

Summary

Figure 6 summarizes the quality of evidence of the identified prognostic factors, categorized as ‘strong’, ‘moderate’ or ‘weak’.

Publication bias

The Egger’s regression test did not show statistically significant funnel plot asymmetry for any prognostic factor (S42). However, visual inspection of funnel plots suggests asymmetry and thus potential publication bias for male sex, family history of CRC, 5-ASA and thiopurine use (S43).

Meta-regression (univariable OR analyses)

5-ASA, thiopurines and disease extent were evaluated in a meta-regression analysis to assess temporal changes of their respective prognostic values, using ‘year of cohort’ as covariate. None showed statistically significant variation over time, although the scatterplot for thiopurines indicated a trend towards a reduced risk (results and interpretation are provided in S44A-C).

DISCUSSION

Main findings

This is the first systematic review and meta-analysis of all factors that potentially impact the risk of aCRN in IBD patients. Based on 164 studies we identified 31 prognostic factors for which pooled analysis was possible. Using stringent criteria to summarize the level of evidence for all identified prognostic factors (figure 6), there was strong evidence for the risk factor extensive disease; moderate evidence for LGD, strictures, PSC, PIPs, family history CRC, IBD type; and weak evidence for any dysplasia, colon segment resection, aneuploidy, male sex, age in univariable analysis. In multivariable analysis, there was weak evidence for histologic inflammation. Protective factors with moderate evidence in univariable analysis were surveillance colonoscopies, 5-ASA, thiopurines, and smoking. In multivariable analysis there was weak evidence for statin use as a protective factor.

Summary of identified risk factors for aCRN

Several established pre-malignant markers were identified as risk factors for aCRN, including LGD, any dysplasia, and aneuploidy. IBD patients with LGD had an increased risk in both univariable and multivariable analyses, although the magnitude of the impact of LGD varied widely between studies (I^2 69%). The latter can at least partially be ascribed to inter-observer variability between pathologists[38, 39], the heterogeneous morphology of the lesions, differences in quality of endoscopic visualization techniques, and treatment variation (e.g. biopsy, polypectomy, or surgery). Of note, the inter-observer variance might even be greater for IND.[38] Aneuploidy seems to be a promising predictor of aCRN as well (pooled univariable OR of four studies 5.17, 95%CI 2.28-11.71). These results are in line with a previous

meta-analysis that reported a high risk of CRC in patients with aneuploidy,[40] although this meta-analysis included patients with aneuploidy who already had developed dysplasia. The impact of p53 mutations was only assessed in two studies and did not reach statistical significance, and pooled analysis was not possible. The increased aCRN risk in IBD patients with premalignant lesions has been attributed to the concept of 'field cancerization'. This concept implies that clonal molecular abnormalities in otherwise histologically normal-appearing mucosa throughout the colon causes colitis-associated cancer susceptibility.[41, 42] Identification of these pre-neoplastic fields seems a promising and rational approach for surveillance of patients with long-standing colitis.

Although we identified colon segment resection as a risk factor for aCRN, the true impact of this factor remains uncertain. It is conceivable that segment resection was indicated for neoplastic lesions or therapy-refractory disease, which might have led to divergent effects on the risk of aCRN. Since most studies did not specify the indication for surgery a clear answer whether resection protects against aCRN or is associated with a higher risk cannot be provided.

Several (surrogate) markers for chronic inflammation were found to be robust predictors of aCRN, ranging from histological inflammation scores to disease extent, strictures, and possibly the presence of PIPs. Since studies reported different estimates of effects on endoscopic inflammation scores, a pooled analysis was not possible, although all studies showed promising results. Notable is the fact that one cohort study reported endoscopic inflammation scored during surveillance colonoscopies to remain a risk factor for aCRN in a multivariable model (HR 2.39, 95%CI 1.63-3.50).[7] To our knowledge, no previous meta-analysis evaluated these markers for inflammation as risk factors for aCRN. The observed negative

association of thiopurine use, 5-ASA-use, and smoking (in UC) with aCRN probably results from their anti-inflammatory effects. The protective effect of treatment with 5-ASA and thiopurines might be confounded by patient profile or additional excipients, therefore the protective effect should not just be interpreted as a causal effect. Current guidelines use surrogate markers for inflammation such as PIPs and strictures to stratify patients in risk categories.[2-5] It has been hypothesized that cumulative inflammatory burden scores are more direct and reliable predictors for the risk of (a)CRN. Indeed, recent studies support this concept,[43-45] although it is currently not clear how to construct the optimal cumulative inflammatory burden score. It can be questioned whether surrogate markers for inflammation should still be used to stratify patients. For example, we observed that PIPs were not an independent risk factor for aCRN risk if outcomes were adjusted for the mean inflammation score.[46, 47]

A concomitant diagnosis of PSC is an established risk factor for aCRN (univariable OR 4.14, 95%CI 2.85-6.01; multivariable OR 3.53, 95%CI 1.83-6.79). This increased risk is in line with the result of a previous meta-analysis that reported a pooled univariable OR for CRC of 3.41 (95%CI 2.13-5.48).[48] In our study, several relevant new studies were included and aCRN, instead of CRC only, was used as an outcome parameter. The mechanisms underlying the increased risk of CRC in IBD patients with PSC have yet to be clarified. Several studies suggested a role for the altered colonic bile composition in PSC, but intestinal dysbiosis[49] or a distinct genotype might also play a role.[50]

Genetic predisposition contributes importantly to CRC development in the general population,[51] but its role in IBD is less well-defined. We observed an increased risk of aCRN in IBD patients with a family history of CRC (OR 2.62 (95%CI 1.93-3.57)

based on 15 studies. No other meta-analysis is available for comparison. The increased risk in male patients (OR 1.27, 95%CI 1.12-1.44, 60 studies) is in line with the male preponderance of CRC in the general population. In the general population, the cause of this increased risk is believed to be multifactorial.[52] We identified increasing age as a risk factor for aCRN in IBD patients, which is in line with data from the general population[53]. The remaining prognostic factors are discussed in S45.

Strengths and limitations

Our study has several strengths. This meta-analysis was performed in accordance with the MOOSE guidelines for systematic reviews and meta-analysis.[10] An important contribution of this study is that we attempted to determine the level of evidence for all prognostic factors and to quantify the magnitude of impact of all published prognostic factors. The use of broad search terms and the lack of restrictions on country of origin ensured the identification of all prognostic factors for aCRN in IBD. We also included studies that did not report effect estimates but provided sufficient data to calculate the ORs. Moreover, the scale of our endeavor enabled us to perform subgroup analyses based on study design (case-control or cohort study) and type of outcome (univariable/multivariable and OR/HR). Last, we performed a separate synthesis, including only those studies that fulfilled criteria of good quality.

Our study has several limitations worth noting. First, considerable heterogeneity between studies for several prognostic factors was found, possibly due to regional differences and changes over time with respect to screening and therapeutic strategies. Of note, the level of heterogeneity as expressed by I^2 could incorrectly be

too high or too low in small meta-analyses.[13] By performing subgroup analyses per estimate of effect and per study design we aimed to reduce heterogeneity caused by methodology. Moreover, multivariable data on prognostic factors was derived from studies using different techniques of model building and taking into account a varying set of covariates (specified in S4). Second, the majority of included studies had a retrospective study design, introducing inherent biases such as selection, missing data, and lack of predefined endpoints. Moreover, we could not correct for the interval between surveillance colonoscopies as this information was rarely provided. Of note, prospective studies are often not performed in this field, given the large number of patients and the long-term follow-up that is needed. Third, some of the included studies assessed the aCRN risk in patients with only proctitis (UC) or ileal disease (CD), which must have influenced the effect sizes of the prognostic factors. To overcome this problem we adjusted the study selection criteria for the analysis of disease extent and IBD type as a risk factor (S7G and S8F), and additional selection criteria were applied for the good quality synthesis.

The present study provides information on all relevant predictors for aCRN and their respective effect sizes, and can therefore help us and other research groups design novel prediction tools for patient stratification in this setting. We feel that a reliable and easy-to-use model should be based on a combination of clinical or endoscopic risk factors accounting for the number of risk factors present and the associated effect size of these factors, rather than the presence of just one risk factor. The addition of (a set of) biomarkers can be expected to considerably improve the predictive power of a new model. We identified several biomarkers for which the evidence is still incomplete, such as IND, aneuploidy, and p53 mutations. Future studies should clarify the impact of these factors. In addition, whereas univariable

data are abundant, there is a lack of evidence on prognostic factors for aCRN from multivariable models (only 37 of the 164 included studies reported multivariable data). This demonstrates the need for large surveillance cohorts with long-term follow-up that correct for important confounders.

Conclusion

In this systematic review and meta-analysis we provided more precise risk estimates of all known prognostic factors for aCRN in IBD patients. We identified 13 risk and 5 protective factors based on univariable and/or multivariable pooled analyses for aCRN in IBD patients. These findings may aid in the development of an improved CRC risk stratification model in IBD patients.

Figure legends

Figure 1: Flow diagram of the selection process
N=number, OR=odds ratio, HR=hazard ratio.

Figure 2: Univariable (A) and multivariable (B) odds ratios of all potential prognostic factors
Prognostic factor (number of studies), right column: odds ratio (OR) and confidence interval (CI) from pooled analysis (pooled data if ≥2 studies included in analysis).

Figure 3: Univariable (A) and multivariable (B) hazard ratios of all potential prognostic factors
Prognostic factor (number of studies), right column: hazard ratio (HR) and confidence interval (CI) from pooled analysis (pooled data if ≥2 studies included in analysis).

Figure 4: Univariable odds ratios good quality synthesis
Prognostic factor (number of studies), right column: odds ratio (OR) and confidence interval (CI) from pooled analysis (pooled data if ≥2 studies included in analysis).

Figure 5: Univariable (A) and multivariable (B) hazard ratios good quality synthesis
Prognostic factor (number of studies), right column: hazard ratio (HR) and confidence interval (CI) from pooled analysis (pooled data if ≥2 studies included in analysis).

Figure 6: Summary of all identified risk and protective factors for aCRN

- Prognostic factors were included in the summary table if pooled analysis was possible (≥2 studies in pooled analysis)
- Categorization based on the sub-analysis (OR or HR) including most studies, if equal, the sub-analysis with the lowest heterogeneity was selected.
- Level of evidence:
    - **Strong evidence**: OR/HR ≥2 (risk factor) or ≤0.50 (protective factor) *and* P-value < .05 & heterogeneity ≤50% *and* ≥5 studies in pooled analysis *and* P-value < .05 in pooled good quality synthesis
    - **Moderate evidence**: OR/HR ≥1.5 (risk factor) or ≤0.67 (protective factor) *and* P-value < .05 *and* ≥5 studies in pooled analysis
    - **Weak evidence**: OR/HR >1 (risk factor) or <1 (protective factor) *and* P-value < .05 in pooled analysis

*: significant prognostic factor in good quality synthesis.

#: equal number of studies and heterogeneity, estimate of effect is based on the smallest CI.

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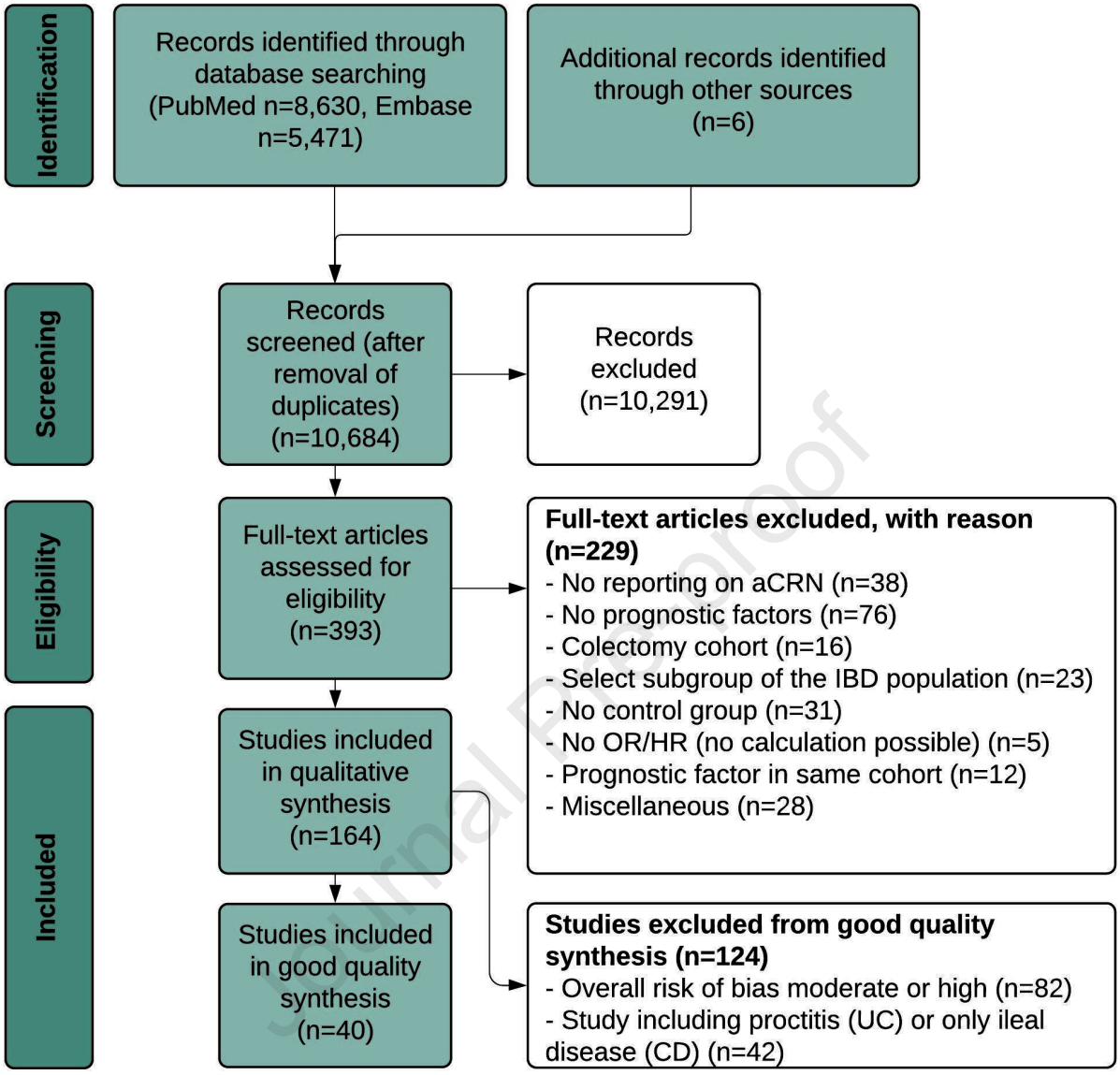
Author names in bold designate shared co-first authorship, author names in bold and italic designate shared co-last authorship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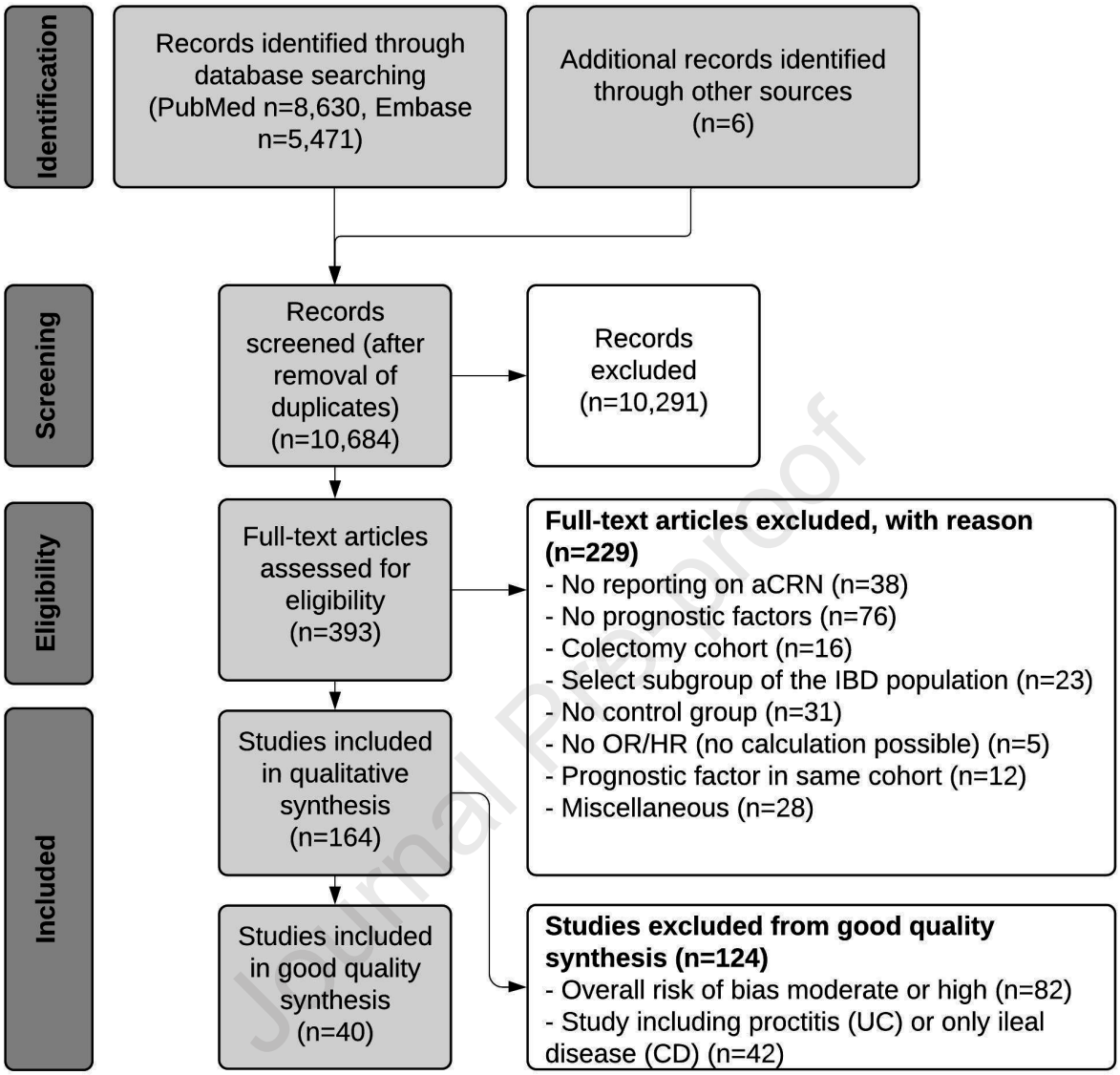
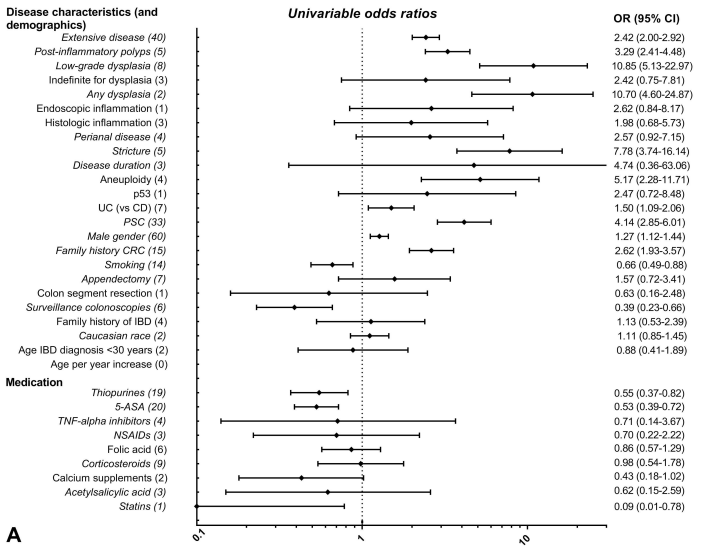
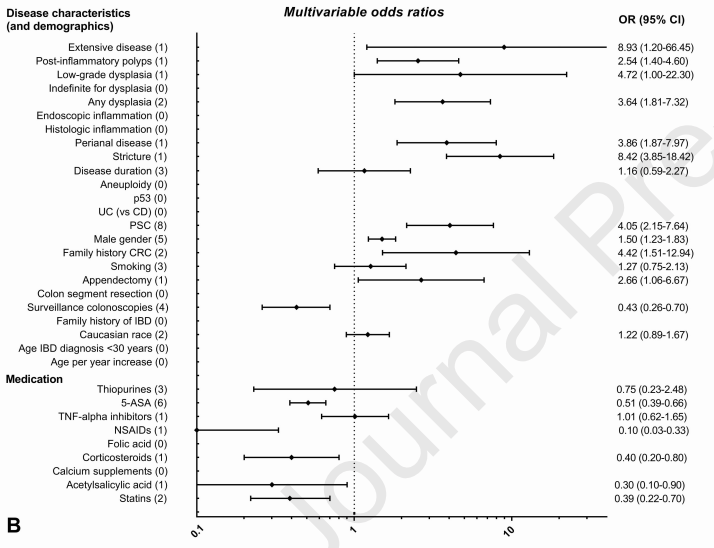
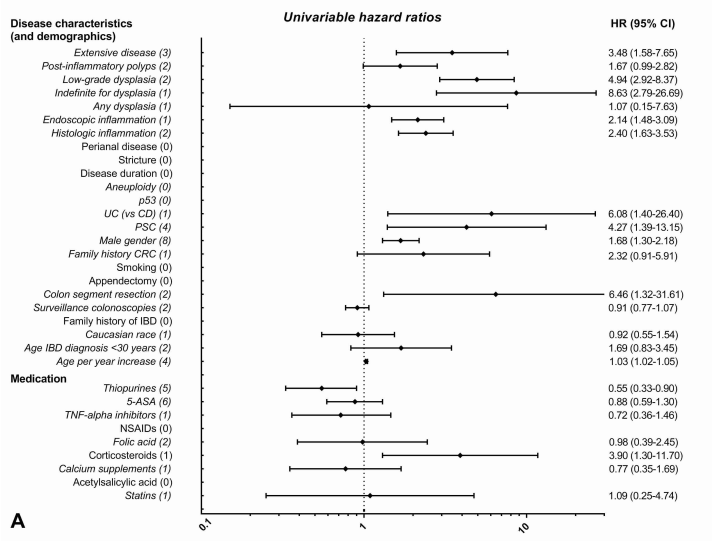
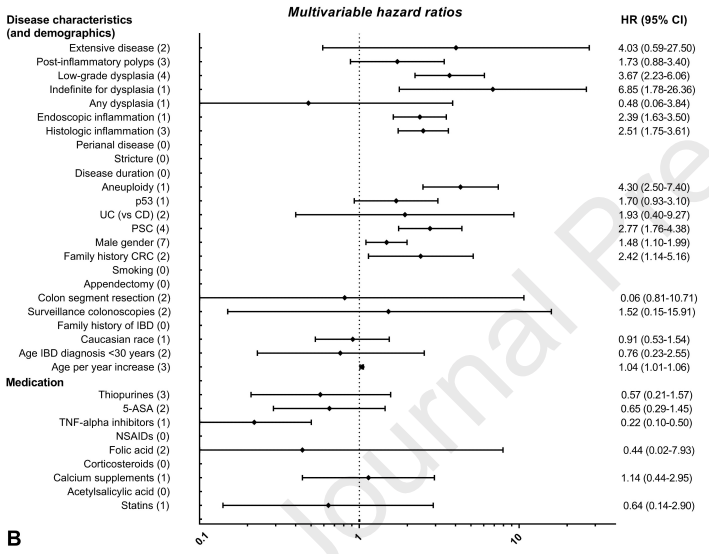
Additional records identified through other sources (n=6)
Screening
Records screened (after removal of duplicates) (n=10,684)
Records excluded (n=10,291)
Eligibility
Full-text articles assessed for eligibility (n=393)
Full-text articles excluded, with reason (n=229)
- No reporting on aCRN (n=38)
- No prognostic factors (n=76)
- Colectomy cohort (n=16)
- Select subgroup of the IBD population (n=23)
- No control group (n=31)
- No OR/HR (no calculation possible) (n=5)
- Prognostic factor in same cohort (n=12)
- Miscellaneous (n=28)
Included
Studies included in qualitative synthesis (n=164)
Studies included in good quality synthesis (n=40)
Studies excluded from good quality synthesis (n=124)
- Overall risk of bias moderate or high (n=82)
- Study including proctitis (UC) or only ileal disease (CD) (n=42)

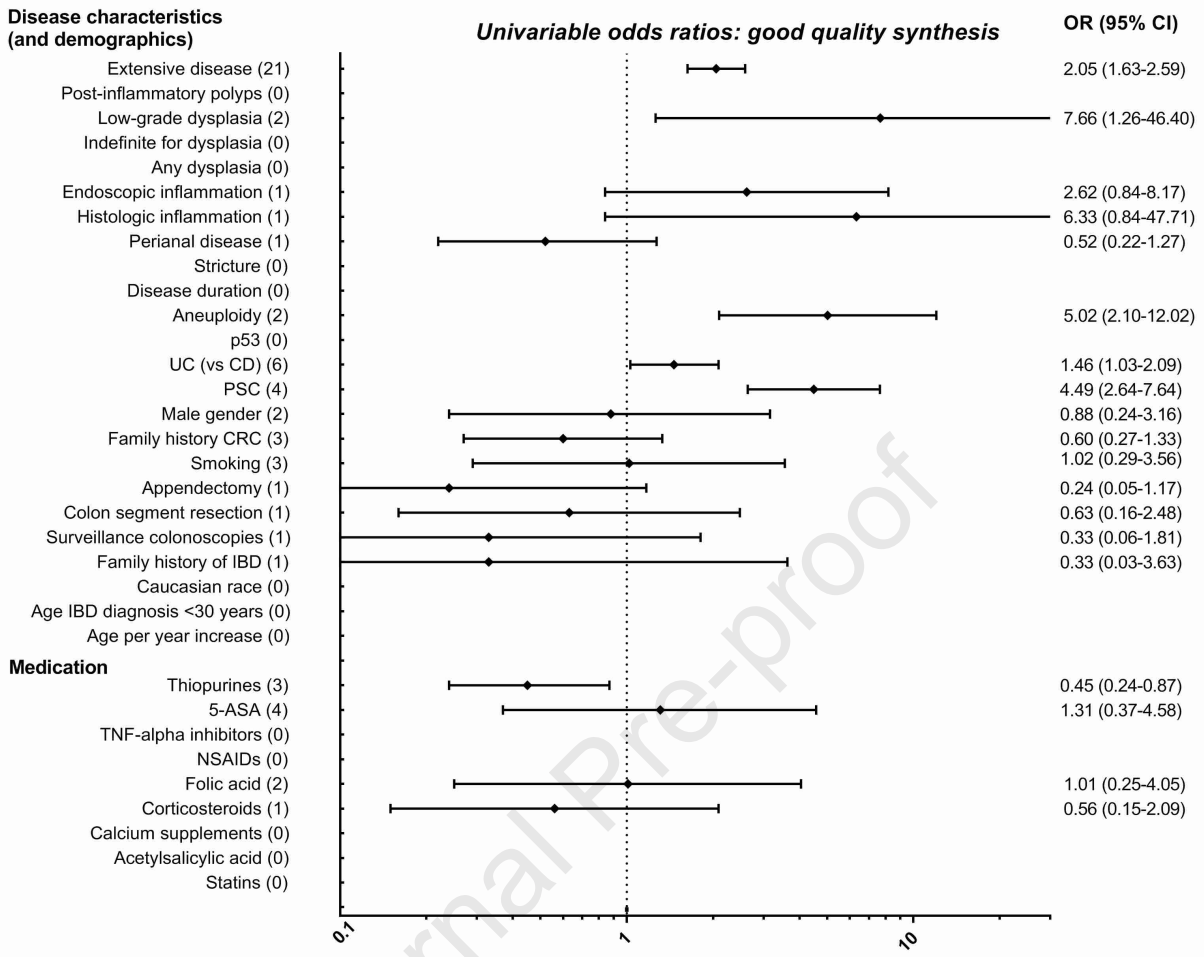


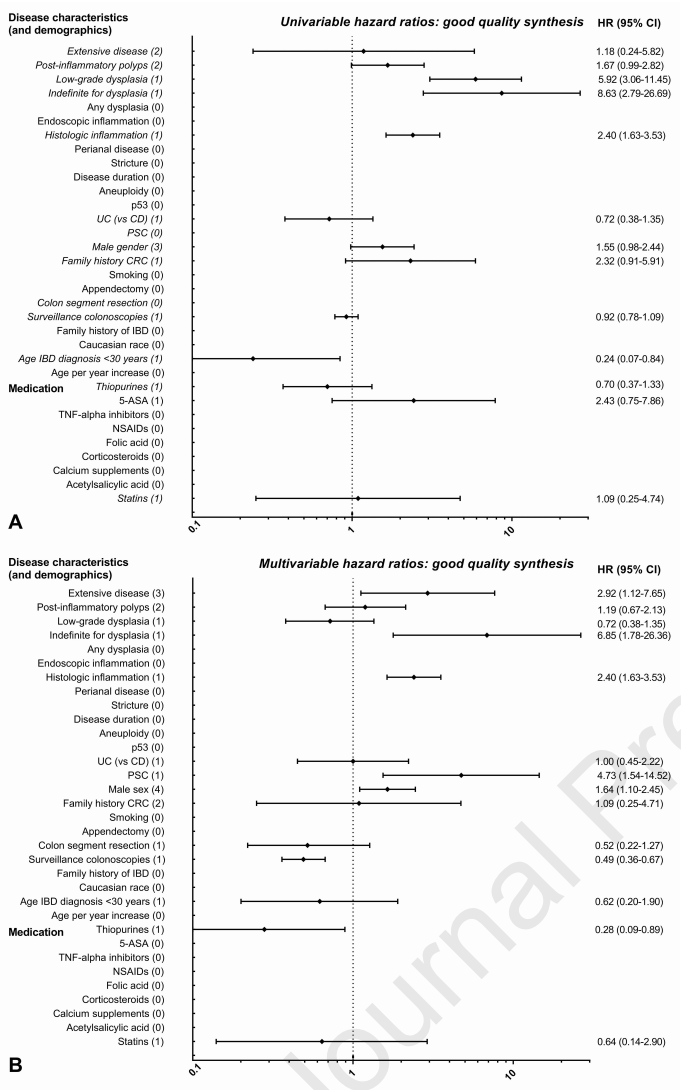












Univariable analysis

Strong		Moderate		Weak	
Extensive disease*	2.43 (2.01-2.93)	LGD*	10.85 (5.13-22.97)	Any dysplasia	10.70 (4.60-24.87)
		Stricture	7.78 (3.74-16.18)	Colon segment resection	6.46 (1.32-31.61)
		PSC*	4.14 (2.85-6.01)	Aneuploidy*	5.17 (2.28-11.71)
		PIPs	3.29 (2.41-4.48)	Male sex	1.27 (1.12-1.44)
		Family history CRC	2.62 (1.93-3.57)	Age	1.03 (1.02-1.05)
		IBD type*	1.50 (1.09-2.06)		
		Surveillance colonoscopies	0.39 (0.23-0.66)		
		5-ASA	0.53 (0.39-0.72)		
		Thiopurines*	0.55 (0.37-0.82)		
		Smoking	0.66 (0.49-0.88)		

Multivariable analysis

Moderate		Weak	
PSC	4.05 (2.15-7.64)	LGD	3.67 (2.23-6.06)
		Any dysplasia	3.64 (1.81-7.32)
		Histologic inflammation	2.51 (1.75-3.61)
		Family history CRC#	2.42 (1.14-5.16)
		Male sex*	1.48 (1.10-1.99)
		Age	1.04 (1.01-1.06)
5-ASA	0.51 (0.39-0.66)	Statin use	0.39 (0.22-0.70)
		Surveillance colonoscopies	0.43 (0.26-0.70)

Univariable analysis

Strong		Moderate		Weak	
Extensive disease*	2.43 (2.01-2.93)	LGD*	10.85 (5.13-22.97)	Any dysplasia	10.70 (4.60-24.87)
		Stricture	7.78 (3.74-16.18)	Colon segment resection	6.46 (1.32-31.61)
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		PIPs	3.29 (2.41-4.48)	Male sex	1.27 (1.12-1.44)
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		IBD type*	1.50 (1.09-2.06)		
		Surveillance colonoscopies	0.39 (0.23-0.66)		
		5-ASA	0.53 (0.39-0.72)		
		Thiopurines*	0.55 (0.37-0.82)		
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Multivariable analysis

Moderate		Weak	
PSC	4.05 (2.15-7.64)	LGD	3.67 (2.23-6.06)
		Any dysplasia	3.64 (1.81-7.32)
		Histologic inflammation	2.51 (1.75-3.61)
		Family history CRC#	2.42 (1.14-5.16)
		Male sex*	1.48 (1.10-1.99)
		Age	1.04 (1.01-1.06)
5-ASA	0.51 (0.39-0.66)	Statin use	0.39 (0.22-0.70)
		Surveillance colonoscopies	0.43 (0.26-0.70)

WHAT YOU NEED TO KNOW

Background and context

Evidence for the use of prognostic factors in stratifying patients with inflammatory bowel disease for surveillance colonoscopies is only based on modest evidence.

New findings

This is the first systematic review and meta-analysis that evaluated all prognostic factors for advanced colorectal neoplasia, identifying 13 risk and 5 protective factors.

Limitations

The majority of studies included in this meta-analysis had a retrospective design. For several prognostic factors considerable heterogeneity between studies was found.

Impact

The results of this study can be used to guide future risk stratification models for colorectal cancer in inflammatory bowel disease.

LAY SUMMARY

This comprehensive systematic review and meta-analysis identified 13 risk factors and 5 protective factors for advanced colorectal neoplasia in inflammatory bowel disease.

Supplementary files 1 - 46

Supplementary file 1: MOOSE checklist

Reporting Criteria	Reported (Yes/No)	Reported on Page
Reporting of Background		
Problem definition	Yes	7
Hypothesis statement	No	N/A
Description of Study Outcome(s)	Yes	7-9
Type of exposure or intervention used	Yes	10
Type of study design used	Yes	8
Study population	Yes	8
Reporting of Search Strategy		
Qualifications of searchers (e.g., librarians and investigators)	Yes	8
Search strategy, including time period included in the synthesis and keywords	Yes	8; S1
Effort to include all available studies, including contact with authors	Yes	8 (no contact with authors)
Databases and registries searched	Yes	8
Search software used, name and version, including special features used (e.g., explosion)	No	N/A
Use of hand searching (e.g., reference lists of obtained articles)	Yes	8
List of citations located and those excluded, including justification	Yes	S42; figure 1
Method for addressing articles published in languages other than English	Yes	8
Method of handling abstracts and unpublished studies	Yes	8
Description of any contact with authors	No	N/A
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	8-9
Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	Yes	9
Documentation of how data were classified and coded (e.g., multiple raters, blinding, and interrater reliability)	Yes	9
Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate	Yes	11, S4
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible	Yes	9, 13; S4-5

predictors of study results		
Assessment of heterogeneity	Yes	11; S6-40
Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	11
Provision of appropriate tables and graphics	Yes	S2-42; figures 1-6
Reporting of Results		
Table giving descriptive information for each study included	Yes	S2
Results of sensitivity testing (e.g., subgroup analysis)	Yes	S6-40
Indication of statistical uncertainty of findings	Yes	S6-40
Reporting of Discussion		
Quantitative assessment of bias (e.g., publication bias)	Yes	11, 24; S41-42
Justification for exclusion (e.g., exclusion of non–English-language citations)	Yes	8, 9, 13; figure 1
Assessment of quality of included studies	Yes	Figure 4-5; S4-5
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	25-29
Generalization of the conclusions (e.g., appropriate for the data presented and within the domain of the literature review)	Yes	30-31
Guidelines for future research	Yes	30-31
Disclosure of funding source	Yes	31

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology
(MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. JAMA.
2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

Supplementary file 2: Search strategies Embase and PubMed

Embase

('inflammatory bowel disease'/exp OR 'inflammatory bowel disease*':ti,ab,kw OR 'ibd':ti,ab,kw OR 'proctocolitis'/exp OR 'proctocolitis':ti,ab,kw OR 'ulcerative rectocolitis':ti,ab,kw OR 'ulcerative proctocolitis':ti,ab,kw OR 'ulcerative colitis':ti,ab,kw OR 'colitis gravis':ti,ab,kw OR 'colitis ulcerosa':ti,ab,kw OR 'crohn*':ti,ab,kw)
AND
('colorectal cancer'/mj OR 'colorectal carcinoma'/exp OR 'rectum cancer'/exp OR 'Rectum tumor'/mj OR 'sigmoid cancer'/exp OR 'colon carcinoma'/exp OR 'colon adenocarcinoma'/exp OR 'colon tumor'/mj OR 'cecum cancer'/exp OR 'intestine tumor'/mj OR 'intestine cancer'/mj OR 'large intestine cancer'/mj OR 'Colorectal tumor'/mj OR 'malignant neoplasm'/exp OR 'malignant neoplas*':ti,ab,kw OR 'malignancy':ti,ab,kw OR 'neoplas*':ti,ab,kw OR 'neoplasm'/exp OR 'adenocarcinoma'/mj OR 'adenocarcinoma in situ'/exp OR 'adenocarcinoma*':ti,ab,kw OR 'cancer*':ti,ab,kw OR 'carcinoma*':ti,ab,kw OR 'dysplasia'/exp OR 'dysplasia':ti,ab,kw OR 'high grade dysplasia':ti,ab,kw OR 'Precancerous condition*':ti,ab,kw OR 'Tumour*':ti,ab,kw OR 'Tumor*':ti,ab,kw OR 'surveillance':ti,ab,kw OR 'screening':ti,ab,kw)
AND
('large intestine':ti,ab,kw OR 'large intestine'/mj OR 'colon'/mj OR 'colon':ti,ab,kw OR 'sigmoid'/exp OR 'sigmoid':ti,ab,kw OR 'colon sigmoideum':ti,ab,kw OR 'colon, sigmoid':ti,ab,kw OR 'rectum'/exp OR 'rectum':ti,ab,kw OR 'Rectal':ti,ab,kw OR 'Colorectal':ti,ab,kw OR 'ascending colon'/exp OR 'ascending colon':ti,ab,kw OR 'colon ascend*':ti,ab,kw OR 'proximal colon':ti,ab,kw OR 'descending colon'/exp OR 'descending colon':ti,ab,kw OR 'colon descend*':ti,ab,kw OR 'distal colon':ti,ab,kw OR 'cecum'/exp OR 'Cecum':ti,ab,kw OR 'Coecum':ti,ab,kw)
AND
'article'/it
NOT
('animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'mouse model'/de OR 'nonhuman'/de)
AND
[embase]/lim

PubMed

("Inflammatory Bowel Diseases"[Mesh] OR "Inflammatory Bowel Disease*"[Title/Abstract] OR "inflammatory bowel disorder*"[Title/Abstract] OR IBD[Title/Abstract] OR ulcerative colitis[Title/Abstract] OR colitis ulcerosa[Title/Abstract] OR "Proctocolitis"[Mesh] OR "Idiopathic Proctocolitis"[Title/Abstract] OR "Ulcerative rectocolitis"[Title/abstract] OR "Ulcerative proctocolitis"[Title/Abstract] OR "Colitis Gravis"[Title/Abstract] OR Crohn*[Title/Abstract])
AND
("Colorectal Neoplasms"[Mesh] OR "Intestinal Neoplasms"[Mesh:NoExp] OR “Cecal neoplasms”[Mesh:NoExp] OR "Precancerous Conditions"[Mesh:noexp] OR "Population Surveillance"[Mesh:noexp] OR “Cancer*”[Title/Abstract] OR “Carcinoma*”[Title/Abstract] OR “Tumor*”[Title/Abstract] OR “Tumour*”[Title/Abstract] OR “Adenocarcinoma*”[Title/Abstract] OR “Adenocarcinoma”[Mesh] OR “Dysplasia”[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR “Neoplas*”[Title/Abstract] OR “Malignancy”[Title/Abstract] OR “High grade dysplasia”[Title/Abstract] OR Surveillance[Title/Abstract] OR Screening[Title/Abstract])
AND
(“Intestine, large”[Mesh] OR “Large intestine”[Title/Abstract] OR “Cecum”[Title/Abstract] OR “Colon”[Title/Abstract] OR “Colon ascendens”[Title/Abstract] OR “Ascending colon”[Title/Abstract] OR “Colon descendens”[Title/Abstract] OR “Descending colon”[Title/Abstract] OR “Proximal colon”[Title/Abstract] OR “Distal colon”[Title/Abstract] OR “Sigmoid”[Title/Abstract] OR “Sigmoid colon”[Title/Abstract] OR “Rectum”[Title/Abstract] OR "Colorectal"[Title/Abstract])
NOT
(((((animals[mh] NOT humans[mh])))))

Supplementary file 3: Study characteristics included studies

Author [Year]	Country	Study design	Prospective or retrospective design	OR/ HR	Start study period	End study period	Number of patients	Number of events (aCRN)	IBD type	Prognostic factors
Ananthakrishnan [2014][1]	USA	Cohort	Retrospective	OR	1996		11001	167	UC, CD	18*
Ananthakrishnan [2014a][2]	USA	Cohort	Retrospective	OR			2809	41	UC, CD	35*
Ananthakrishnan [2014b][3]	USA	Cohort	Retrospective	OR			4726	33	UC, CD	35*
Ananthakrishnan [2015][4]	USA	Cohort	Retrospective	OR			6823	154	UC, CD, IBD -U	15*,18,19,28, 25,35
Ananthakrishnan [2016][5]	USA	Cohort	Retrospective	OR	1998	2010	11001	317	UC, CD	19*, 20,23*, 25*,28*,32*,35*
Askling [2001][6]	Sweden	Cohort	Retrospective	OR	1955	1995	19876	143	UC, CD	21
Baars [2011][7]	The Netherlands	Case control	Retrospective	OR	1990	2006	566	173	UC, CD	7,18,19, 21,26,27,28,29, 30,31,33,34,35
Bansal [1996][8]	USA	Cohort	Retrospective	OR	1981	1993	11446	371	UC	18*,19*,25*,35*
Beaugerie [2013][9]	France	Cohort	Prospective	OR HR	2004	2007	19486	57	UC, CD, IBD -U	3*,19*,20*,26*,3 5
Beaugerie [2018][10]	France	Case control	Prospective	OR	2004	2007	19486	22	UC, CD, IBD -U	11
Bergeron [2010][11]	France	Case control	Partial	OR HR	1994	2010	855	33	UC, CD	11,14*,18*,21*,2 3,26,27
Bernstein [2011][12]	Canada	Cohort	Retrospective	HR	1995	2008	8744		UC, CD	27
Biancone [2016][13]	Italy	Case control	Partial	OR	2012	2014	522	19	UC, CD	11*,35*
Boland [1984][14]	USA	Cohort	Prospective	OR	1979	1982	18	1	UC	35
Bopanna[2017][15]	India	Cohort	Partial	OR HR	2004	2015	1012	20	UC	2,7,18,19
Braden [2012][16]	United Kingdom	Case control	Retrospective	OR			382	5	UC, CD, IBD -U	18

Brentnall [1996][17]	USA	Case control	Prospective	OR			45	8	UC	18
Broomé [1995][18]	Sweden	Case control	Retrospective	OR	1973	1984	40	18	UC	18
Bröström [1986][19]	Sweden	Cohort	Retrospective	OR	1945	1979	1274	25	UC	19
Campos [2013][20]	Brazil	Cohort	Prospective	OR	1984	2007	1607	17	UC, CD	2,18,19
Camus [2013][21]	France	Case control	Prospective	OR	1986	2011	660		CD	26
Carrat [2017][22]	France	Case control	Prospective	OR	2004	2007	420		UC, CD, IBD-U	18*,23*,26*,27*, 35*
Cheddani [2016][23]	France	Cohort	Retrospective	OR	1988	2006	844	15	UC, CD	18
Choi [2019][24]	United Kingdom	Cohort	Retrospective	OR	2003	2012	987		UC	4
Chow [2009][25]	China	Cohort	Prospective	OR	1985	2006	172	1	UC	2,19
Connell [1994][26]	United Kingdom	Case control	Prospective	OR	1962	1991	266	23	UC	26
Cosnes [2002] [27]	France	Cohort	Partial	OR	1997	2000	638	11	UC	24
De Dombal [1966][28]	United Kingdom	Cohort	Retrospective	OR	1952	1963	465	8	UC	7,10
de Jong [2019][29]	The Netherlands	Cohort	Retrospective	HR		2017	519	19	UC, CD	7*
Desai [2015][30]	India	Cohort	Prospective	OR	2005		430	12	UC	2,19,22,23,26
Eaden [2000][31]	United Kingdom	Case control	Retrospective	OR			204	62	UC	15*,21*,23,27*,31,34,35*
Ekbom [1990a][32]	Sweden	Cohort	Retrospective	OR	1958	1984	3117	91	UC	2,19
Florin [2004][33]	Australia	Cohort	Retrospective	OR	1995	2002	372	11	UC	18,24
Fraga [2017][34]	Switzerland	Cohort	Prospective	OR	2006	2014	1188	11	UC, CD	18
Fraser [2002][35]	New Zealand	Cohort	Retrospective	OR			1349	36	UC, CD	2,26
Freeman [2001][36]	Canada	Cohort	Retrospective	OR	1979	1998	877	6	CD	19

Fujita [2010][37]	Japan	Cohort	Retrospective	OR	1998	2006	314	7	UC	2,19,21,23,27,31
Fuson [1980][38]	USA	Cohort	Retrospective	OR	1972	1977	75	11	UC	19
Gerrits [2011][39]	The Netherlands	Case control	Retrospective	HR	1985	2008	54	26	UC, CD, IBD-U	4*,9*,16*,17*
Gilat [1974][40]	Israel	Cohort	Retrospective	OR	1961	1970	504	4	UC	19
Gillen [1994a][41]	Sweden and United Kingdom	Cohort	Retrospective	OR	1945	1975	611	37	UC, CD	3
Gomez-Garcia [2013][42]	Spain	Cohort	Retrospective	OR	1996	2013	812	12	UC, CD	26
Gong [2012][43]	China	Cohort	Retrospective	OR	1998	2009	3922	34	UC	2*,6,15,19,27*,31,35
Gordillo [2015][44]	Spain	Cohort	Retrospective	OR	2006	2010	831	45	UC	2,12*,13,15*,18*,19*,21,22,23,24*,26*,27,31,35*
Greenstein [1979][45]	USA	Cohort	Retrospective	OR	1960	1976	267	26	UC	2
Gupta [2007][46]	USA	Cohort	Retrospective	HR	1996	1997	418	15	UC	9*,13,15*,19,26,27,30,31
Hajek [2005][47]	Czech	Cohort	Retrospective	OR	1993	2003	353	3	UC, CD	19
Hou [2012][48]	USA	Cohort	Retrospective	HR	1998	2009	20949	168	UC	13*,15,19*,25*,35*
Hovde [2017][49]	Norway	Cohort	Prospective	OR	1990		756		UC, CD	19
Jablonska [1993][50]	Czech	Cohort	Prospective	OR			191	9	UC	2,19
Jacobsen [1994][51]	Norway	Cohort	Retrospective	OR	1979	1988	641	6	UC, CD, IBD-U	19
Jess [2012][52]	Denmark	Cohort	Retrospective	OR	1979	2008	47374	338	UC, CD	19
Jonsson [1994][53]	Sweden	Cohort	Prospective	OR	1977	1991	131	8	UC	2
Joo [2009][54]	USA	Case control	Retrospective	OR	1989	2005	80	4	UC	18
Jung [2017][55]	Korea	Case	Retrospective	OR	2010	2014	15644	28	UC,	3,19,26,27,28,3

		control							CD	5
Jussila [2013][56]	Finland	Cohort	Retrospective	OR	1987	2010	21964	190	UC, CD	19
Kamiya [2012][57]	Japan	Cohort	Retrospective	OR	1998	2010	174	2	CD	19,21
Katzka [1983][58]	USA	Cohort	Retrospective	OR	1955	1980	258	9	UC	2
Kishikawa [2018][59]	Japan	Cohort	Retrospective	HR	1979	2014	289	15	UC	2,13*,19*
Kobayashi [2002][60]	Japan	Cohort	Retrospective	OR	1987	2001	246	7	UC	2,19
Kochhar [1991][61]	India	Cohort	Retrospective	OR	1977	1988	436	8	UC	2,19
Kopylov [2015][62]	Canada	Case control	Retrospective	OR			19582	343	UC, CD	19
Kottachchi [2009][63]	Canada	Cohort	Retrospective	OR	1980	2005	141	3	UC	2
Kuo [2014][64]	Taiwan	Cohort	Retrospective	OR	2000	2010	2617	6	UC, CD	19
Kvist [1989][65]	Denmark	Cohort	Retrospective	OR	1964	1983	759	20	UC	2,19
Lai [2015][66]	USA	Case control	Retrospective	OR	1989	2004	111	9	UC, CD	5
Laish [2017][67]	Isreal	Cohort**	Retrospective	OR	2005	2014	229	5	UC	2,18
Lakatos [2004][68]	Hungary	Cohort	Retrospective	OR	1991	2001	812	12	UC, CD, IBD-U	3
Lakatos [2006][69]	Hungary	Cohort	Partial	OR	1974		723	13	UC	2,4*,6*,12*,18*,19*,22,23,24,26,31,35*
Lakatos [2011][70]	Hungary	Cohort	Partial	OR	1977	2008	506	5	CD	19,35
Langholz[1992][71]	Denmark	Cohort	Partial	OR	1962	1987	1161	6	UC	19
Lashner [1989a][72]	USA	Cohort	Prospective	OR	1977	1985	99	12	UC	4
Lashner [1989] [73]	USA	Cohort	Retrospective	OR	1986	1992	98	15	UC	30
Lashner [1990][74]	USA	Cohort	Retrospective	OR	1984	1986	186	18	UC	15
Lashner [1999][75]	USA	Cohort	Retrospective	OR	1986	1992	95	23	UC	17
Lee[2015][76]	South Korea	Cohort	Partial	OR	1989	2013	5212	30	UC, CD	2,3,11,13, 18,19

Leidenius [1991][77]	Finland	Cohort	Retrospective	OR	1976	1989	66	1	UC	2
Leidenius [1997][78]	Finland	Case control	Retrospective	OR	1984	1995	90	8	UC	18
Lennard-Jones [1977][79]	United Kingdom	Cohort	Prospective	OR	1966	1976	229	14	UC	4
Lennard-Jones [1990][80]	United Kingdom	Cohort	Prospective	OR	1966	1987	401	34	UC	19
Lim [2003][81]	United Kingdom	Cohort	Retrospective	OR	1978	2000	128	7	UC	4,19
Lindberg [1999][82]	Sweden	Cohort	Prospective	OR	1984	1997	147	11	UC	16
Lindberg [2001][83]	Sweden	Cohort	Partial	OR		1993	143	17	UC	18,27
Lindberg[2005][84]	Sweden	Cohort	Prospective	OR	1977	2002	211	15	UC	2
Lindström [2011][85]	Denmark	Case control	Retrospective	OR	1978	2005	74	4	CD	18
Löfberg [1991][86]	Sweden	Cohort	Prospective	OR			24	1	CD	2,16
Loftus [2005][87]	USA	Case control	Prospective	HR	1987	1992	213	18	UC, CD	18
Lovasz [2013][88]	Hungary	Cohort	Retrospective	OR	1977	2011	640	6	CD	10,19
Lutgens [2015][89]	The Netherlands	Case control	Retrospective	HR	1990	2009	528	186	UC, CD	4*,7*,13*,18*,28
MacDougall [1954][90]	United Kingdom	Cohort	Unclear	OR	1947	1951	126	5	UC	19
Madanchi [2016][91]	Switzerland	Cohort	Retrospective	OR	2007	2014	1026	4	UC, CD, IBD-U	19
Mahmoud [2019][92]	USA and the Netherlands	Cohort	Retrospective	HR	1997	2017	1582	41	UC, CD, IBD-U	2*,3,4*,7*,9*,15, 19*,21*,26,27, 35*
Mahmoud [2019b][93]	USA and the Netherlands	Cohort	Retrospective	HR	2001	2017	492	32	UC, CD, IBD-U	5*,15*
Manninen [2013][94]	Finland	Cohort	Retrospective	OR	1986	2007	1915	21	UC, CD, IBD	2,3,13,18,19

									-U	
Maratka [1985][95]	Czech Republic	Cohort	Retrospective	OR	1942	1984	959	6	UC	2,19
Markowitz [1997][96]	USA	Cohort	Prospective	OR	1992	1995	35	2	UC, CD	2
Mir-Madjlessi [1986][97]	USA	Cohort	Retrospective	OR		1984	1160	82	UC	2
Navaneethan [2016][98]	USA	Case control	Retrospective	OR	1985	2012	202	18	CD	18
Nieminen [2014][99]	Finland	Case control	Retrospective	OR			190	31	UC, CD	9,18,26,27,35
Nkontchou [1996][100]	France	Cohort	Retrospective	OR	1962	1993	130	6	UC	19
Nowacki [2015][101]	Germany	Cohort	Retrospective	OR	2002	2013	434	15	UC	2,12,18,19,20,26,27,28,35*
Nuako [1998][102]	USA	Case control	Retrospective	OR	1976	1994	342	171	UC	18*
Nuako [1998a][103]	USA	Case control	Retrospective	OR	1976	1994	297	147	UC	21
Nugent [1991][104]	USA	Cohort	Prospective	OR	1974	1986	213		UC	4,5
Paris [1994][105]	Italy	Cohort	Retrospective	OR	1987	1992	74	1	UC	19
Peng [2015][106]	Taiwan	Cohort	Retrospective	HR	1998	2011	10650	59	UC, CD	19*
Peng [2017][107]	Taiwan	Case control	Retrospective	OR	1998	2010	1050		UC, CD	3,20,35
Picazo-Ferrera [2011][108]	Mexico	Case control	Retrospective	OR	2007	2010	114		UC	24
Pinczowski [1994][109]	Sweden	Case control	Retrospective	OR			298	102	UC	23,27,35
Prior [1982][110]	United Kingdom	Cohort	Retrospective	OR	1940	1976	676	35	UC	19
Radford-Smith [2002][111]	Australia	Case control	Retrospective	OR	1995	1999	307	6	UC	24
Ray [2011][112]	India	Cohort	Partial	OR	2003	2009	50	5	UC, CD	2, 12*
Rozen [1995][113]	Israel	Cohort	Prospective	OR	1976	1994	154	13	UC	2,19
Rubin [2013][114]	USA	Case control	Retrospective	OR			200	20	UC	9,18,19,21,23,26,27,30

Rubio [2009][115]	Sweden	Cohort	Retrospective	OR	1996	2007	121	6	CD	19
Rutegard [1988][116]	Sweden	Cohort	Retrospective	OR	1961	1983	127	3	UC	2
Rutegard [1988b][117]	Sweden	Cohort	Retrospective	OR	1984	1987	73	2	UC	16
Rutter [2004][118]	United Kingdom	Case control	Retrospective	OR	1988	2002	204	22	UC	8,9,21,23,26,27,30
Rutter[2006][119]	United Kingdom	Cohort	Partial	OR	1971	2001	600	57	UC	19
Samadder [2011][120]	Israel	Case control	Partial	OR	1998	2004	60		UC, CD, IBD-U	32,35*
Samadder [2018][121]	USA	Cohort	Retrospective	HR	1996	2011	9505	101	UC, CD, IBD-U	18,19,20,21
Satchi [2013][122]	USA	Case control	Retrospective	OR			54	13	UC, CD	26
Scharl [2018][123]	Switzerland	Cohort	Retrospective	HR	2006	2016	3119		UC, CD, IBD-U	14,20,26,35
Selinger [2014][124]	Australia	Cohort	Retrospective	OR HR	1977	1992	881	29	UC, CD	2,35
Senanayake [2013][125]	Sri Lanka	Cohort	Retrospective	OR	1995	2002	348	2	UC	2
Setshedi [2012][126]	South-Africa	Cohort	Retrospective	OR	1960	2007	959	12	UC, CD, IBD-U	26
Shah [2018][127]	USA	Cohort	Retrospective	HR	2000	2015	1911	64	UC, CD, IBD-U	8*,13,18*,20*,28
Shah[2019] [128]	USA	Cohort	Retrospective	OR	2005	2016	642	60	UC, CD, IBD-U	32*
Shetty [1999] [129]		Case control	Retrospective	OR	1976	1994	329	38	UC	18
Shi [2016][130]	China	Cohort	Partial	OR	1981	2013	1255	15	UC	13

Shivakumar [2013][131]	India	Cohort	Prospective	OR	2008	2012	29	4	UC	2
Siegel [2006][132]	USA	Case control	Retrospective	OR	1990	2004	54	27	CD	14,15,21,22, 23,24,27,30,31, 35
Söderlund [2009][133]	Sweden	Cohort	Partial	OR	1960	2004	7607	188	UC, CD	2,3
Söderlund [2010][134]	Sweden	Cohort	Partial	OR	1960	2004	7607	196	UC, CD	19
Söderlund [2011][135]	Sweden	Cohort	Retrospective	OR	1982		245	12	CD, IBD -U	16
Sokol [2008][136]	France	Case control	Partial	OR	1974		225	9	UC, CD, IBD -U	18*
Sonnenberg [2015][137]	USA	Case control	Retrospective	OR	2008	2014	53568	98	UC, CD, IBD -U	6*,10*,19*,20*
Sørensen [2018][138]	Denmar k	Case control	Retrospective	HR	1977	2011	8453	11	UC, CD, IBD -U	18
Stewénius [1995][139]	Sweden	Cohort	Prospective	OR	1958	1990	571	12	UC, IBD -U	2,3,19
Stolwijk [2013][140]	The Netherla nds	Cohort	Prospective	HR	1980	2005	293	23	UC	2,4,15,18,19
Tang [2010][141]	USA	Case control	Retrospective	OR	1970	2005	48	18	UC, CD	21,23,26,27*,30
Ten Hove [2019][142]	USA and the Netherla nds	Cohort	Retrospective	OR			775	12	UC, CD, IBD -U	15
Terdiman [2007][143]	USA	Case control	Retrospective	OR	2001	2003	1536	364	UC, CD	15,26,27, 29, 31,35
Terg [2008][144]	Argentin a	Case control	Prospective	OR	1990	2003	106	9	UC	18
Triantafillidis [1998][145]	Greece	Cohort	Prospective	OR	1978	1993	413	6	UC	2
Triantafillidis [2000][146]	Greece	Cohort	Prospective	OR	1981	1996	155	3	CD	19

Triantafillidis [2001][147]	Greece	Cohort	Retrospective	OR			413	3	UC	13
Ullman [2008][148]	USA	Cohort	Retrospective	OR HR	1994	2001	393	31	UC	4,5,27
Ünal [2019][149]	Turkey	Cohort	Retrospective	OR	1993	2016	801	11	UC	2,7,18,19,21,23
van den Heuvel [2016][150]	The Netherlands	Cohort	Prospective	OR	1991	2013	2801	23	UC, CD	2,3,19
van Schaik [2012][151]	Van Schaik	Cohort	Retrospective	HR	2001	2009	2578	28	UC, CD, IBD-U	6*,14*,19*,20*,26*,27*,30,33*
van Schaik [2013][152]	The Netherlands	Case control	Retrospective	HR	1995	2005	233	25	UC, CD, IBD-U	3*,4*,18*,19*,26*,27*
van Staa [2005][153]	United Kingdom	Case control	Retrospective	OR	1987	2001	700	100	UC, CD	27*
Velayos [2006][154]	USA	Case control	Retrospective	OR	1976	2002	376	188	UC	7,15*,18*,21*,23*,26*,27*,29*,30,31*,33,34*,35
Venkataraman [2005][155]	India	Cohort	Retrospective	OR	1978	2002	532	6	UC	2
Walmsley [1997][156]	United Kingdom	Cohort	Retrospective	OR	1970	1993	62	4	CD	19
Wang [2013][157]	China	Cohort	Retrospective	OR	2000	2012	603	4	UC	19
Winther [2004][158]	Denmark	Cohort	Retrospective	OR	1962	1987	1160	13	UC	2,13,19
Wright [1983][159]	South Africa	Cohort	Retrospective	OR	1975	1980	220	2	UC	2,19
Yamazaki [1991][160]	USA	Cohort	Retrospective	OR	1959	1985	980	15	CD	10
Yano [2008][161]	Japan	Cohort	Retrospective	OR	1985	2005	512	6	CD	11
Yano [2013][162]	Japan	Cohort	Retrospective	OR	1985	2010	770	3	CD	19
Ye [2011][163]	Korea	Case control	Retrospective	OR	1977	2009	84	3	UC	18
Zhang [2015][164]	China	Cohort	Retrospective	OR	2000	2012	642	4	UC	19,27,35

Prognostic factors: 2 = Disease extent; 3 = IBD type; 4 = Low-grade dysplasia; 5 = Indefinite for dysplasia; 6 = Any dysplasia (not specified); 7 = Post-inflammatory polyps; 8 = Endoscopic inflammation; 9 = Histological inflammation; 10 = Stricture; 11 = Perianal disease; 12 = Disease duration; 13 = Age at IBD diagnosis; 14 = Colon segment resection; 15 = Surveillance colonoscopies; 16 = Aneuploidy; 17 = P53 mutation; 18 = Primary

sclerosing cholangitis; 19 = Sex; 20 = Age; 21 = Family history of colorectal carcinoma; 22 = Family history of IBD; 23 = Smoking; 24 = Appendectomy; 25 = Race; 26 = Thiopurines; 27 = 5-Aminosalicylates; 28 = TNF-alpha inhibitors; 29 = NSAIDs; 30 = Folic acid; 31 = Corticosteroids; 32 = Statins; 33 = Calcium supplements; 34 = Acetylsalicylic acid; 35 = Other risk factors;
* = *multivariable analysis*
** = *original case-control; we only used UC part*

Supplementary file 4: Covariates within multivariable and adjusted models

Study ID	Author [Year]	Multivariable or adjusted model	Covariates
1	Ananthakrishnan [2014]1	Multivariable model	PSC,Gender,anti-TNF/biological,Duration of followup,Immunomoduators,Race
2	Ananthakrishnan [2014a]2	Adjusted model	Age,Gender,IBD type,Duration followup, Immunosuppression use,Season measurement,Race,Plasma 25(OH)D
3	Ananthakrishnan [2014b]3	Multivariable model	Age,Gender,IBD type,PSC,CRP,ESR,Race,Duration followup
4	Ananthakrishnan [2015]4	Multivariable model	IBD type,PSC,Age,Disease duration,Gender,Recent colonoscopy within 3 years
5	Ananthakrishnan [2016]5	Multivariable model	Gender,IBD type,anti-TNF/biological,Smoking,PSC,Age,Statin use, Increased inflammatory markers,Colonoscopy within 3 years,Race,Duration followup
8	Bansal [1996]8	Multivariable model	Age,Gender,IBD type,PSC,Race,NSAID associated diagnoses
9	Beaugerie [2013]9	Multivariable model	Gender,Age,Disease duration,Extent disease,Thiopurine,IBD type,Age,Gender,IBD type
11	Bergeron [2010]11	Multivariable model	PSC,Family history CRC,Colon segment resection
13	Biancone [2016]13	Multivariable model	Perianal disease,Colon segment resection,Extent disease,Smoking,Disease duration,Age,Disease duration,,Remark UC and CD multivarible analyses seperatly,Montreal behaviour,Surgery
22	Carrat [2017]22	Multivariable model	5-ASA,Thiopurine,PSC,Smoking,1 or more surgical procedures over the 5 years preceding cancer
29	de Jong [2019]29	Multivariable model	Pseudopolyps,´All confounders´
31	Eaden [2000]31	Multivariable model	5-ASA,Family history CRC,Contact with hospital doctor,Colonoscopies after diagnosis
39	Gerrits [2011]39	Multivariable model	LGD,Aneuploidy,Aneuploidy,p53 mutation,Endoscopic inflammation
43	Gong [2012]43	Multivariable model	Disease duration,Extent disease,LGD,5-ASA
44	Gordillo [2015]44	Multivariable model	Gender,Extent disease,Age,PSC,Appendectomy,Disease duration,Thiopurine,Included in surveillance program,Corticosteroids,5ASA or thiopurine versus no use
46	Gupta [2007]46	Multivariable model	Histologic inflammation,One or more colonoscopies per year
48	Hou [2012]48	Multivariable model	IBD age at onset,Gender,Race, Deyo score, Priority level,History of endoscopy in VA,VA encounters,UC index year
59	Kishikawa [2018]59	Multivariable model	Gender,Extent disease,IBD age at onset
69	Lakatos [2006]69	Multivariable model	Gender,Disease duration,LGD,Extent disease,PSC,Chronic continuous disease
89	Lutgens [2015]89	Multivariable model	Age,Extent disease,PSC,Pseudopolyps,anti-TNF/biological,HGD
92	Mahmoud [2019]92	Multivariable model	Gender,Pseudopolyps,PSC,Histologic inflammation,Disease duration,Family history CRC,USA cohort,Cecum reached,LGD or IND before index scopy
93	Mahmoud	Multivariable	IND,Age,LGD,PSC,Histologic inflammation,Disease

	[2019b]93	model	duration,Extent disease,5-ASA,Immunomodulators,Surveillance colonoscopies
101	Nowacki [2015]101	Multivariable model	Anti inflammatory and or immunosuppresive therapy,Disease duration 9-15 years,Disease duration more than 15 years
102	Nuako [1998]102	Adjusted model	PSC,Disease duration,Extent disease,IBD age at onset
107	Peng [2017]107	Adjusted model	Age,Gender,Cholecystectomy,Comorbidities
112	Ray [2011]112	Multivariable model	Disease duration,Unclear
120	Samadder [2011]120	Adjusted model	Age,Gender,Smoking,Family history CRC,Other,Ethnic group,Vegetable consumption,NSAIDs,Statin use
127	Shah [2018]127	Multivariable model	Age,Gender,PSC,Endoscopic inflammation
128	Shah[2019] 128	Adjusted model	Age,Gender,PSC,Disease duration,Thiopurine,anti-TNF/biological,Histologic inflammation,Number of colonoscopies
136	Sokol [2008]136	Multivariable model	PSC,PSC,5-ASA,Immunomosuppressors,Extraintestinal manifestations,Initial sigmoi colon involvement
137	Sonnenberg [2015]137	Multivariable model	Age,Gender,IBD type,IBD type,Stricture
140	Stolwijk [2013]140	Multivariable model	Gender,Extent disease,Age at first surveillance
141	Tang [2010]141	Multivariable model	5-ASA,Folic acid
151	van Schaik [2012]151	Multivariable model	5-ASA,Thiopurine,IBD type,Gender,Age,Disease duration,Extent disease,Colon segment resection,History of dysplasia,Folic acid
152	van Schaik [2013]152	Multivariable model	LGD,Gender,IBD type,Extent disease,5-ASA,Thiopurine,PSC
153	van Staa [2005]153	Adjusted model	5-ASA,Disease duration,Other,BMI,History colorectal polyps,NSAIDs,Paracetamol,Immunosuppressants,Glucocorticosteroids,Prior gastrointestinal hospitalisation,Recorded colonoscopies
154	Velayos [2006]154	Multivariable model	Family history,Smoking,PSC,Pseudopolyps,5-ASA, NSAIDs,Surveillance colonoscopies,Corticosteroid use,Immunosuppressive use,Aspirin

Supplementary file 5: Risk of bias assessment (QUIPS)

Study ID	Author [Year]	Q1: Study Participation	Q2: Study Attrition	Q3: Prognostic Factor Measurement	Q4: Outcome Measurement	Q5: Study Confounding (Covariates)	Q6: Statistical Analysis and Reporting	Overall quality assesment
1	Ananthakrishnan [2014]1	Low	Moderate	Low	Moderate	Low	Low	Moderate
2	Ananthakrishnan [2014a]2	Moderate	Moderate	Low	Moderate	Moderate	Low	High
3	Ananthakrishnan [2014b]3	Moderate	Moderate	Low	Moderate	Low	Low	High
4	Ananthakrishnan [2015]4	Low	Low	Low	Moderate	Low	Low	Low
5	Ananthakrishnan [2016]5	Low	Moderate	Low	Moderate	Low	Low	Moderate
6	Askling [2001]6	Low	Low	Moderate	Moderate	High*	Low	Moderate
7	Baars [2011]7	Low	Low	Low	Low	Low	Low	Low
8	Bansal [1996]8	Moderate	High	Moderate	Moderate	Low	Low	High
9	Beaugerie [2013]9	Low	Low	Low	Low	Low	Moderate	Low
10	Beaugerie [2018]10	Low	Low	Low	Low	Moderate	Low	Low
11	Bergeron [2010]11	Low	Low	Low	Low	Low	Low	Low
12	Bernstein [2011]12	Moderate	Moderate	Low	Moderate	Moderate	Low	High
13	Biancone [2016]13	Low	Low	Low	Low	Low	Moderate	Low
14	Boland [1984]14	High	Low	Low	Low	High	Moderate	High
15	Bopanna[2017]15	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
16	Braden [2012]16	Low	Low	Low	Low	High*	Low*	Low
17	Brentnall [1996]17	High	Moderate	Low	Low	High*	Moderate	Moderate
18	Broomé [1995]18	Low	Moderate	Low	Low	High*	Moderate	Moderate
19	Broström [1986]19	Low	Low	Low*	Low	High*	Moderate*	Low
20	Campos [2013]20	Low	Low	Low	Low	High	Moderate*	Low
21	Camus [2013]21	High	Low	Low	Low	High*	Moderate*	High
22	Carrat [2017]22	Low	Low	Low	Low	Low	Low	Low
23	Cheddani [2016]23	Moderate	Low	Low	Low	High*	Moderate*	Moderate
24	Choi [2019]24	Low	Low	Low	Low	High*	Moderate*	Low
25	Chow [2009]25	Low	Low	Low	Low	High*	Moderate*	Low
26	Connell [1994]26	Low	Low	Low	Low	High*	Moderate*	Low
27	Cosnes [2002] 27	Low	Low	Low	Low	High*	Moderate*	Low
28	De Dombal [1966]28	Low	High	Low	Low	High*	Moderate*	High
29	de Jong [2019]29	Low	Low	Low	Low	Low	Low	Low
30	Desai [2015]30	Low	Moderate	Moderate	Low	High*	Moderate*	High
31	Eaden [2000]31	Moderate	Low	Low	Low	Low	Low	Low
32	Ekbom [1990a]32	Low	Low	Low	Low	High*	Moderate*	Low
33	Florin [2004]33	Low	High	Low	Low	High*	Moderate*	High
34	Fraga [2017]34	Low	Moderate	Low	Moderate	High*	Moderate*	High
35	Fraser [2002]35	Low	Low	Low	Low	High	Moderate	Low
36	Freeman [2001]36	Low	Low	Moderate*	Low	High*	Moderate*	Moderate
37	Fujita [2010]37	Low	Moderate	High	Moderate	High*	Moderate*	High
38	Fuson [1980]38	Low	High	Low*	Low	High*	Moderate*	High
39	Gerrits [2011]39	Moderate	Low	Low	Low	Low	Low	Low
40	Gilat [1974]40	Low	Low	Low	Low	High*	Moderate*	Low
41	Gillen [1994a]41	Low	Low	Low	Low	High*	Moderate*	Low
42	Gomez-Garcia [2013]42	Low	Low	Low	Low	High*	Moderate*	Low
43	Gong [2012]43	Low	Moderate	Low	Low	Moderate	Moderate*	Moderate
44	Gordillo [2015]44	Low	Low	Low	Low	Low	Low	Low
45	Greenstein [1979]45	High	Low	Low	Low	High*	Moderate*	High

46	Gupta [2007]46	Low	Low	Low	Low	Low	Low	Low
47	Hajek [2005]47	Moderate	Low	Low	Moderate	High*	Moderate*	High
48	Hou [2012]48	Moderate	Low	Moderate	Moderate	Moderate	Low	High
49	Hovde [2017]49	Low	Moderate	Low	Low	High*	Moderate*	Moderate
50	Jablonska [1993]50	Low	Low	Low	Low	High*	Moderate*	Low
51	Jacobsen [1994]51	Low	Low	Low	Low	High*	Moderate*	Low
52	Jess [2012]52	Moderate	Low	Low	Moderate	High*	Moderate*	High
53	Jonsson [1994]53	Low	Low	Low	Low	High*	Moderate*	Low
54	Joo [2009]54	Moderate	Low	Low	Low	High*	Moderate*	Moderate
55	Jung [2017]55	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
56	Jussila [2013]56	Moderate	Moderate	Low*	Low	High*	Moderate*	High
57	Kamiya [2012]57	Low	Moderate	Low*	Low	High*	Moderate*	Moderate
58	Katzka [1983]58	Moderate	Low	Low	Low	High*	Moderate*	Moderate
59	Kishikawa [2018]59	Low	Moderate	Low	Low	Low	Low	Low
60	Kobayashi [2002]60	Low	Low	Low	Low	High*	Moderate*	Low
61	Kochhar [1991]61	Low	High	Moderate	Low	High*	Moderate*	High
62	Kopylov [2015]62	Moderate	Moderate	Low*	Moderate	High*	Moderate*	High
63	Kottachchi [2009]63	Low	Low	Low	Low	High*	Moderate*	Low
64	Kuo [2014]64	Moderate	Low	Low*	Moderate	High*	Moderate*	High
65	Kvist [1989]65	Low	Low	Low	Low	High*	Moderate*	Low
66	Lai [2015]66	Low	Low	Low	Low	High*	Moderate*	Low
67	Laish [2017]67	Moderate*	Moderate*	Low	Low	High*	Moderate*	High
68	Lakatos [2004]68	Low	Moderate	Low	Low	High*	Moderate	Moderate
69	Lakatos [2006]69	Low	Low	Low	Low	Moderate	Moderate	Low
70	Lakatos [2011]70	Low	Low	Low	Low	High*	Moderate*	Low
71	Langholz[1992]71	Low	Low	Low	Low	High*	Moderate*	Low
73	Lashner [1989] 73	Moderate	High	Moderate	Low	High*	Moderate	High
72	Lashner [1989a]72	Low	Low	Low	Low	High*	Moderate*	Low
74	Lashner [1990]74	Moderate	Low	Low	Low	High*	Moderate*	Moderate
75	Lashner [1999]75	Moderate	Low	Low	Low	High*	Moderate*	Moderate
76	Lee[2015]76	Low	Low	Low	Low	High*	Moderate*	Low
77	Leidenius [1991]77	Low	Low	Low	Low	High*	Moderate*	Low
78	Leidenius [1997]78	Moderate	Low	Low	Low	High*	Moderate*	Moderate
79	Lennard-Jones [1977]79	Moderate	Low	Low	Low	High*	Moderate*	Moderate
80	Lennard-Jones [1990]80	Moderate	Low	Low	Low	High*	Moderate*	Moderate
81	Lim [2003]81	Moderate	Low	Low	Low	High*	Moderate*	Moderate
82	Lindberg [1999]82	Low	Low	Low	Low	High*	Moderate*	Low
83	Lindberg [2001]83	Low	Low	Low	Low	High*	Moderate*	Low
84	Lindberg[2005]84	Low	Low	Moderate	Low	High*	Moderate*	Moderate
85	Lindström [2011]85	Low	Low	Low	Low	High*	Moderate*	Low
86	Löfberg [1991]86	High	Low	Moderate	Low	High*	Moderate*	High
87	Loftus [2005]87	Low	Low	Low	Low	High*	Low	Low
88	Lovasz [2013]88	Low	Low	Moderate	Low	High*	Moderate*	Moderate
89	Lutgens [2015]89	Low	Low	Low	Low	Low	Low	Low
90	MacDougall [1954]90	Low	Low	Low	Low	High*	Moderate*	Low
91	Madanchi [2016]91	Low	Low	Low	Low	High*	Moderate*	Low
92	Mahmoud [2019]92	Low	Low	Low	Low	Low	Low	Low
93	Mahmoud [2019b]93	Low	Low	Low	Low	Low	Low	Low
94	Manninen [2013]94	Low	Low	Low	Low	High*	Moderate*	Low
95	Maratka [1985]95	Low	Low	Low	Low	High*	Moderate*	Low
96	Markowitz [1997]96	High	Low	Low	Low	High*	Moderate*	High

97	Mir-Madjlessi [1986]97	Low	Moderate	Low	Low	High*	Moderate*	High
98	Navaneethan [2016]98	Low	Low	Low	Low	High*	Moderate*	Low
99	Nieminen [2014]99	Low	Low	Low	Low	Moderate	Low	Low
100	Nkontchou [1996]100	Moderate	High	Low	Moderate	High*	Moderate*	High
101	Nowacki [2015]101	Low	Low	Low	Low	Low	Low	Low
102	Nuako [1998]102	Low	Low	Low	Low	Low	Low	Low
103	Nuako [1998a]103	Moderate	Unclear	Low	Low	Low	Low	Low
104	Nugent [1991]104	Low	Moderate	Low	Low	High*	Moderate*	Moderate
105	Paris [1994]105	Low	High	Low	Moderate	High*	Moderate*	High
106	Peng [2015]106	Moderate	Low	Low	Moderate	High*	Moderate*	High
107	Peng [2017]107	Moderate	Low	Low	Moderate	Moderate	Moderate	High
108	Picazo-Ferrera [2011]108	Low	Moderate	Low	Low	High	High	High
109	Pinczowski [1994]109	Moderate	High	Low	Low	High	Moderate	High
110	Prior [1982]110	Low	Low	Low	Low	High*	Moderate*	Low
111	Radford-Smith [2002]111	Low	High	Low	Low	High*	Moderate*	High
112	Ray [2011]112	Low	Low	Low	Low	Moderate	Moderate*	Low
113	Rozen [1995]113	Low	Low	Low	Low	High*	Moderate*	Low
114	Rubin [2013]114	Low	Low	Low	Low	Low	Low	Low
115	Rubio [2009]115	High	High	Low	Low	High*	Moderate*	High
116	Rutegard [1988]116	Low	Low	Low	Low	High*	Moderate*	Low
117	Rutegard [1988b]117	Low	High	Low	Low	High*	Moderate*	High
118	Rutter [2004]118	Moderate	Low	Low	Low	Low	Low	Low
119	Rutter[2006]119	Moderate	Low	Low	Low	High*	Moderate*	Moderate
120	Samadder [2011]120	Moderate	High	Moderate	Moderate	Moderate	Moderate	High
121	Samadder [2018]121	Moderate	Moderate	Moderate	Moderate	High*	Moderate	High
122	Satchi [2013]122	Moderate	Low	Low	Low	High*	Moderate*	Moderate
123	Scharl [2018]123	Low	Low	Low	Low	Moderate	Moderate	Moderate
124	Selinger [2014]124	Low	Low	Low	Low	High	Moderate	Low
125	Senanayake [2013]125	Low	Moderate	Low	Moderate	High*	Moderate*	High
126	Setshedi [2012]126	Low	Moderate	Low	Moderate	High*	Moderate*	High
127	Shah [2018]127	Low	Low	Low	Low	Low	Low	Low
128	Shah[2019] 128	Low	Low	Low	Low	Low	Low	Low
129	Shetty [1999] 129	Low	Low	Low	Low	High*	Moderate*	Low
130	Shi [2016]130	Low	Low	Low	Low	High*	Moderate*	Low
131	Shivakumar [2013]131	Low	Moderate	Low	Low	High*	Moderate*	Moderate
132	Siegel [2006]132	Low	Low	Low	Low	Low	Low	Low
133	Söderlund [2009]133	Low	Low	Low	Low	High*	Moderate*	Low
134	Söderlund [2010]134	Low	Low	Low	Low	High*	Moderate*	Low
135	Söderlund [2011]135	Low	Low	Low	Low	High*	Moderate*	Low
136	Sokol [2008]136	Low	Low	Low	Low	Low	Low	Low
137	Sonnenberg [2015]137	Moderate	High	High	Low	Moderate	Low	High
138	Sørensen [2018]138	Low	Low	Low	Low	Moderate	Low	Low
139	Stewénius [1995]139	Low	Low	Low	Low	High*	Moderate*	Low
140	Stolwijk [2013]140	Low	Low	Low	Low	Low	Low	Low
141	Tang [2010]141	Low	Low	Low	Low	Moderate	Moderate	Low
142	Ten Hove [2019]142	Moderate	Low	Low	Low	High*	Moderate*	Moderate
143	Terdiman [2007]143	Moderate	High	Moderate	Moderate	Low	Low	High
144	Terg [2008]144	Low	Low	Low	Low	High*	Moderate*	Low
145	Triantafillidis [1998]145	Low	Low	Low	Low	High*	Moderate*	Low
146	Triantafillidis [2000]146	Low	Low	Low	Low	High*	Moderate*	Low
147	Triantafillidis [2001]147	Low	Moderate	Low	Low	High*	Moderate*	High

148	Ullman [2008]148	Low	Low	Low	Low	High	Moderate*	Low
149	Ünal [2019]149	Low	Low	Moderate	Low	High*	Moderate*	Moderate
150	van den Heuvel [2016]150	Low	Low	Low	Low	High*	Moderate*	Low
151	van Schaik [2012]151	Moderate	Low	Low	Low	Low	Low	Low
152	van Schaik [2013]152	High	Low	Low	Low	Low	Low	High
153	van Staa [2005]153	Moderate	Low	Moderate	Moderate	Low	Low	High
154	Velayos [2006]154	Low	Low	Low	Low	Low	Low	Low
155	Venkataraman [2005]155	Low	Moderate	High*	Low	High	High	High
156	Walmsley [1997]156	High	Low	Low	Low	High*	Moderate*	High
157	Wang [2013]157	Moderate	Low	Low	Low	High*	Moderate*	Moderate
158	Winther [2004]158	Low	Low	Moderate	Moderate	High*	Moderate*	High
159	Wright [1983]159	Moderate	Low	Low	Moderate	High*	Moderate*	High
160	Yamazaki [1991]160	Low	Moderate	High	Moderate	High*	Moderate*	High
161	Yano [2008]161	Low	Low	Moderate	Low	High*	Moderate*	Moderate
162	Yano [2013]162	Low	Low	Low	Low	High*	Moderate*	Low
163	Ye [2011]163	Low	Low	Low	Low	High*	Moderate*	Low
164	Zhang [2015]164	Low	High	Moderate	Low	High	Moderate	High

***** *The risk of bias is high because the aim of the study was not specifically to study the impact of risk factors on the advanced colorectal neoplasia risk, but data to calculate an OR was provided. Therefore it was not possible to analyze these risk factors adjusted for important covariates.*

Supplementary file 6: Risk of bias: QUIPS explanation

In addition to the QUIPS tool, through consensus, we have stated additional criteria to evaluate risk of bias in the included studies. The main reason for this addition is the fact that the majority of the included studies was originally not intended for prognostic factor research or did not provide sufficient information to be able to grade in accordance with the original QUIPS tool. As a recent Cochrane systematic review has done, we added a fourth 'unclear' option to the QUIPS tool.[1]

Q1: Study participation

Low risk: Surveillance cohort or cohort of total IBD population.

Moderate risk: ICD codes (or comparable codes) without chart review; sub-selection of IBD patients (e.g. only extensive disease, only above a certain age).

High risk: Extreme selection (e.g. only patients using 5-ASA or another prescription); no random selection of cohort or the selection process is not described.

Q2: Study Attrition

Low risk: Documentation of follow-up and actions are undertaken to retrieve information from these cases.

Moderate risk: Intermediate.

High risk: No information or mentioning on loss-to follow-up.

Q3: Prognostic factor (PF) Measurement

Low risk: Definition of PF is provided and reproducible. The risk of misclassification is extremely low (e.g. sex; dose of medication).

Moderate risk: Definition is given, but not specific (e.g. unclear definition of medication use)

High risk: No clear definition given for all factors.

Q4: Outcome Measurement

Low risk: Definition of outcome is provided and reproducible. The risk of misclassification is extremely low. Chart review was executed (pathology or patient chart).

Moderate risk: Definition is given, outcome is based on coding (no revision of patient chart).

High risk: No clear definition of outcome is given or process of collection information on occurrence of outcomes is not described.

Q5: Study Confounding (Covariates)

Low risk: Most important covariates were evaluated and the result was either adjusted for these variables or reported in a multivariable model.

Moderate risk: Some important covariates were unadjusted for or missing in the cohort.

High risk: Only univariable analysis was provided or we calculated or own OR based on data in article (last category indicated with an asterisk).

Q6: Statistical analysis and Reporting

Low risk: A fitting analysis was undertaken (e.g. conditional logistic regression in the setting of a case-control design); steps in model building were undertaken well and adequate reporting (univariable as well as multivariable).

Moderate: Only univariable data are provided in a study in which a multivariable model could have been performed. Or we calculated or own OR from either a case-control study or cohort study.

High risk: Multivariable analysis is performed with a low number of cases.

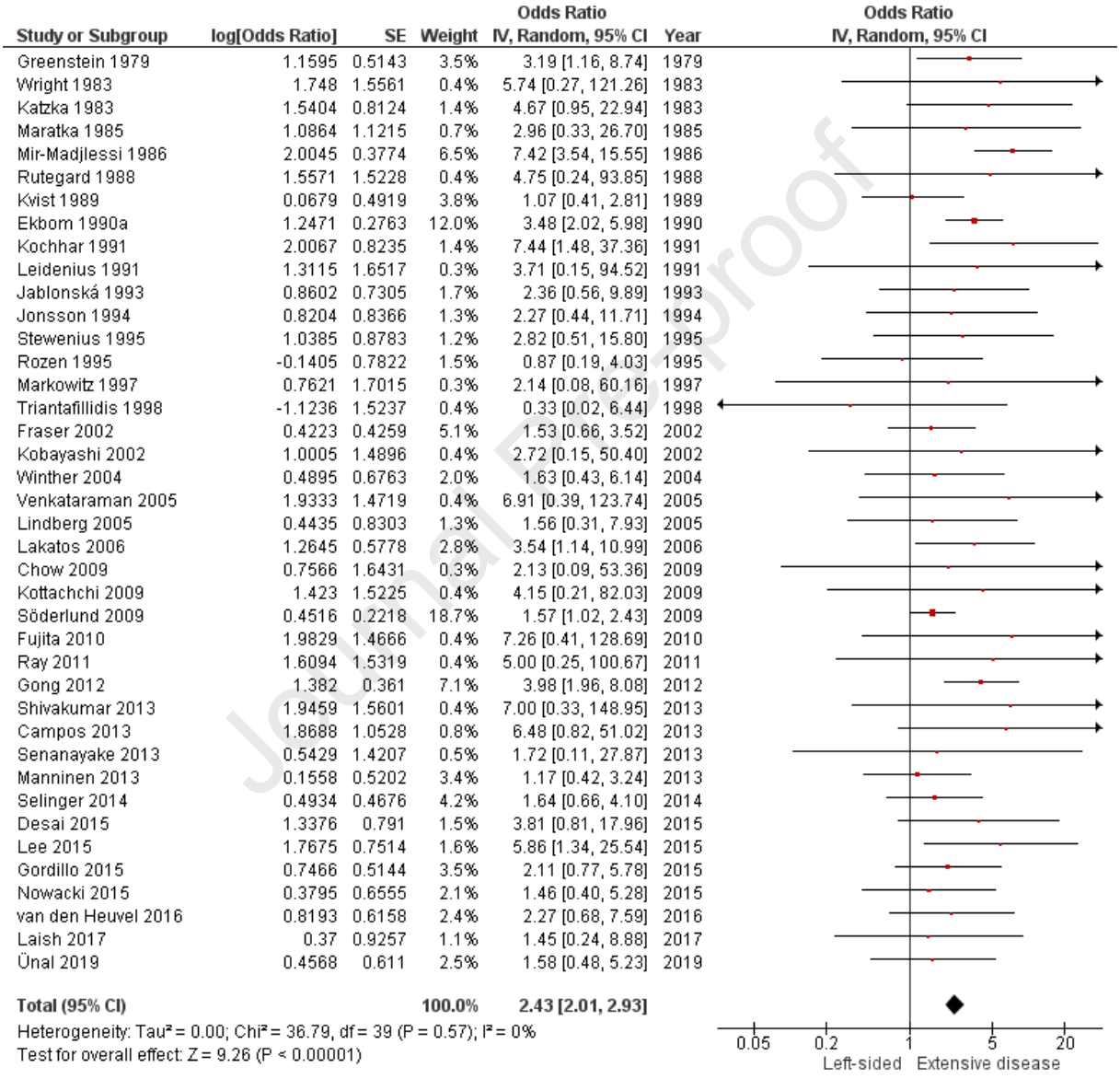
Reference

1. Aldin A, Umlauff L, Estcourt LJ, Collins G, Moons KG, Engert A, et al. Interim PET-results for prognosis in adults with Hodgkin lymphoma: a systematic review and meta-analysis of prognostic factor studies. The Cochrane database of systematic reviews. 2020;1:CD012643.

DISEASE CHARACTERISTICS (AND DEMOGRAPHICS)

Supplementary file 7A-G Disease extent

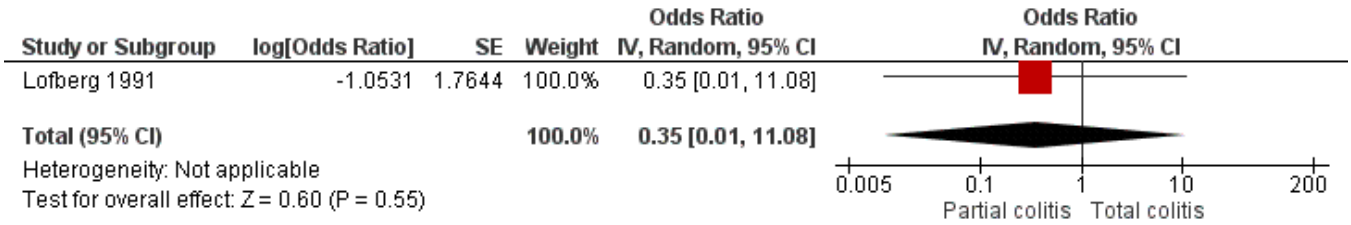
Supplementary Figure 7A: Forest plot of univariable ORs extensive disease versus non-extensive disease in UC (cohort studies)



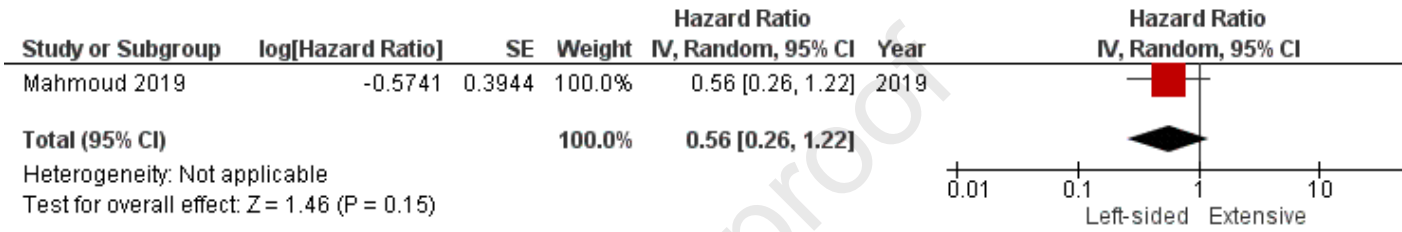
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Greenstein 1979	1.1595	0.5143	3.5%	3.19 [1.16, 8.74]	1979
Wright 1983	1.748	1.5561	0.4%	5.74 [0.27, 121.26]	1983
Katzka 1983	1.5404	0.8124	1.4%	4.67 [0.95, 22.94]	1983
Maratka 1985	1.0864	1.1215	0.7%	2.96 [0.33, 26.70]	1985
Mir-Madjlessi 1986	2.0045	0.3774	6.5%	7.42 [3.54, 15.55]	1986
Rutegard 1988	1.5571	1.5228	0.4%	4.75 [0.24, 93.85]	1988
Kvist 1989	0.0679	0.4919	3.8%	1.07 [0.41, 2.81]	1989
Ekbom 1990a	1.2471	0.2763	12.0%	3.48 [2.02, 5.98]	1990
Kochhar 1991	2.0067	0.8235	1.4%	7.44 [1.48, 37.36]	1991
Leidenius 1991	1.3115	1.6517	0.3%	3.71 [0.15, 94.52]	1991
Jablonská 1993	0.8602	0.7305	1.7%	2.36 [0.56, 9.89]	1993
Jonsson 1994	0.8204	0.8366	1.3%	2.27 [0.44, 11.71]	1994
Stewenius 1995	1.0385	0.8783	1.2%	2.82 [0.51, 15.80]	1995
Rozen 1995	-0.1405	0.7822	1.5%	0.87 [0.19, 4.03]	1995
Markowitz 1997	0.7621	1.7015	0.3%	2.14 [0.08, 60.16]	1997
Triantafillidis 1998	-1.1236	1.5237	0.4%	0.33 [0.02, 6.44]	1998
Fraser 2002	0.4223	0.4259	5.1%	1.53 [0.66, 3.52]	2002
Kobayashi 2002	1.0005	1.4896	0.4%	2.72 [0.15, 50.40]	2002
Winther 2004	0.4895	0.6763	2.0%	1.63 [0.43, 6.14]	2004
Venkataraman 2005	1.9333	1.4719	0.4%	6.91 [0.39, 123.74]	2005
Lindberg 2005	0.4435	0.8303	1.3%	1.56 [0.31, 7.93]	2005
Lakatos 2006	1.2645	0.5778	2.8%	3.54 [1.14, 10.99]	2006
Chow 2009	0.7566	1.6431	0.3%	2.13 [0.09, 53.36]	2009
Kottachchi 2009	1.423	1.5225	0.4%	4.15 [0.21, 82.03]	2009
Söderlund 2009	0.4516	0.2218	18.7%	1.57 [1.02, 2.43]	2009
Fujita 2010	1.9829	1.4666	0.4%	7.26 [0.41, 128.69]	2010
Ray 2011	1.6094	1.5319	0.4%	5.00 [0.25, 100.67]	2011
Gong 2012	1.382	0.361	7.1%	3.98 [1.96, 8.08]	2012
Shivakumar 2013	1.9459	1.5601	0.4%	7.00 [0.33, 148.95]	2013
Campos 2013	1.8688	1.0528	0.8%	6.48 [0.82, 51.02]	2013
Senanayake 2013	0.5429	1.4207	0.5%	1.72 [0.11, 27.87]	2013
Manninen 2013	0.1558	0.5202	3.4%	1.17 [0.42, 3.24]	2013
Selinger 2014	0.4934	0.4676	4.2%	1.64 [0.66, 4.10]	2014
Desai 2015	1.3376	0.791	1.5%	3.81 [0.81, 17.96]	2015
Lee 2015	1.7675	0.7514	1.6%	5.86 [1.34, 25.54]	2015
Gordillo 2015	0.7466	0.5144	3.5%	2.11 [0.77, 5.78]	2015
Nowacki 2015	0.3795	0.6555	2.1%	1.46 [0.40, 5.28]	2015
van den Heuvel 2016	0.8193	0.6158	2.4%	2.27 [0.68, 7.59]	2016
Laish 2017	0.37	0.9257	1.1%	1.45 [0.24, 8.88]	2017
Ünal 2019	0.4568	0.611	2.5%	1.58 [0.48, 5.23]	2019
Total (95% CI)			**100.0%**	**2.43 [2.01, 2.93]**	

Heterogeneity: Tau² = 0.00; Chi² = 36.79, df = 39 (P = 0.57); I² = 0%
Test for overall effect: Z = 9.26 (P < 0.00001)

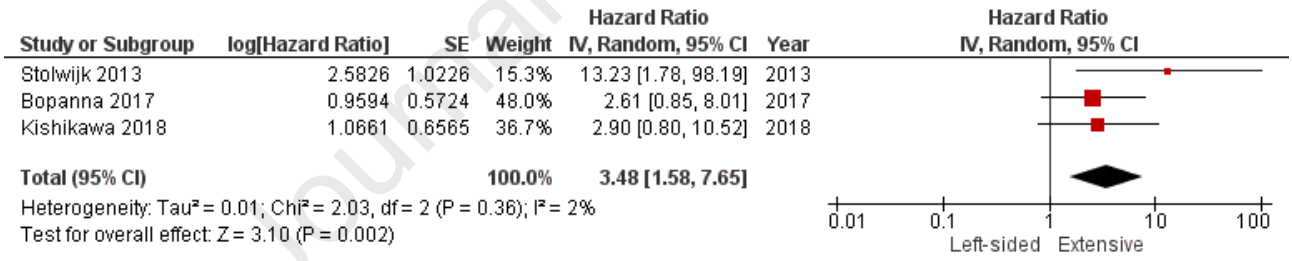
Supplementary Figure 7B: Forest plot of univariable ORs extensive disease versus non-extensive disease in CD (cohort study)



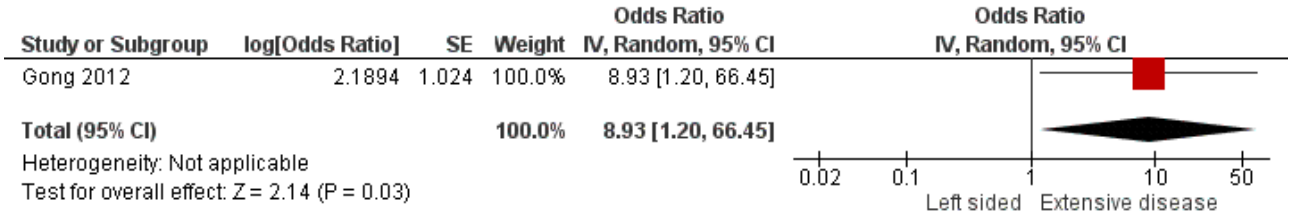
Supplementary Figure 7C: Forest plot of univariable HRs extensive disease versus non-extensive disease in IBD (cohort studies)



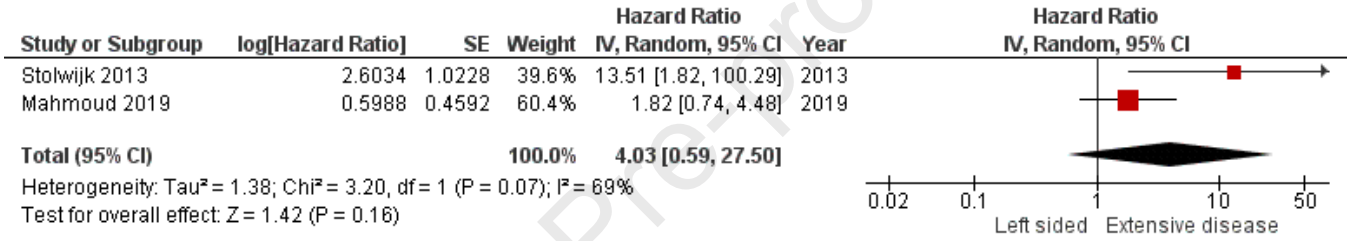
Supplementary Figure 7D: Forest plot of univariable HRs extensive disease versus non-extensive disease in UC (cohort studies)



Supplementary Figure 7E: Forest plot of multivariable ORs extensive disease versus non-extensive disease in UC (cohort study)



Supplementary Figure 7F: Forest plot of multivariable HRs extensive disease versus non-extensive disease in all IBD (cohort studies)

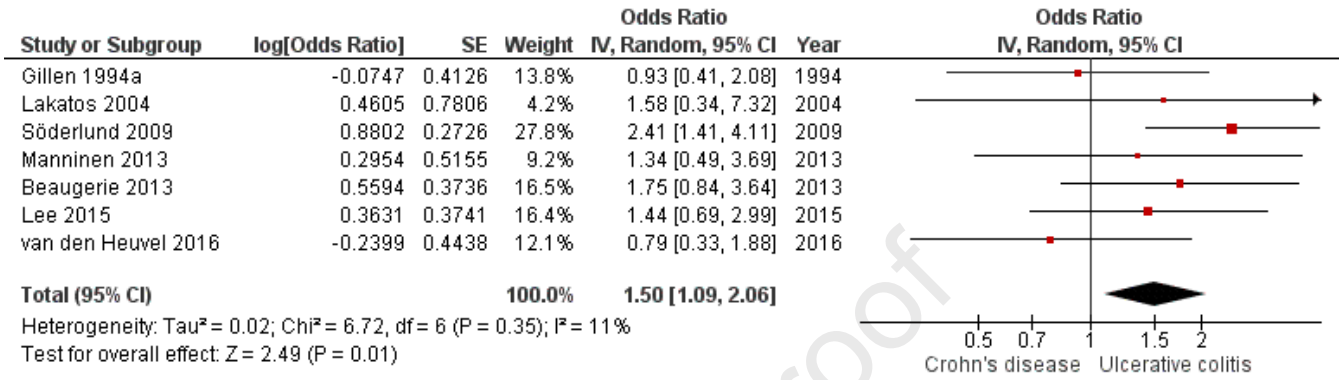


Supplementary notation 7G: Definition disease extent

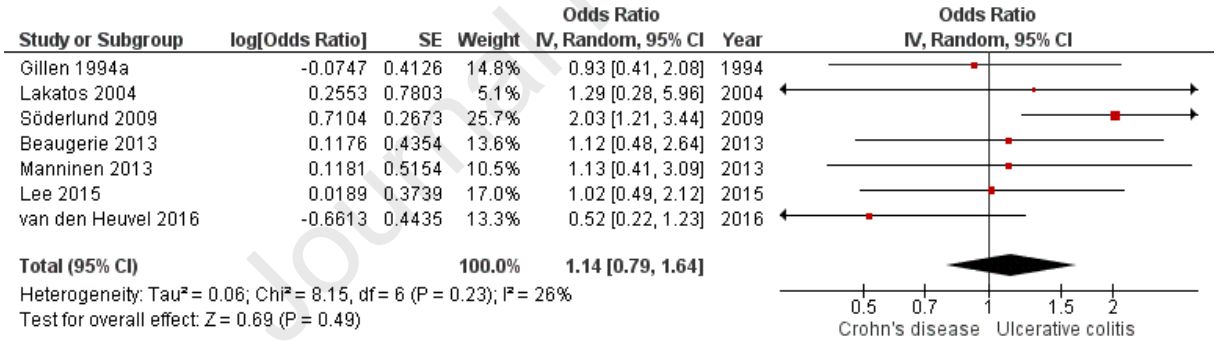
To assess extent of disease we included studies that provided data on patients with left-sided UC versus extensive disease (inflammation extending at least proximal of the splenic flexure). In CD, an estimated involvement of >50% of the colon was regarded as extensive disease. Studies not clearly defining disease extent were excluded.

Supplementary file 8A-F IBD type

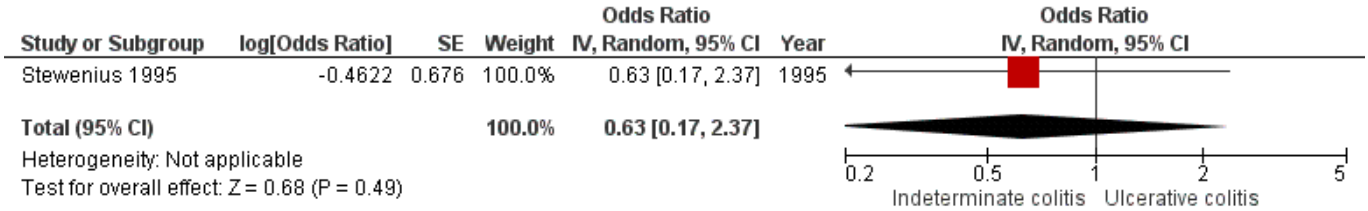
Supplementary Figure 8A: Forest plot Univariable analysis OR cohort studies (UC excluding proctitis versus CD (ileo-)colitis)



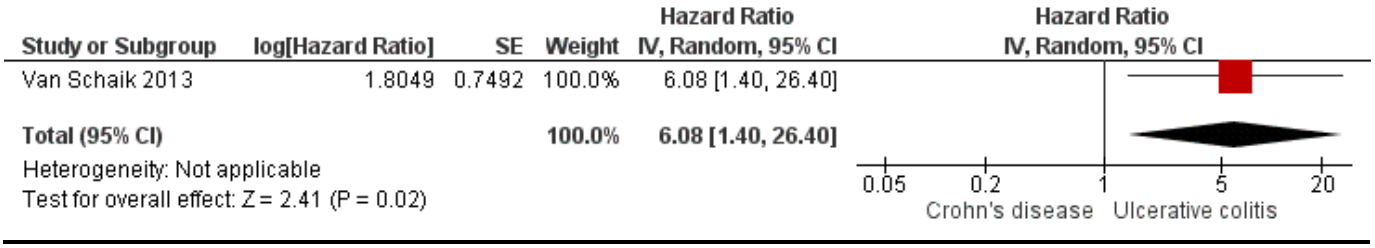
Supplementary Figure 8B: Forest plot Univariable analysis OR cohort studies (UC including proctitis versus CD (ileo-)colitis)



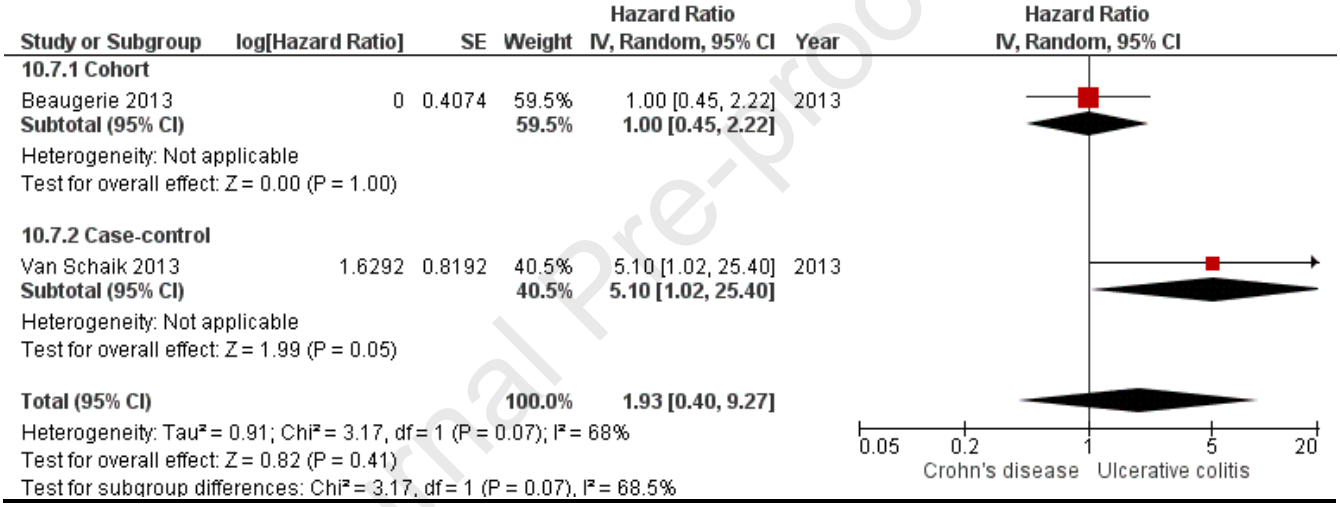
Supplementary Figure 8C: Forest plot Univariable analysis OR cohort studies (indeterminate colitis versus UC)



Supplementary Figure 8D: Forest plot of Univariable analysis HR case-control (UC versus CD)



Supplementary Figure 8E: Forest plot of Multivariable analysis HR (UC versus CD)



Supplementary notation 8F: Definition IBD type

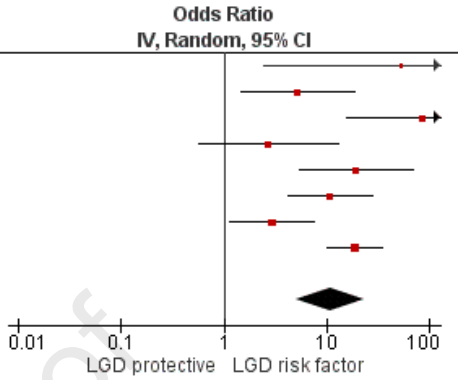
To compare the risk of UC versus CD we only included studies that reported the risk of aCRN in IBD patients with colonic involvement. Studies were excluded if the provided data did not allow for calculation of the OR after exclusion of patients without colonic involvement.

Supplementary file 9A-E Low-grade dysplasia

Supplementary Figure 9A: Forest plot of Univariable OR (cohort studies)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Lennard-Jones 1977	3.9723	1.5682	4.6%	53.11 [2.46, 1148.16]	1977
Lashner 1989a	1.6514	0.6469	12.9%	5.21 [1.47, 18.53]	1989
Nugent 1991	4.4543	0.8694	9.9%	86.00 [15.65, 472.62]	1991
Lim 2003	0.9868	0.7953	10.8%	2.68 [0.56, 12.75]	2003
Lakatos 2006	2.9601	0.6559	12.8%	19.30 [5.34, 69.80]	2006
Ullman 2008	2.3804	0.4741	15.5%	10.81 [4.27, 27.37]	2008
Stolwijk 2013	1.0804	0.4771	15.5%	2.95 [1.16, 7.50]	2013
Choi 2019	2.92	0.3106	18.0%	18.54 [10.09, 34.08]	2019
Total (95% CI)			**100.0%**	**10.85 [5.13, 22.97]**	

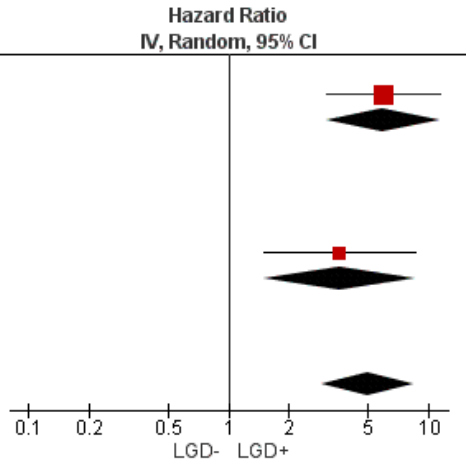
Heterogeneity: Tau² = 0.72; Chi² = 22.27, df = 7 (P = 0.002); I² = 69%
Test for overall effect: Z = 6.23 (P < 0.00001)



Supplementary Figure 9B: Forest plot of Univariable HR

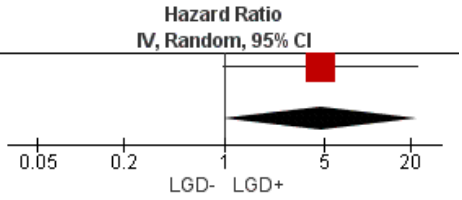
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
12.2.1 Cohort					
Mahmoud 2019	1.7783	0.3367	63.8%	5.92 [3.06, 11.45]	2019
Subtotal (95% CI)			**63.8%**	**5.92 [3.06, 11.45]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 5.28 (P < 0.00001)					
12.2.2 Case-control					
Van Schaik 2013	1.2809	0.4467	36.2%	3.60 [1.50, 8.64]	2013
Subtotal (95% CI)			**36.2%**	**3.60 [1.50, 8.64]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 2.87 (P = 0.004)					
Total (95% CI)			**100.0%**	**4.94 [2.92, 8.37]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 5.94 (P < 0.00001)
Test for subgroup differences: Chi² = 0.79, df = 1 (P = 0.37), I² = 0%

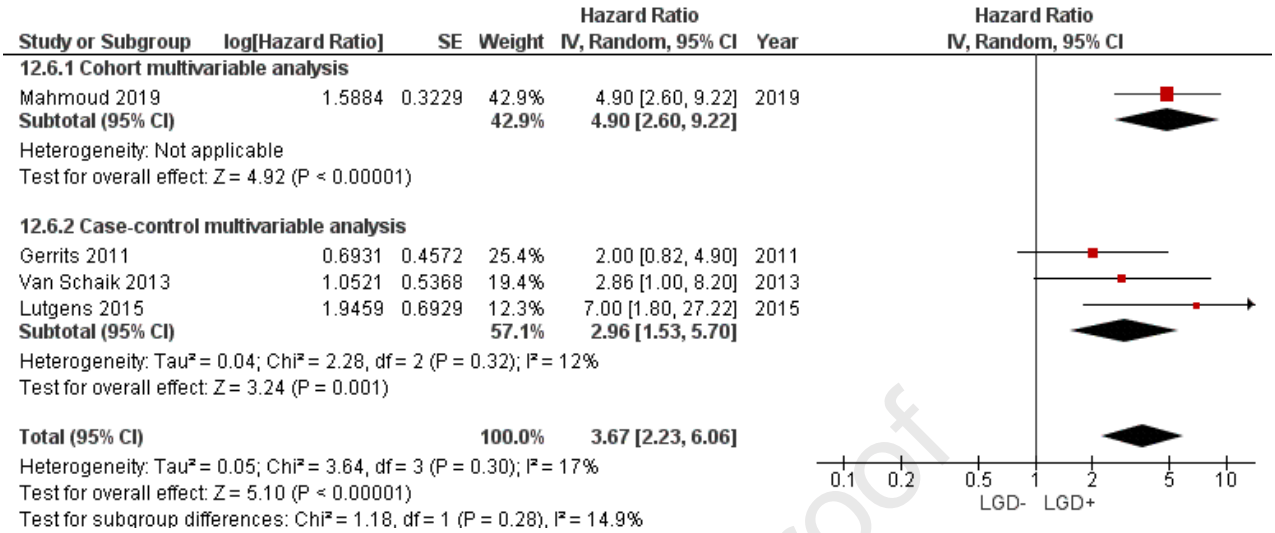


Supplementary Figure 9C: Forest plot of Multivariable OR (cohort study)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Lakatos 2006	1.5518	0.7922	100.0%	4.72 [1.00, 22.30]	2006
Total (95% CI)			**100.0%**	**4.72 [1.00, 22.30]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 1.96 (P = 0.05)					



Supplementary Figure 9D: Forest plot of Multivariable analysis HR



Supplementary Table 9E: Characteristics of LGD

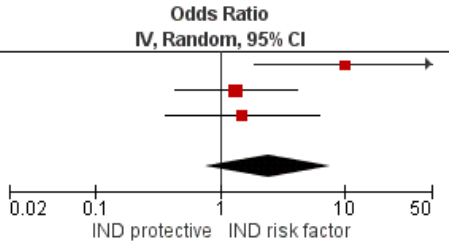
Author	Number of LGD	Number of aCRN	Morphology
Lennard-Jones 1977	20	2	not specified
Lashner 1989a	20	6	not specified
Nugent 1991	18	7	not specified
Lim 2003	29	3	not specified
Lakatos 2006	not specified	not specified	not specified
Ullman 2008	26	10	Flat
Stolwijk 2013	55	10	not specified
Choi 2019	not specified	not specified	Flat
Mahmoud 2019	not specified	not specified	not specified
Van Schaik 2013	42	18	Flat and polypoid
Gerrits 2011	not specified	not specified	Flat and polypoid
Lutgens 2015	not specified	not specified	Polypoid

Supplementary file 10A-C Indefinite for dysplasia

Supplementary Figure 10A: Forest plot of Univariable OR (cohort studies)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Nugent 1991	2.3143	0.8552	27.6%	10.12 [1.89, 54.08]	1991
Ullman 2008	0.2854	0.5757	39.9%	1.33 [0.43, 4.11]	2008
Lai 2015	0.4106	0.732	32.5%	1.51 [0.36, 6.33]	2015
Total (95% CI)			**100.0%**	**2.42 [0.75, 7.81]**	

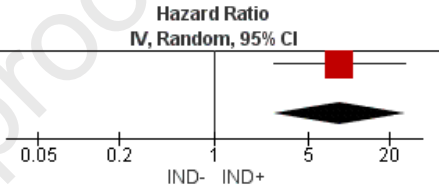
Heterogeneity: Tau² = 0.56; Chi² = 4.21, df = 2 (P = 0.12); I² = 52%
Test for overall effect: Z = 1.48 (P = 0.14)



Supplementary Figure 10B: Forest plot of Univariable HR (cohort study)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Mahmoud 2019b	2.1552	0.5761	100.0%	8.63 [2.79, 26.69]	2019
Total (95% CI)			**100.0%**	**8.63 [2.79, 26.69]**	

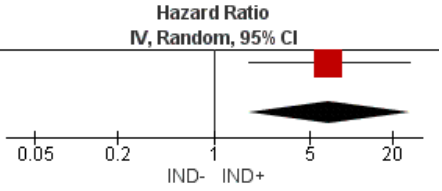
Heterogeneity: Not applicable
Test for overall effect: Z = 3.74 (P = 0.0002)



Supplementary Figure 10C: Forest plot of Multivariable HR (cohort study)

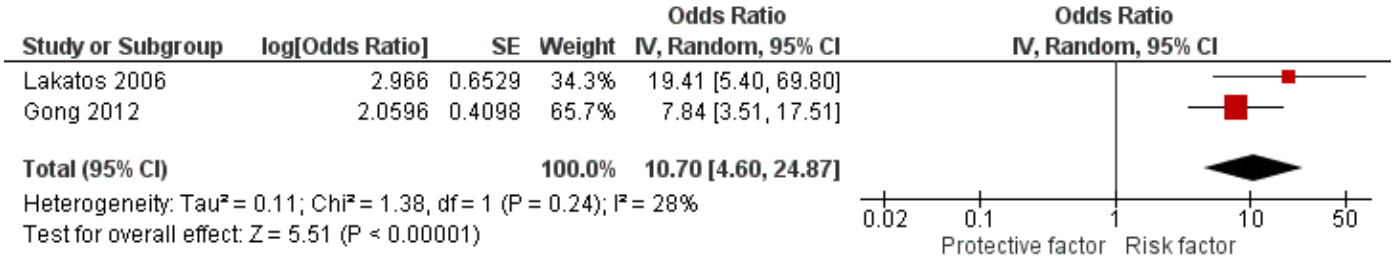
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Mahmoud 2019b	1.9242	0.6876	100.0%	6.85 [1.78, 26.36]	2019
Total (95% CI)			**100.0%**	**6.85 [1.78, 26.36]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 2.80 (P = 0.005)

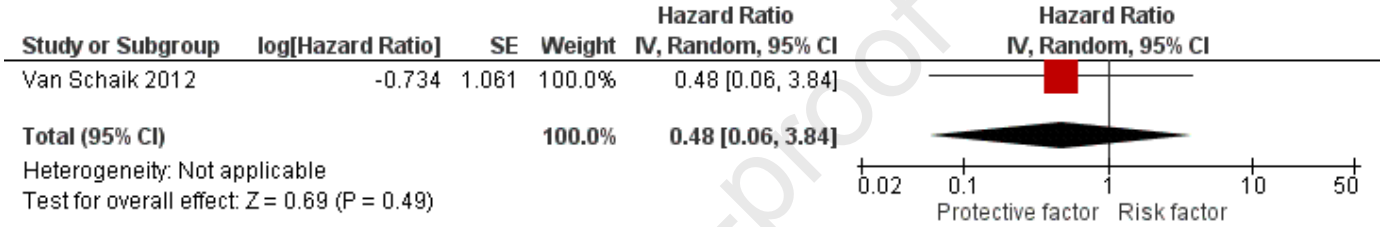


Supplementary file 11A-D Any dysplasia (not specified)

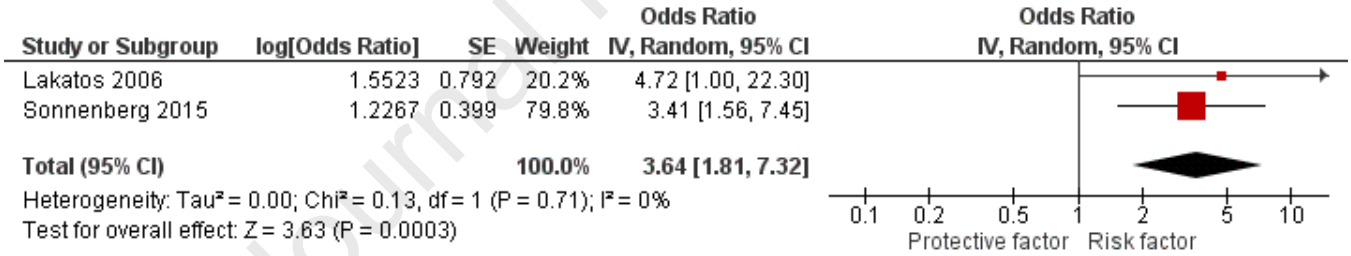
Supplementary Figure 11A: Any dysplasia (not specified), univariable OR cohort



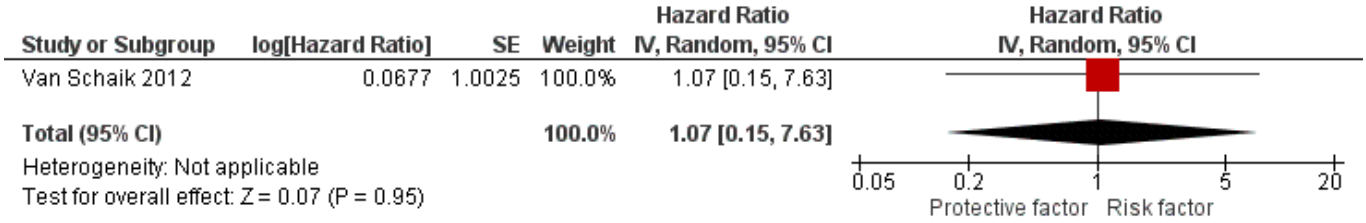
Supplementary Figure 11B: Any dysplasia (not specified), univariable HR cohort



Supplementary Figure 11C: Any dysplasia (not specified), multivariable OR cohort



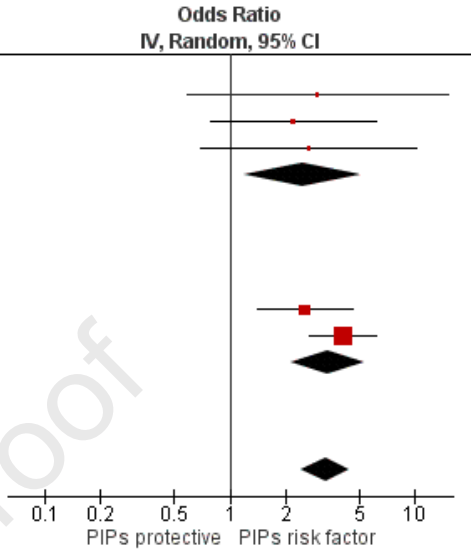
Supplementary Figure 11D: Any dysplasia (not specified), multivariable HR cohort



Supplementary Files 12A-D Post-inflammatory polyps (PIPs)

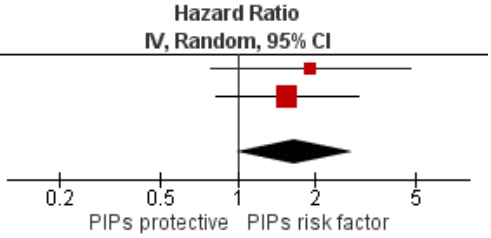
Supplementary Figure 12A: Forest plot of univariable ORs PIPs

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
2.2.1 Cohort					
De Dombal 1966	1.0913	0.8312	3.6%	2.98 [0.58, 15.19]	1966
Bopanna 2017	0.7931	0.5249	9.0%	2.21 [0.79, 6.18]	2017
Ünal 2019	0.9855	0.6856	5.3%	2.68 [0.70, 10.27]	2019
Subtotal (95% CI)			**17.9%**	**2.48 [1.20, 5.16]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 2 (P = 0.95); I² = 0%					
Test for overall effect: Z = 2.44 (P = 0.01)					
2.2.2 Case-control					
Velayos 2006	0.9313	0.3035	27.0%	2.54 [1.40, 4.60]	2006
Baars 2011	1.4095	0.2128	55.0%	4.09 [2.70, 6.21]	2011
Subtotal (95% CI)			**82.1%**	**3.39 [2.14, 5.36]**	
Heterogeneity: Tau² = 0.05; Chi² = 1.66, df = 1 (P = 0.20); I² = 40%					
Test for overall effect: Z = 5.21 (P < 0.00001)					
Total (95% CI)			**100.0%**	**3.29 [2.41, 4.48]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.47, df = 4 (P = 0.65); I² = 0%					
Test for overall effect: Z = 7.54 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² = 0%					



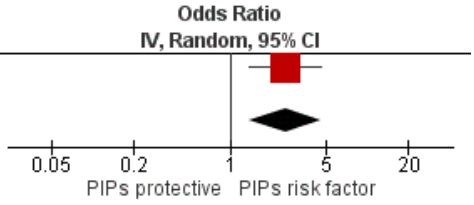
Supplementary Figure 12B: Forest plot of univariable HRs PIPs (cohort studies)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
de Jong 2019	0.6548	0.4609	33.6%	1.92 [0.78, 4.75]
Mahmoud 2019	0.4434	0.3275	66.4%	1.56 [0.82, 2.96]
Total (95% CI)			**100.0%**	**1.67 [0.99, 2.82]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%				
Test for overall effect: Z = 1.93 (P = 0.05)				

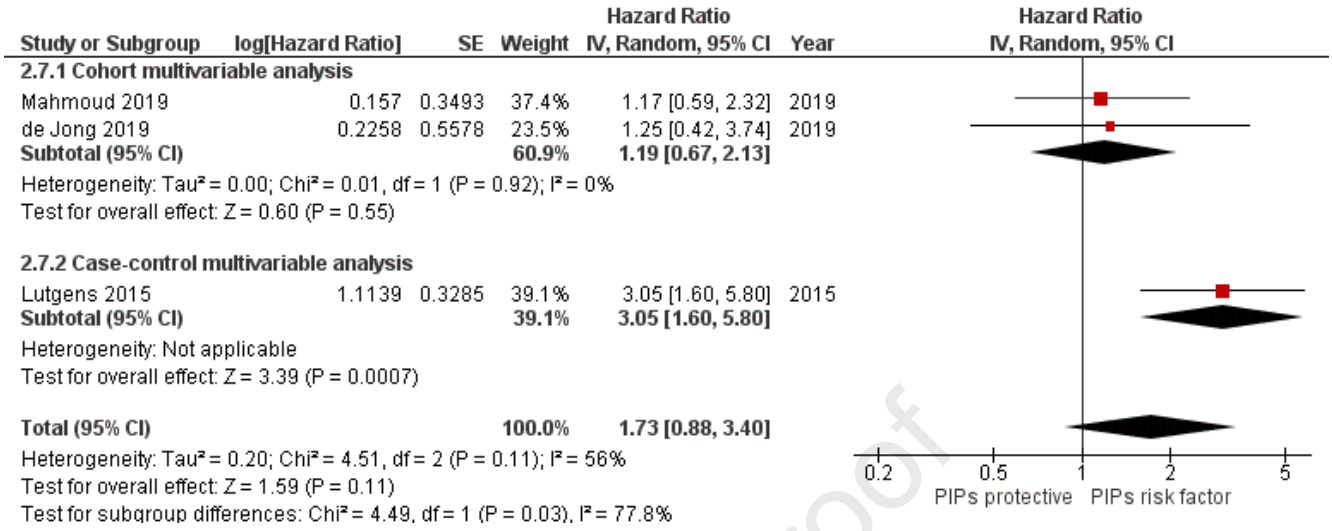


Supplementary Figure 12C: Forest plot Multivariable OR (case-control study)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Velayos 2006	0.9313	0.3035	100.0%	2.54 [1.40, 4.60]	2006
Total (95% CI)			**100.0%**	**2.54 [1.40, 4.60]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 3.07 (P = 0.002)					

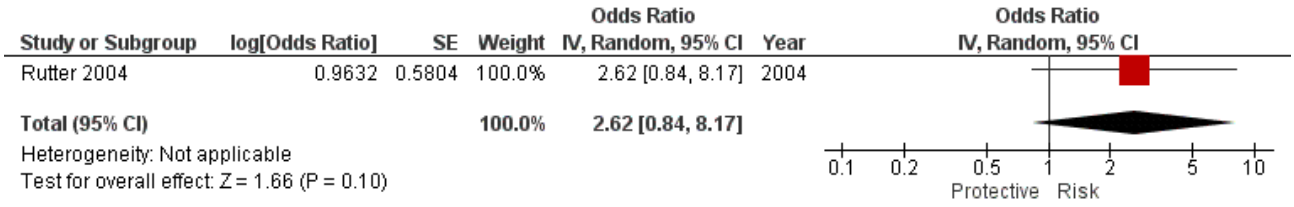


Supplementary Figure 12D: Forest plot of Multivariable analysis HR

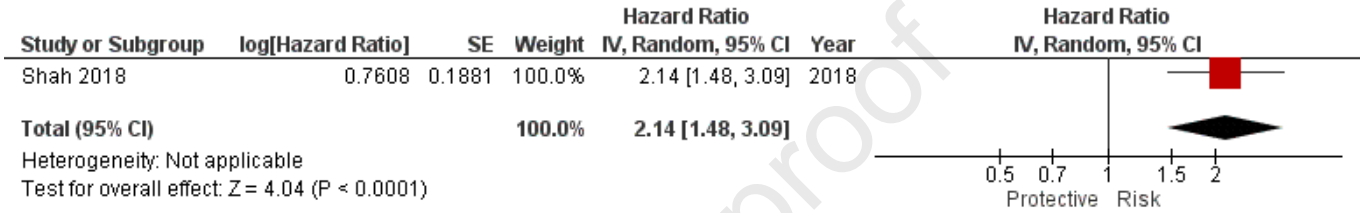


Supplementary file 13A-D Endoscopic inflammation

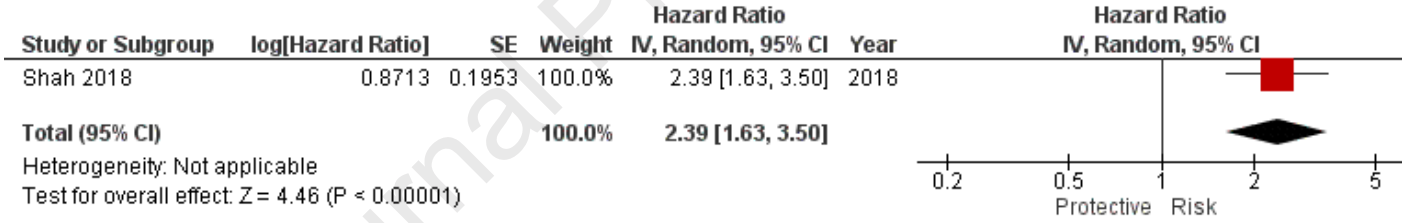
Supplementary Figure 13A: Forest plot of Univariable OR (case-control study)



Supplementary Figure 13B: Forest plot Univariable HR (cohort study)



Supplementary Figure 13C: Forest plot of Multivariable HR (cohort study)



Supplementary Table 13D: Definitions used in studies used in pooled analysis

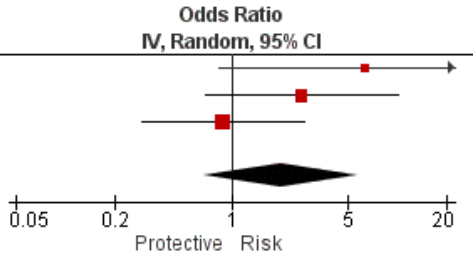
Study, year	Definition	Supplementary figure
Rutter, 2004	Scoring per segment providing a mean endoscopic score (0-4). The mean endoscopic score for all segments of each colonoscopy was calculated and the mean endoscopic score for all surveillance colonoscopies performed in one patient.	13A
Shah, 2018	For each surveillance colonoscopy the severity of active endoscopic inflammation was scored on a 4-point scale for each colonic segment visualized. A mean inflammatory severity score per patient and per colonoscopy was calculated.	13B, 13C

Supplementary file 14A-D Histologic inflammation

Supplementary Figure 14A: Forest plot of Univariable OR (case-control studies)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Rutter 2004	1.8453	1.0305	20.8%	6.33 [0.84, 47.71]	2004
Rubin 2013	0.9708	0.6846	35.9%	2.64 [0.69, 10.10]	2013
Nieminen 2014	-0.1165	0.5721	43.3%	0.89 [0.29, 2.73]	2014
Total (95% CI)			**100.0%**	**1.98 [0.68, 5.73]**	

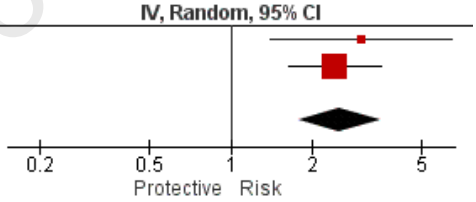
Heterogeneity: Tau² = 0.35; Chi² = 3.31, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 1.26 (P = 0.21)



Supplementary Figure 14B: Forest plot of Univariable HR (cohort studies)

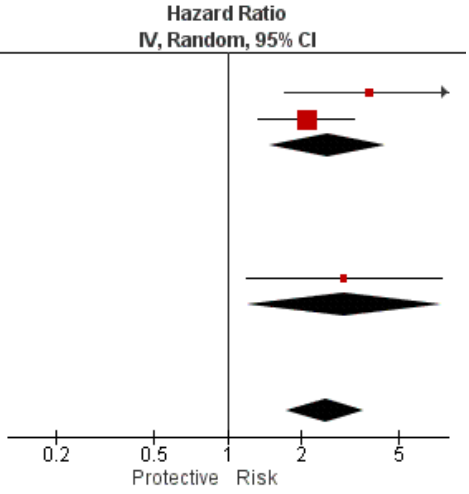
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Gupta 2007	1.0986	0.3889	20.5%	3.00 [1.40, 6.43]	2007
Mahmoud 2019	0.8755	0.1974	79.5%	2.40 [1.63, 3.53]	2019
Total (95% CI)			**100.0%**	**2.51 [1.78, 3.55]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 5.23 (P < 0.00001)



Supplementary Figure 14C: Forest plot of Multivariable analysis HR

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
22.5.1 Cohort multivariable analysis					
Gupta 2007	1.335	0.4104	20.4%	3.80 [1.70, 8.49]	2007
Mahmoud 2019	0.7467	0.2316	63.9%	2.11 [1.34, 3.32]	2019
Subtotal (95% CI)			**84.3%**	**2.57 [1.49, 4.42]**	
Heterogeneity: Tau² = 0.06; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%					
Test for overall effect: Z = 3.40 (P = 0.0007)					
22.5.2 Case-control multivariable analysis					
Gerrits 2011	1.0986	0.4675	15.7%	3.00 [1.20, 7.50]	2011
Subtotal (95% CI)			**15.7%**	**3.00 [1.20, 7.50]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 2.35 (P = 0.02)					
Total (95% CI)			**100.0%**	**2.51 [1.75, 3.61]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.73, df = 2 (P = 0.42); I² = 0%					
Test for overall effect: Z = 4.98 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%					

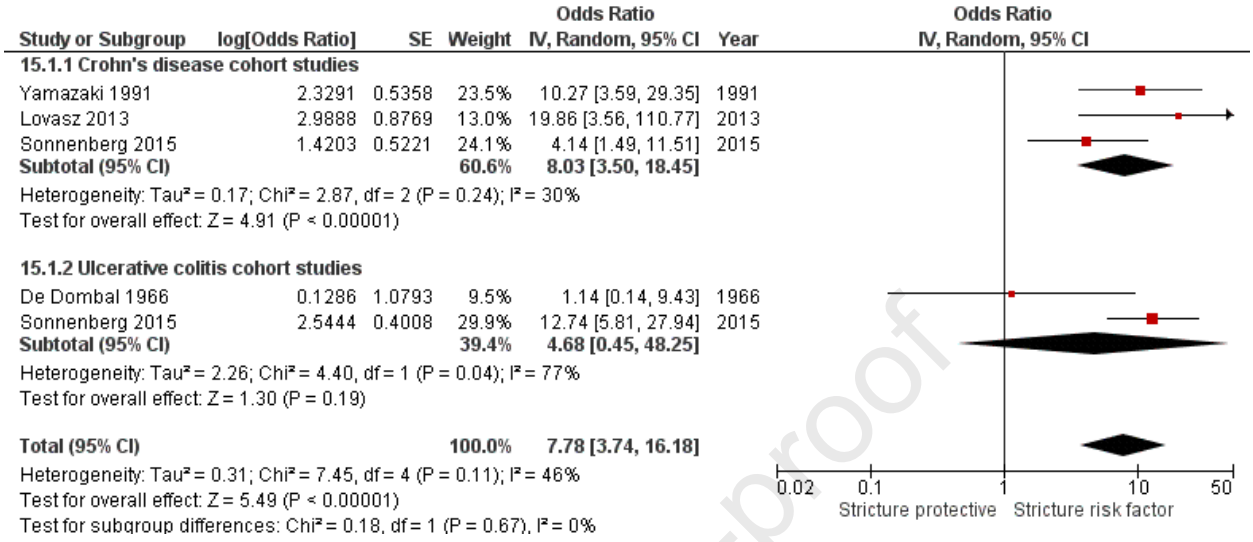


Supplementary Table 14D: Definitions used in studies used in pooled analysis

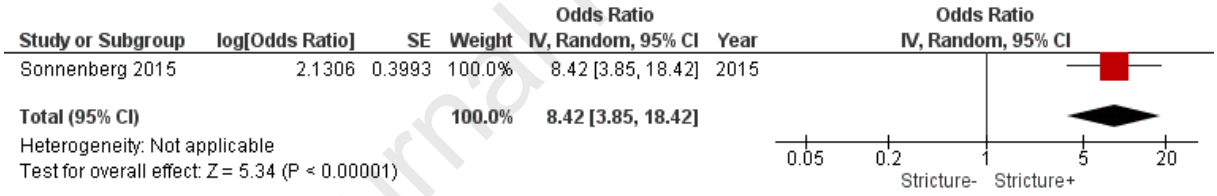
Study, year	Definition	Supplementary figure
Rutter, 2004	Scoring per segment providing a mean histologic score (0-4). The mean histologic score for all segments of each colonoscopy was calculated and the mean histologic score for all surveillance colonoscopies performed in one patient.	14A
Rubin, 2013	6-point histologic inflammatory activity scale (each biopsy taken at each surveillance colonoscopy was taken into account). Two summative inflammation scores were calculated: mean score (average inflammation of each procedure; and the average of all procedure scores) and maximum score (the maximum score for any single biopsy was reported as the maximum score).	14A
Nieminen, 2014	Histological activity of IBD of index patients was based on corresponding endoscopy or operative sample. Score 0-2. The last colonoscopy examination of the control patients served as score for control patients.	14A
Gupta, 2007	'Inflammation summarized in 3 different ways and each included as a time-changing covariate: (1) mean inflammatory score (IS-mean), (2) binary inflammatory score (IS-bin), and (3) maximum inflammatory score (IS-max)'. Scores were documented at biopsy level.	14B, 14C
Mahmoud, 2019	Score 1-5 per segment. A mean inflammation score was calculated by averaging the scores of the most severely inflamed segment of all recorded surveillance colonoscopies.	14B, 14C
Gerrits, 2011	Degree of inflammation was reevaluated by one expert gastrointestinal pathologist using the Geboes scoring system. Patients were classified according to the most severe abnormality present in the biopsy specimens.	14C

Supplementary file 15A-C Stricture

Supplementary Figure 15A: Forest plot of Univariable OR (cohort studies)



Supplementary Figure 15B: Forest plot Multivariable OR (cohort study)

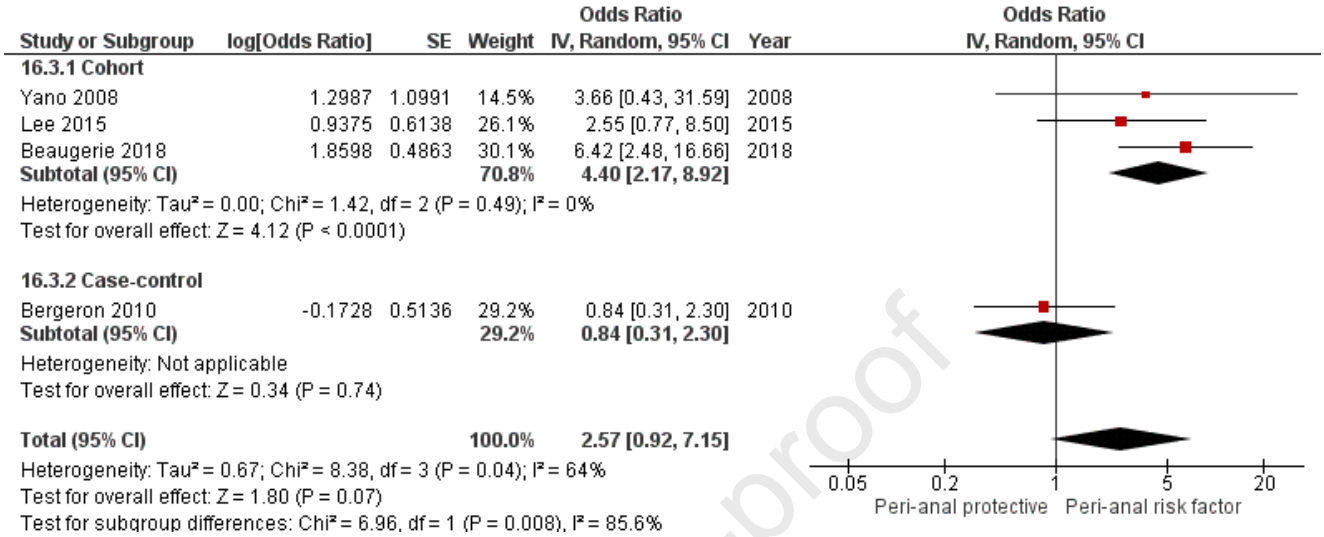


Supplementary Table 15C: Definitions used in studies used in pooled analysis

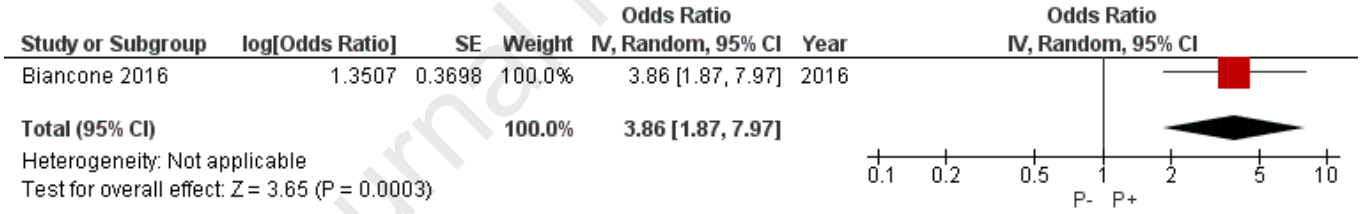
Study, year	Definition	Supplementary figure
Yamazaki, 1991	Fixed and localized colonic narrowing, defined by radiologists, endoscopists, surgeons or pathologists. Strictures were identified as benign or malignant on the basis of radiology and histology.	15A
Lovasz, 2013	Stenosing disease in patients with colonic Crohn's disease. Stenotic lesion seen by endoscopy.	15A
Sonnenberg, 2015	Colonic stricture diagnosed by the endoscopists base on endoscopic appearance.	15A
De Dombal, 1966	Stricture is defined as a constant narrowing of the lumen of the colon or rectum. Diagnosed by barium enema or found upon examination of the bowel after excision.	15A, 15B

Supplementary file 16A-B Perianal disease

Supplementary Figure 16A: Forest plot Univariable analysis OR

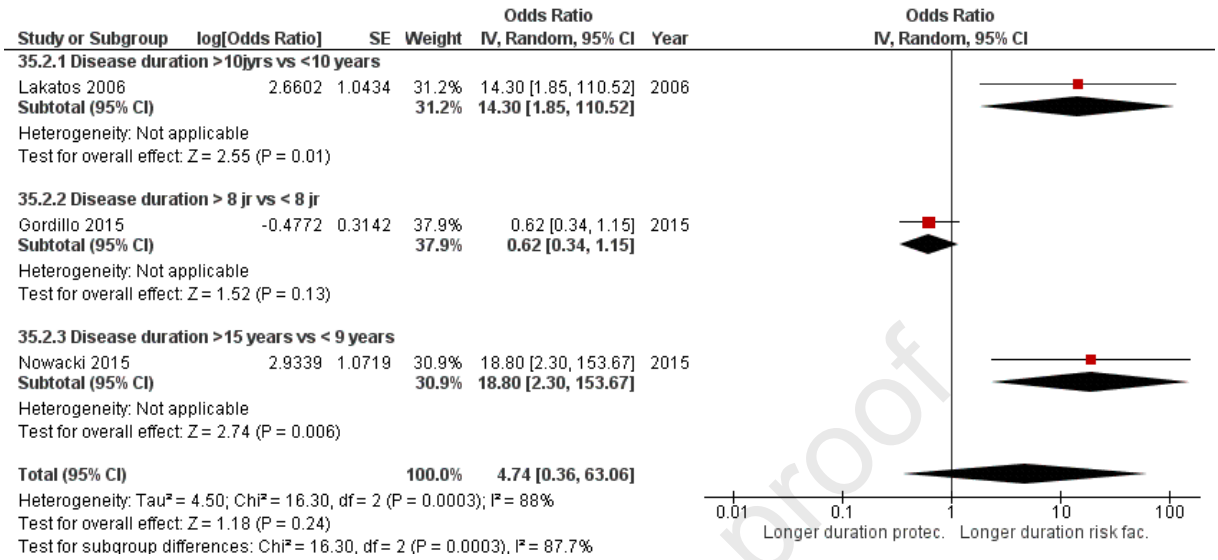


Supplementary Figure 16B: Forest plot Multivariable OR (case-control study)

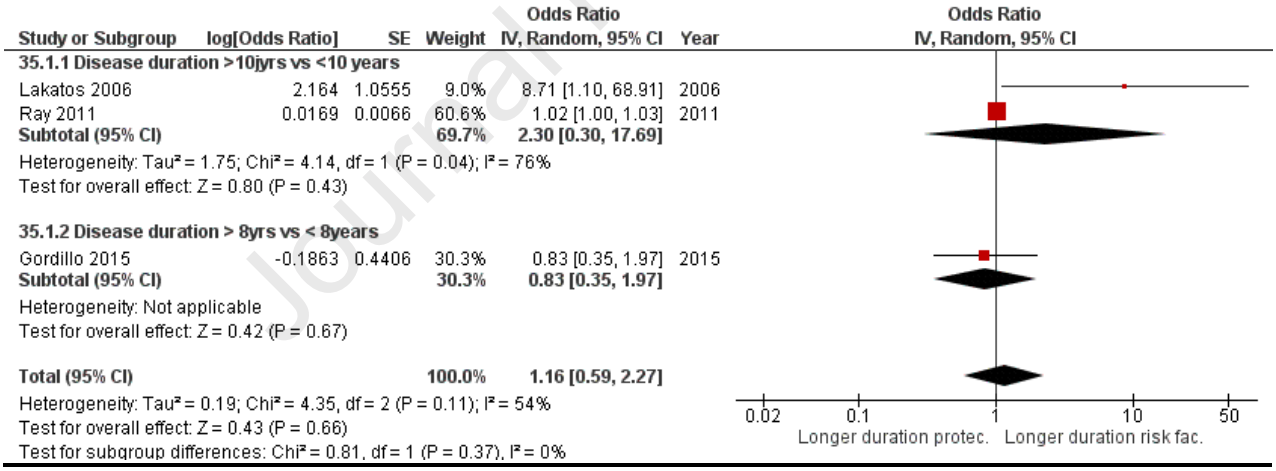


Supplementary file 17A- B Disease duration

Supplementary Figure 17A: Forest plot of Univariable analysis OR , cohort studies

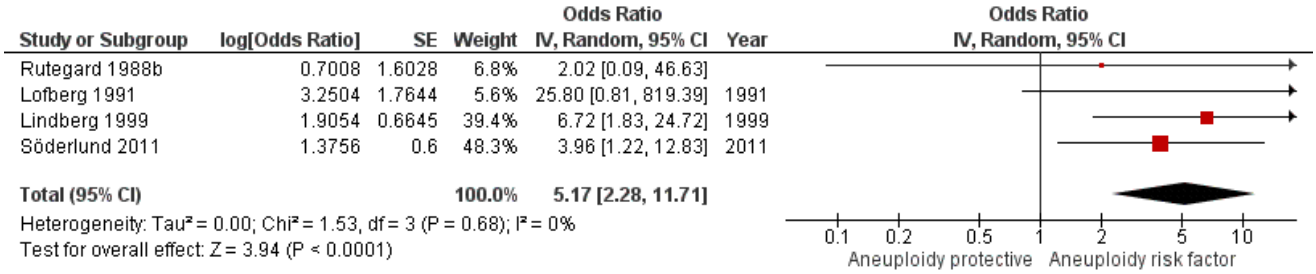


Supplementary Figure 17B: Forest plot of Multivariable analysis OR, cohort studies

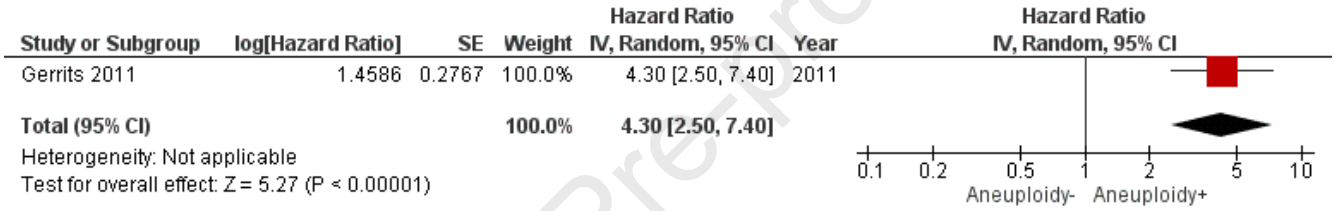


Supplementary file 18A-C Aneuploidy

Supplementary Figure 18A: Forest plot of Univariable OR (cohort studies)



Supplementary Figure 18B: Forest plot of Multivariable HR (case-control study)



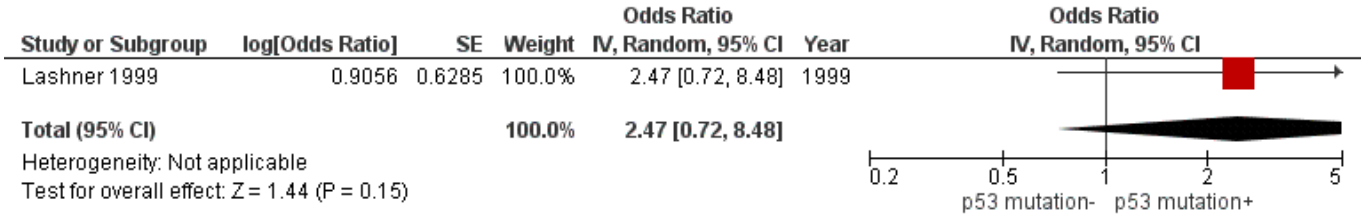
Supplementary Table 18C: Definitions used in studies used in pooled analysis

Study, year	Definition aneuploidy	Supplementary figure
Rutegard 1988	Aneuploidy before HGD or CRC. Biopsy samples with more than one peak in the histogram were judged as aneuploidy	18A
Lofberg 1991	Aneuploidy before HGD or CRC. An aneuploid cell population was considered to be present when, in addition to the diploid peak, another distinct peak in the DNA histogram was observed.	18A
Lindberg 1999	Aneuploidy before HGD or CRC. Samples with more than one peak in the histogram were judged as aneuploid	18A
Söderlund 2011	Aneuploidy (unifocal, unifocal reproducible or extensive) before HGD or CRC. Any DNA aneuploidy findings were classified as unifocal if occurring only once in one fraction, unifocal reproducible if occurring in one fraction but repeatedly in the same fraction over several examinations, and multifocal if occurring in several (at least four fractions).	18A
Gerrits 2011	The DNA index (DI) was calculated as the ratio of the abnormal G0/G1 mean peak channel number to the normal diploid G0/G1 mean peak channel number. Histograms displaying a G0/G1 peak with a coefficient of variation (CV) of 1%≤CV≤10% were included in the analysis.Samples were considered diploid when the	18B

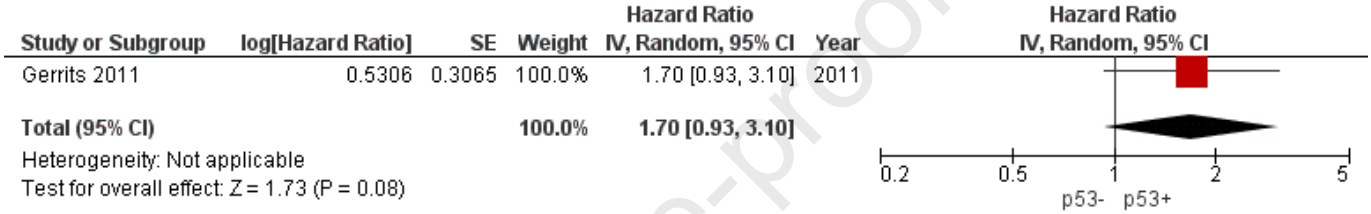
	DNA index was 0.95≤DI≤1.05, near diploid in case of 1.06≤DI≤1.34, and aneuploid in case of a DI >1.34 [11, 32].	

Supplementary file 19A-C P53 mutation

Supplementary Figure 19A: Forest plot Univariable OR (cohort study)



Supplementary Figure 19B: Forest plot Multivariable HR (case-control study)

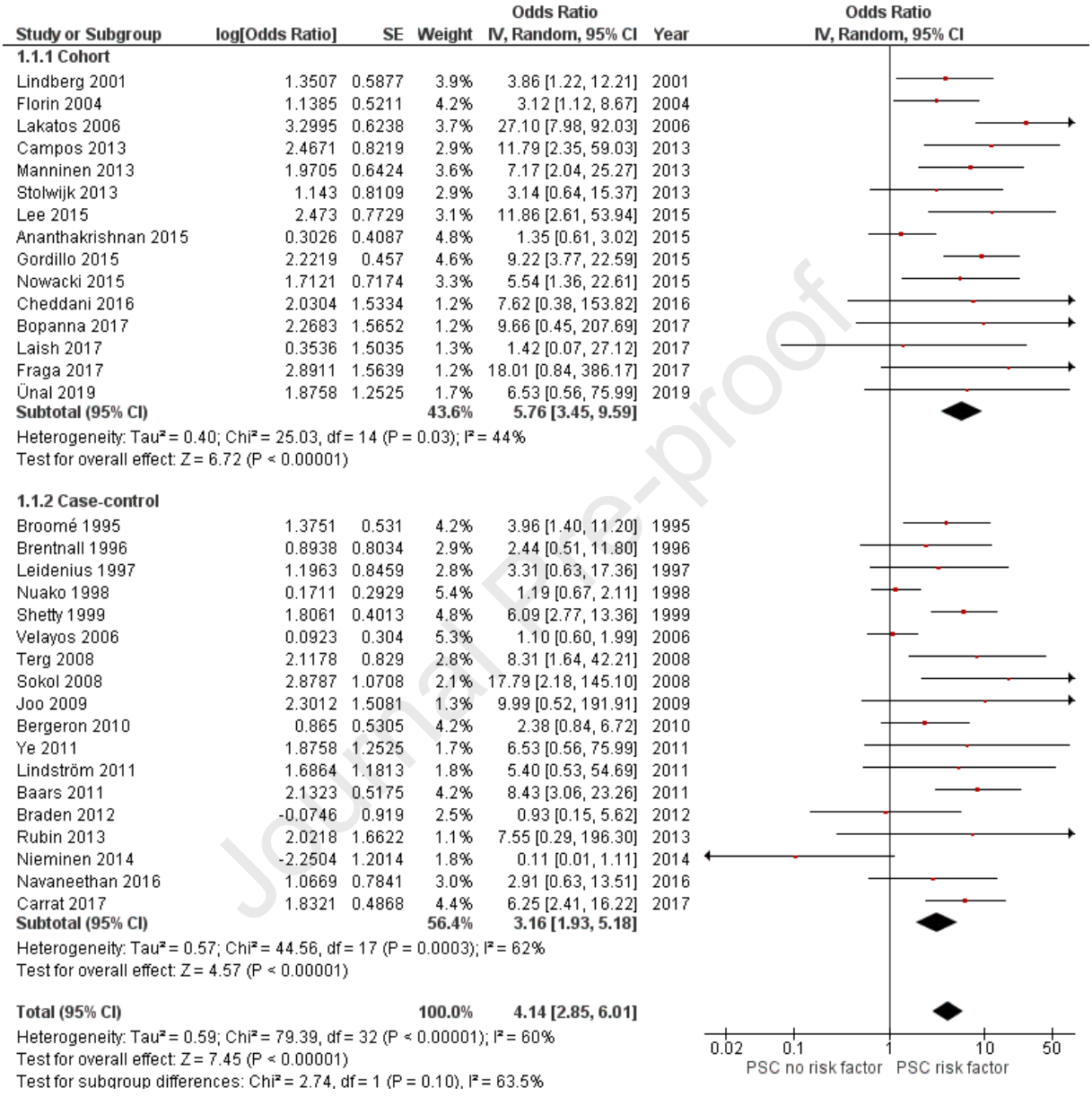


Supplementary Table 19C: Definitions used in studies used in pooled analysis

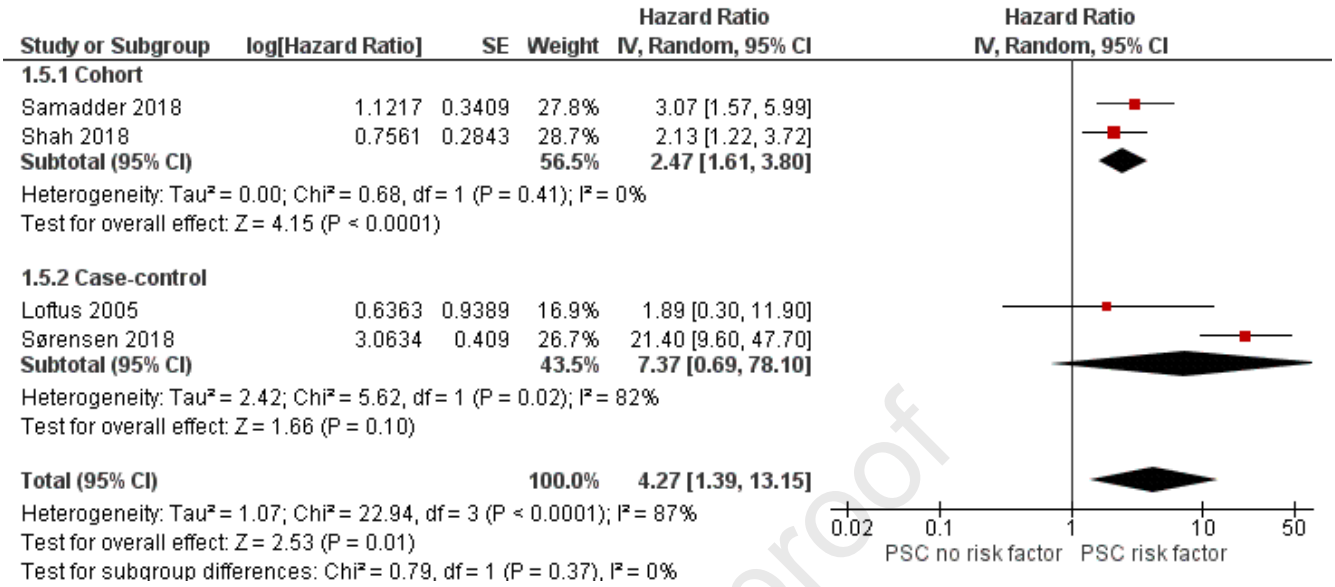
Study, year	Definition P53 mutation	Supplementary figure
Lashner 1999	P53 mutation in colonic biopsy specimens in patients with long standing pancolitis. Risk of cancer in patients with ever p53 versus patients without ever a p53 mutation. Biopsy specimens were considered positive for the p53 mutation if ≥5% of the epithelial cells in a biopsy specimen exhibited dark brown intranuclear staining	19A
Gerrits 2011	Case-control study. Hazard rate in patients with a p 53 mutation in a biopsy specimen, separately calculated at each follow-up moment. Overexpression of p53 was defined as moderate and intense brown staining in >15% of the nucle	19B

Supplementary file 20A-D Primary Sclerosing Cholangitis

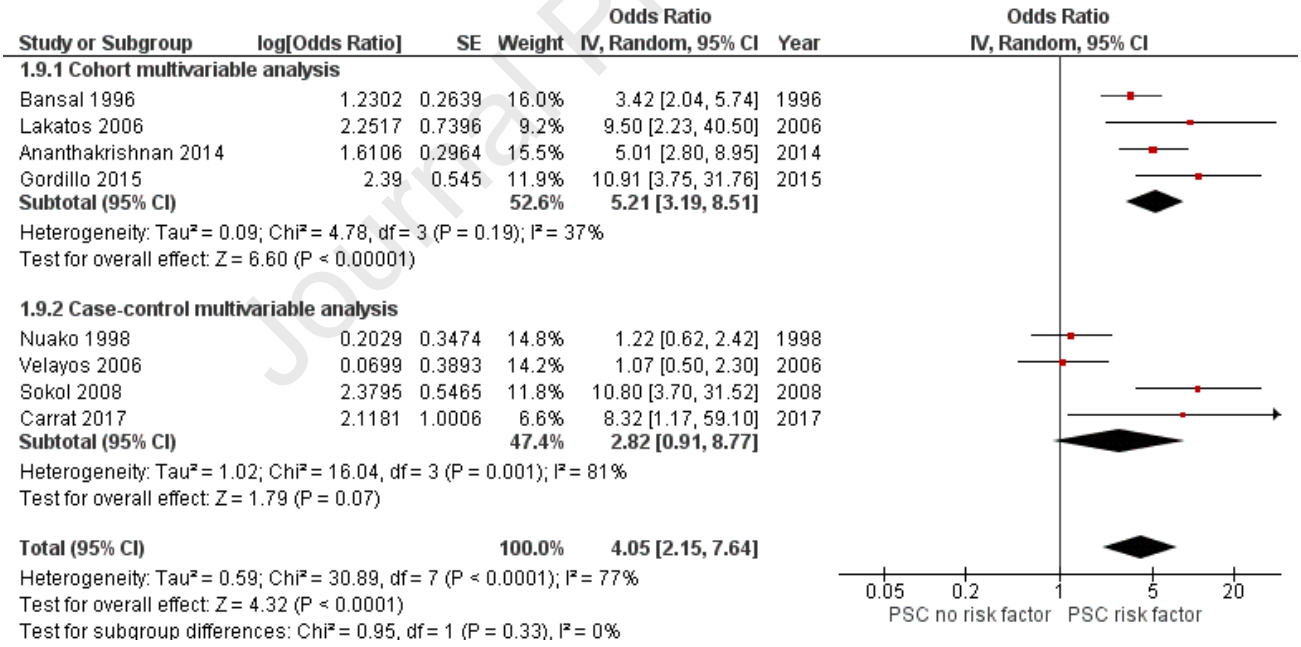
Supplementary Figure 20A: Forest plot of Univariable analysis OR



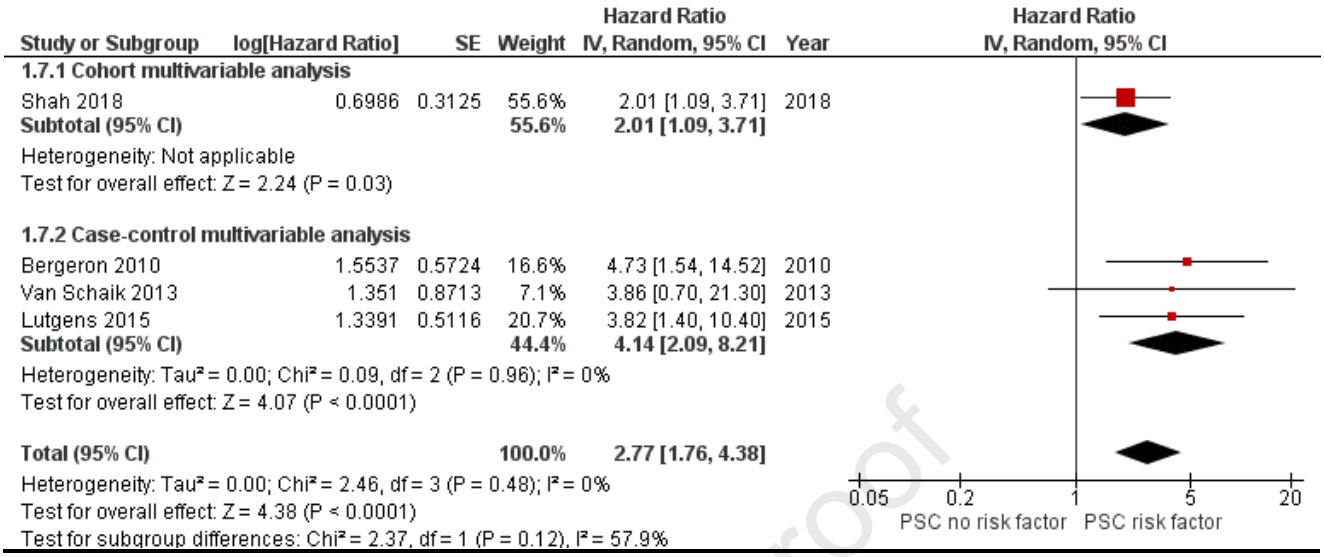
Supplementary Figure 20B: Forest plot of Univariable analysis HR



Supplementary Figure 20C: Forest plot of Multivariable analysis OR

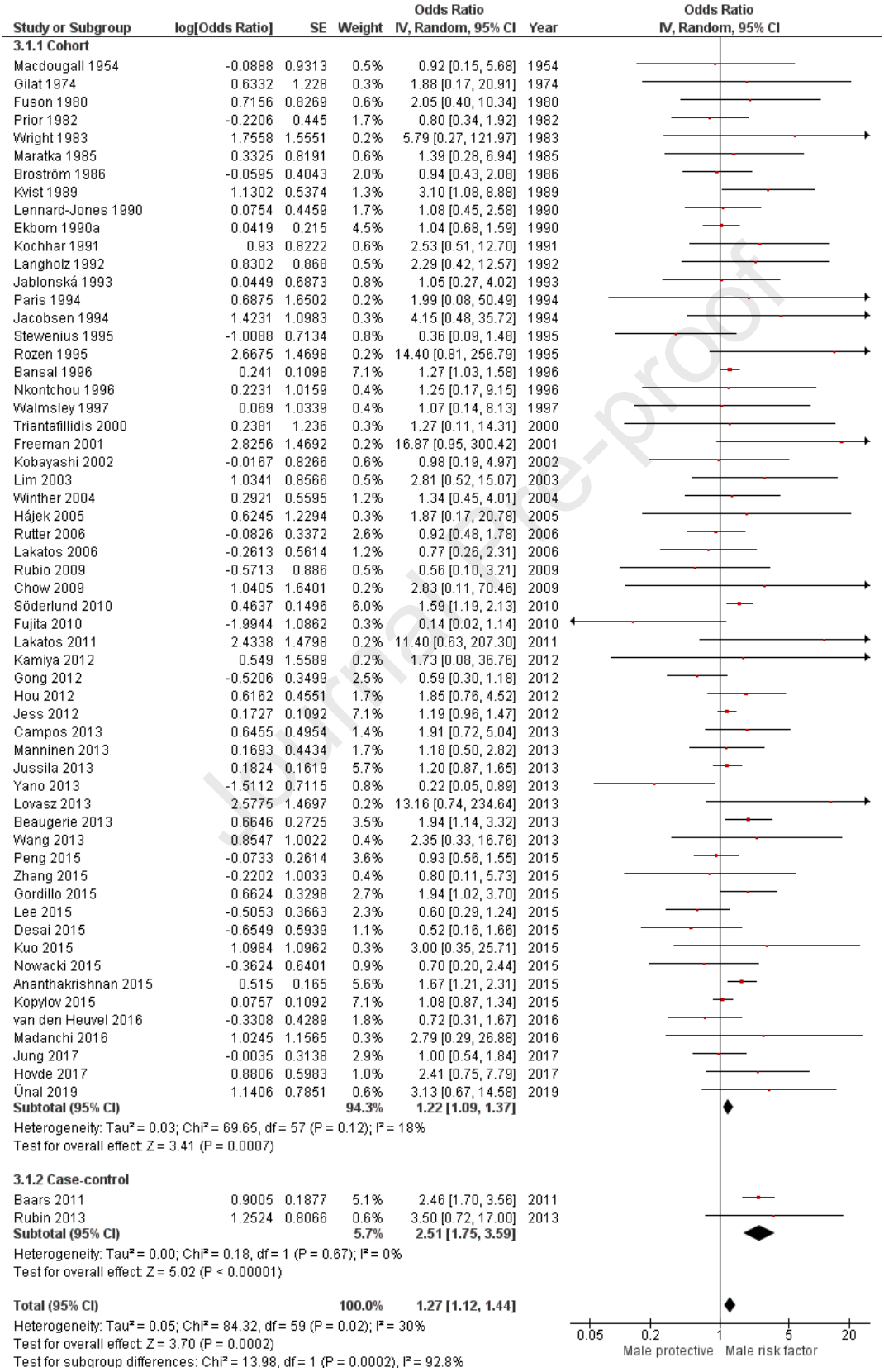


Supplementary Figure 20D: Forest plot of Multivariable analysis HR

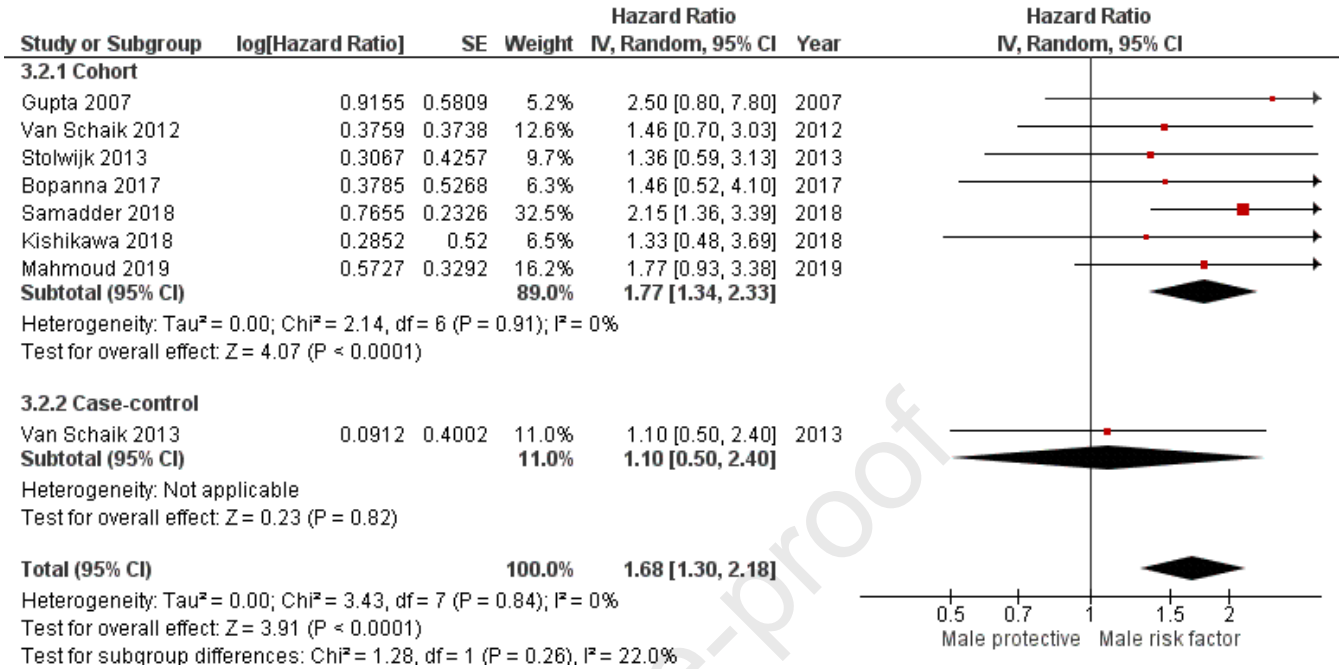


Supplementary file 21A-D Sex

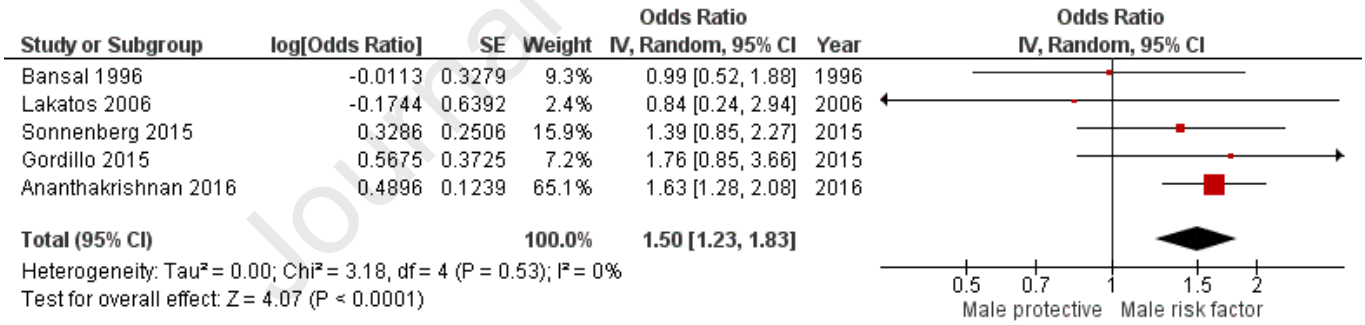
Supplementary Figure 21A: Forest plot of Univariable analysis OR



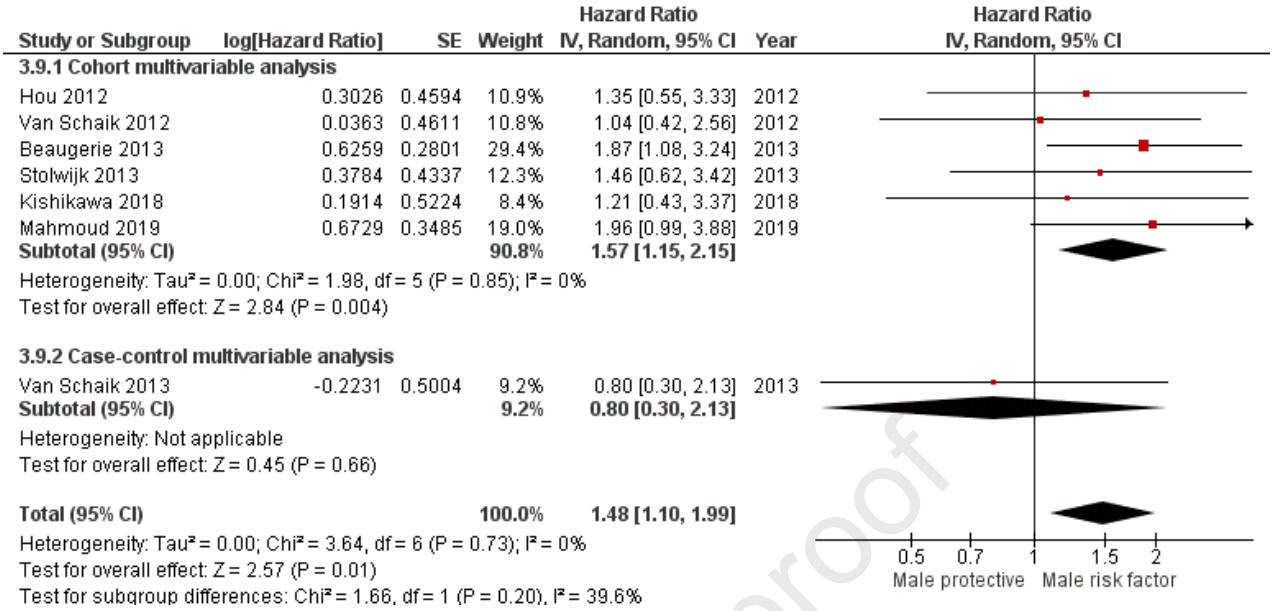
Supplementary Figure 21B: Forest plot of Univariable analysis HR



Supplementary Figure 21C: Forest plot of Multivariable analysis OR (cohort studies)

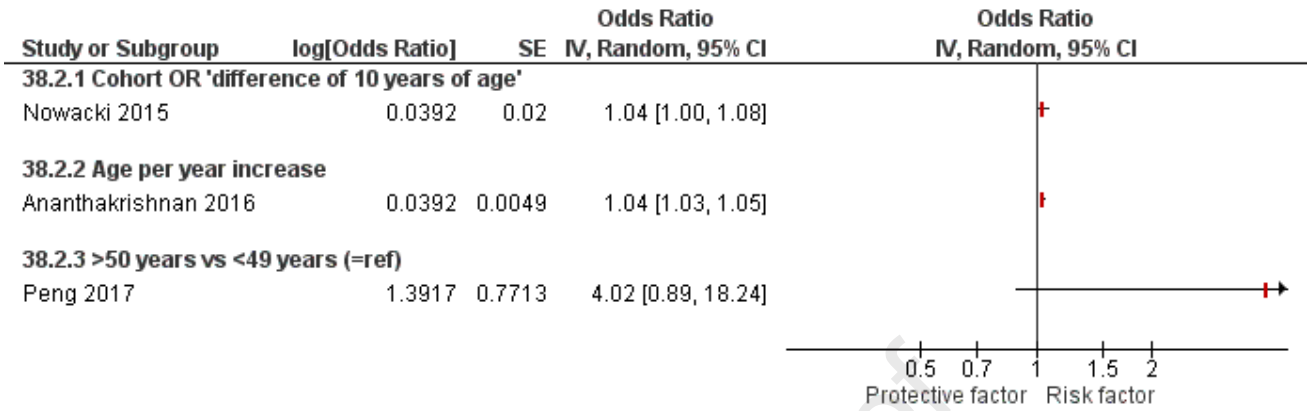


Supplementary Figure 21D: Forest plot of Multivariable analysis HR

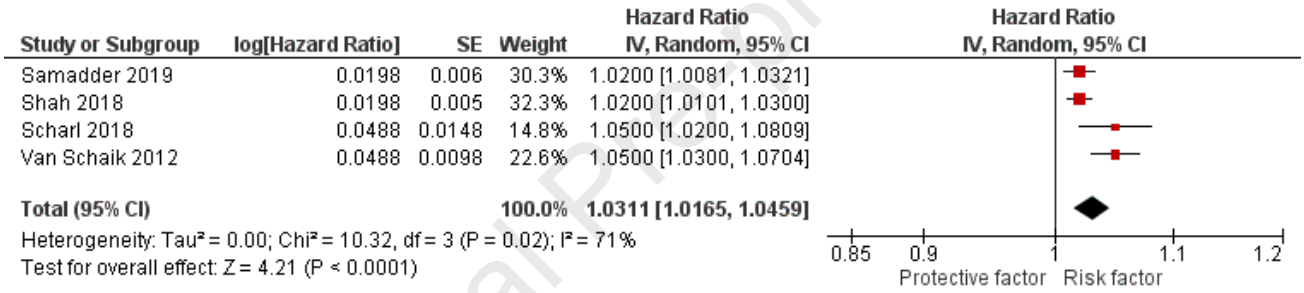


Supplementary file 22A-D Age

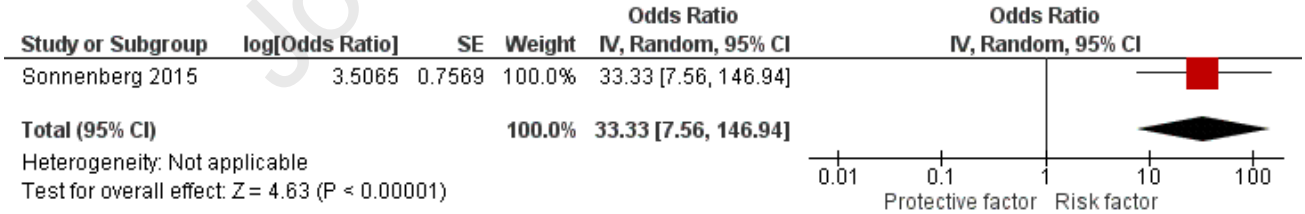
Supplementary Figure 22A: Cohort univariable OR, different age categories/definitions



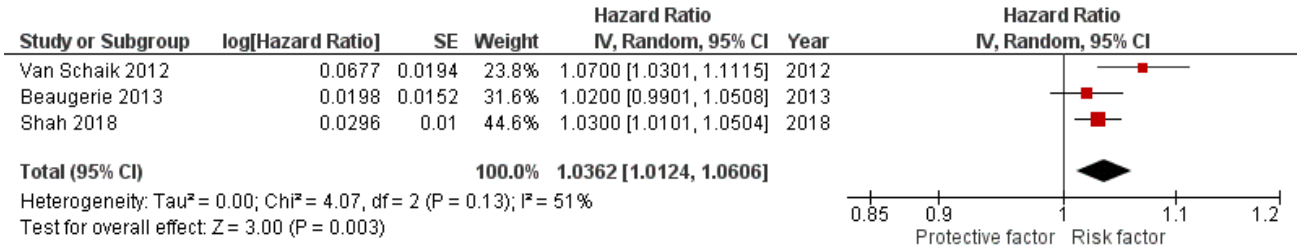
Supplementary Figure 22B: Cohort univariable HR, age per year increase



Supplementary Figure 22C: Cohort multivariable OR, Old age (OR reflects change over the entire age range)



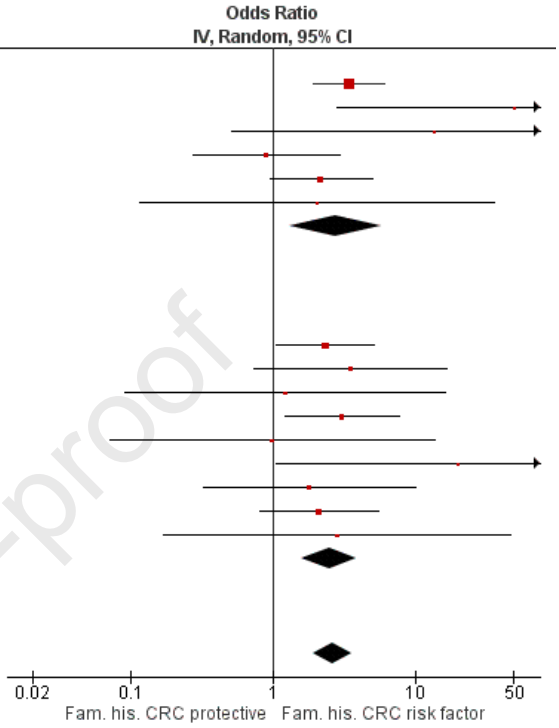
Supplementary Figure 22D: Cohort multivariable HR, age per year increase



Supplementary file 23A-E Family history of colorectal carcinoma

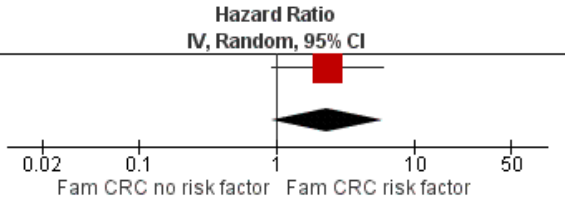
Supplementary Figure 23A: Forest plot of Univariable analysis OR

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
8.1.1 Cohort					
Askling 2001	1.231	0.2941	28.4%	3.42 [1.92, 6.09]	2001
Fujita 2010	3.9318	1.4731	1.1%	51.00 [2.84, 915.09]	2010
Kamiya 2012	2.613	1.6751	0.9%	13.64 [0.51, 363.63]	2012
Gordillo 2015	-0.1092	0.613	6.5%	0.90 [0.27, 2.98]	2015
Samadder 2018	0.7745	0.4255	13.6%	2.17 [0.94, 5.00]	2018
Ünal 2019	0.7134	1.4659	1.1%	2.04 [0.12, 36.11]	2019
Subtotal (95% CI)			**51.7%**	**2.76 [1.32, 5.77]**	
Heterogeneity: Tau² = 0.32; Chi² = 9.10, df = 5 (P = 0.11); I² = 45%					
Test for overall effect: Z = 2.69 (P = 0.007)					
8.1.2 Case-control					
Nuako 1998a	0.8477	0.4028	15.2%	2.33 [1.06, 5.14]	1998
Eaden 2000	1.2528	0.7997	3.8%	3.50 [0.73, 16.78]	2000
Rutter 2004	0.1989	1.33	1.4%	1.22 [0.09, 16.54]	2004
Velayos 2006	1.1118	0.4742	10.9%	3.04 [1.20, 7.70]	2006
Siegel 2006	-0.0173	1.348	1.4%	0.98 [0.07, 13.80]	2006
Bergeron 2010	3.01	1.507	1.1%	20.29 [1.06, 389.03]	2010
Tang 2010	0.5878	0.8777	3.2%	1.80 [0.32, 10.05]	2010
Baars 2011	0.745	0.4939	10.1%	2.11 [0.80, 5.55]	2011
Rubin 2013	1.0402	1.4348	1.2%	2.83 [0.17, 47.10]	2013
Subtotal (95% CI)			**48.3%**	**2.49 [1.60, 3.87]**	
Heterogeneity: Tau² = 0.00; Chi² = 3.34, df = 8 (P = 0.91); I² = 0%					
Test for overall effect: Z = 4.04 (P < 0.0001)					
Total (95% CI)			**100.0%**	**2.62 [1.93, 3.57]**	
Heterogeneity: Tau² = 0.00; Chi² = 12.54, df = 14 (P = 0.56); I² = 0%					
Test for overall effect: Z = 6.14 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%					

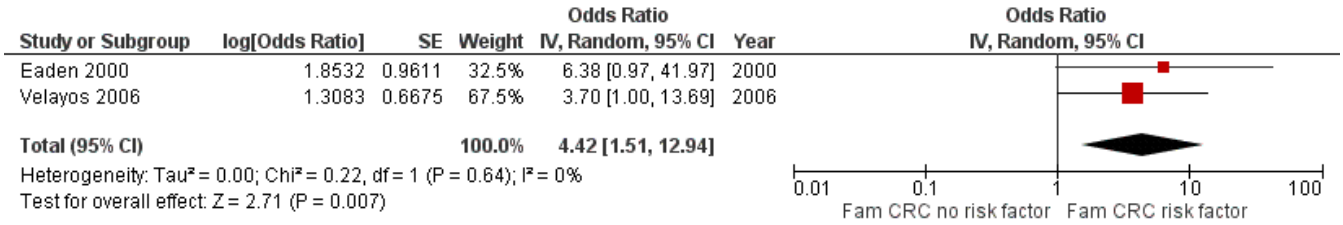


Supplementary Figure 23B: Forest plot of Univariable analysis HR cohort study

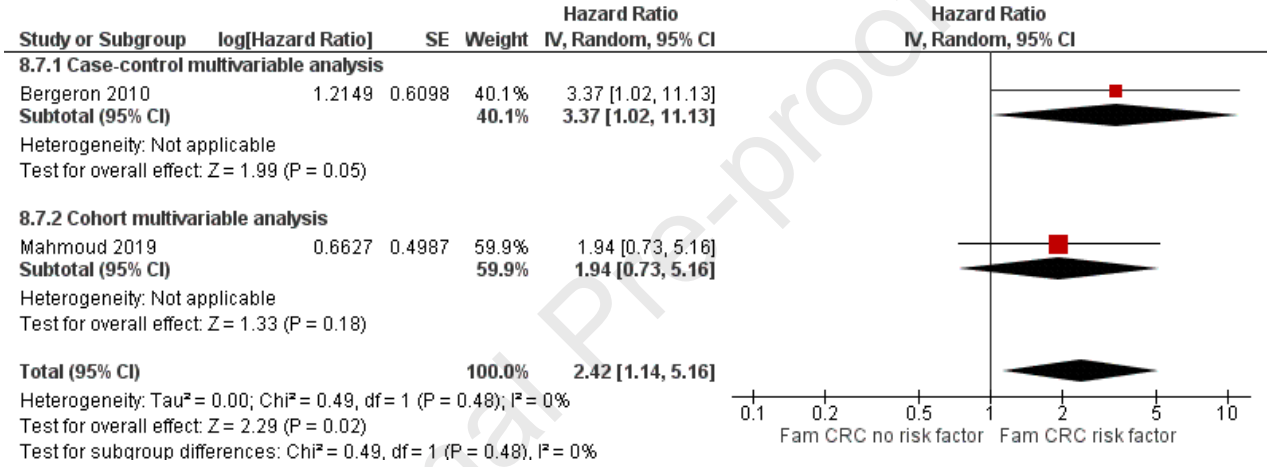
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Mahmoud 2019	0.8412	0.4773	100.0%	2.32 [0.91, 5.91]
Total (95% CI)			**100.0%**	**2.32 [0.91, 5.91]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.76 (P = 0.08)				



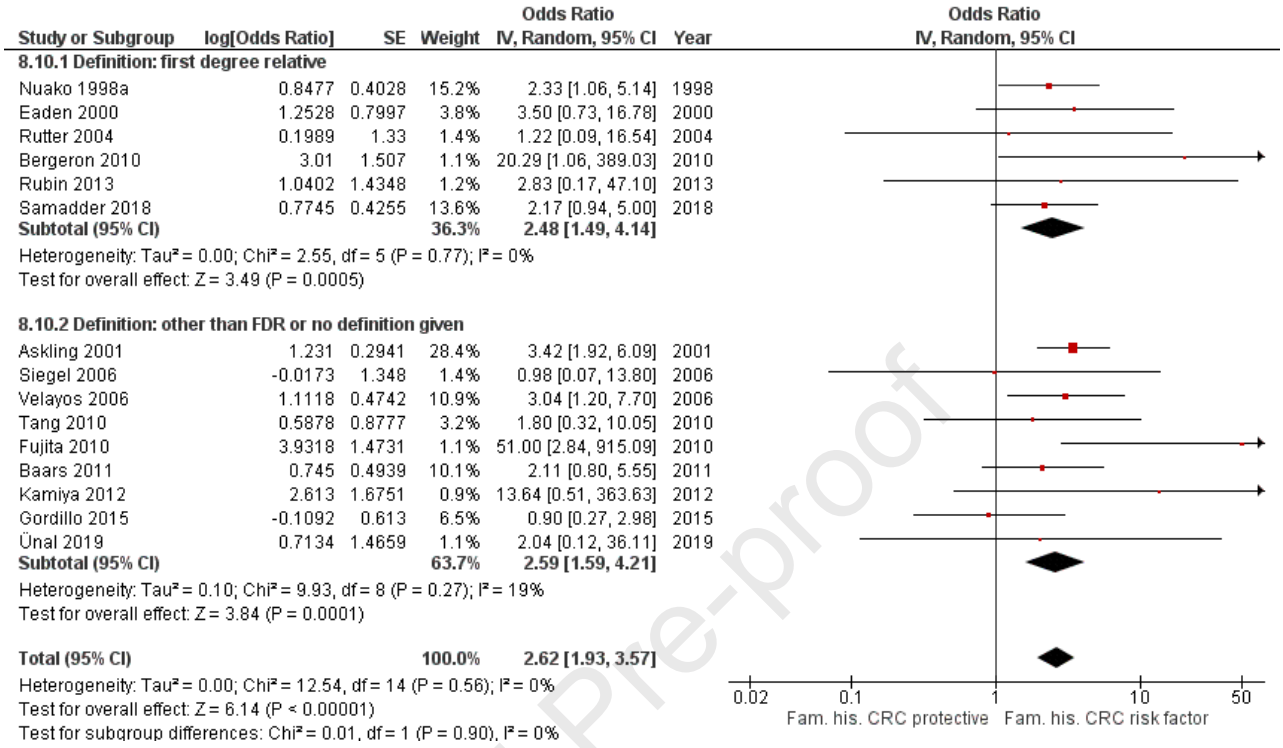
Supplementary Figure 23C: Forest plot of Multivariable analysis OR case-control studies



Supplementary Figure 23D: Forest plot of Multivariable analysis HR

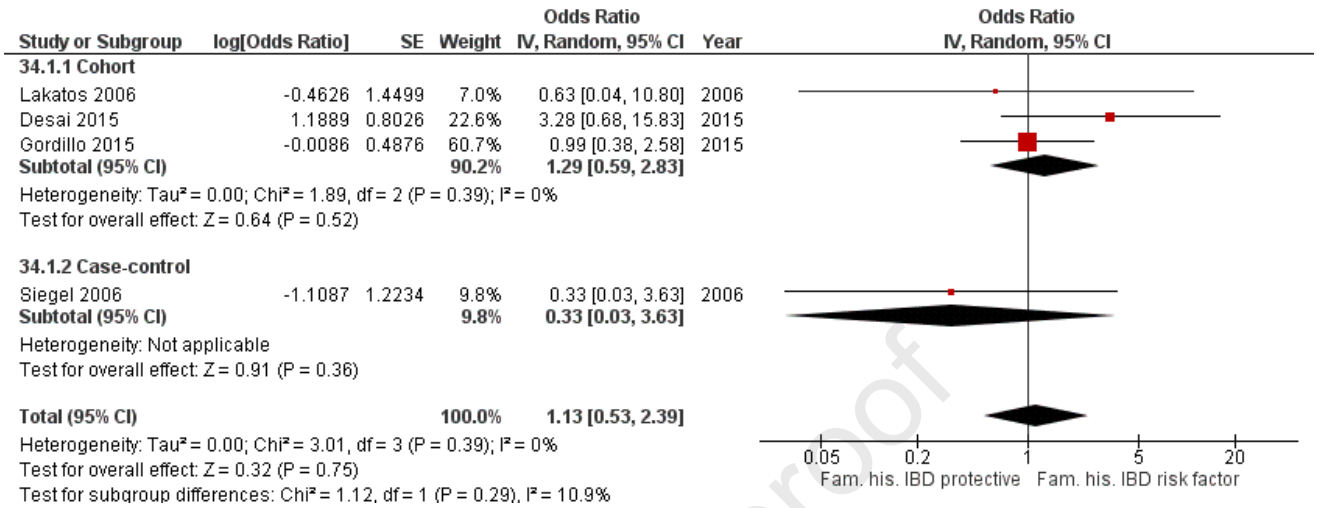


Supplementary Figure 23E: Forest plot of Univariable analysis cohort and case-control OR (separated for first-degree relative and any relative)



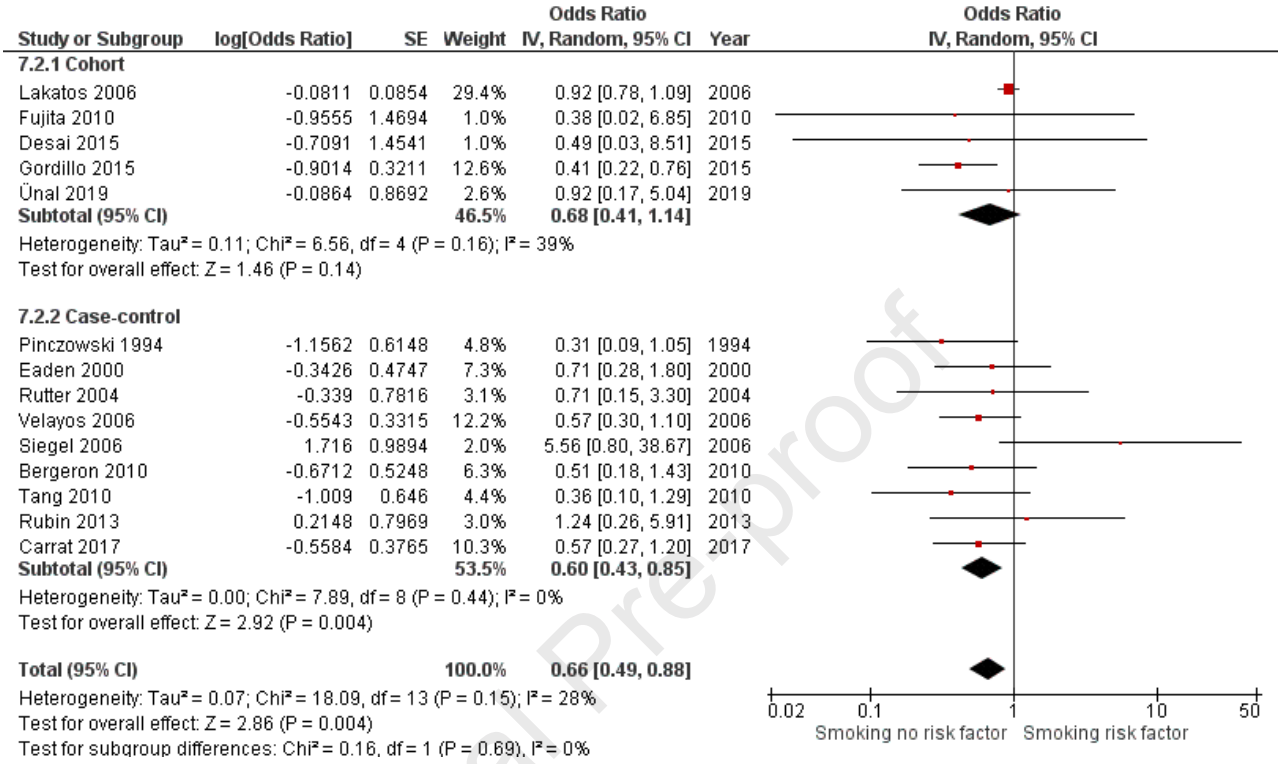
Supplementary file 24A Family history of IBD

Supplementary Figure 24A: Forest plot of Univariable analysis OR

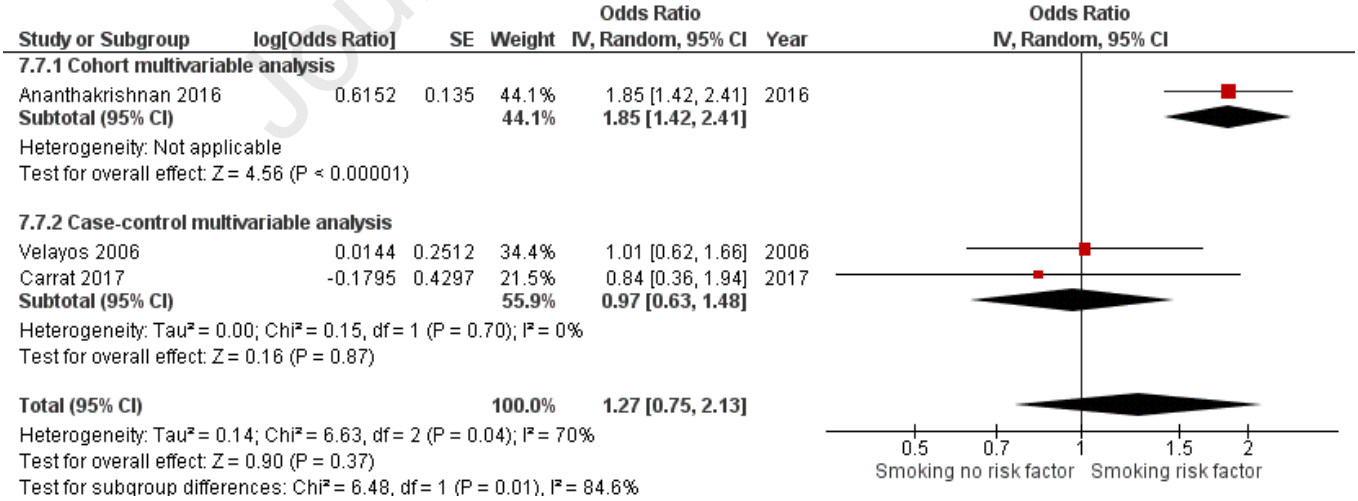


Supplementary 25A-C Smoking

Supplementary Figure 25A: Forest plot of Univariable analysis OR



Supplementary Figure 25B: Forest plot of Multivariable analysis OR



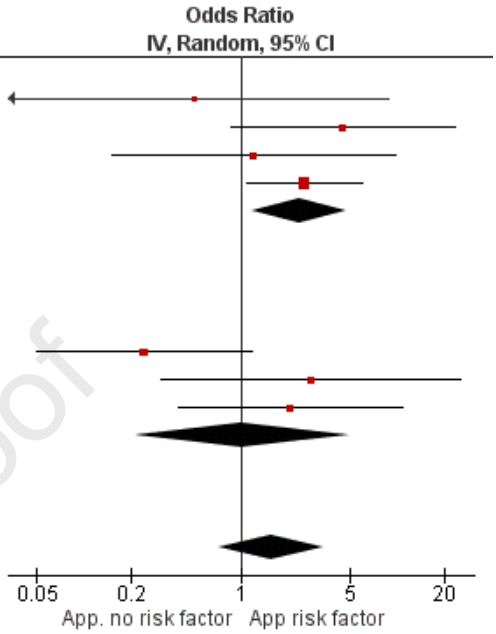
Study, year	Definition smoking	Supplementary figure
Lakatos 2016	Yes and previous smoking versus never smoking	25A
Fujita 2010	Yes and previous smoking versus never smoking	25A
Desai 2015	History of smoking versus no history of smoking	25A
Gordillo 2015	History of smoking versus no history of smoking	25A
Unal 2019	Currently smoking and former smoker versus non-smoker	25A
Pinczowski 1994	Ever having smoked versus no known history of smoking	25A
Eaden 2000	Smoking history at moment of UC diagnosis	25A
Rutter 2004	Smoked since onset of colitis versus not smoked from moment of onset of colitis	25A
Velayos 2006	Current smoker and ex-smoker versus nonsmoker	25A + 25B
Siegel 2006	History of smoking versus no history of smoking	25A
Bergeron 2010	Smoking during the 5 years before neoplasia or censoring	25A
Tang 2010	Current and former smoking versus non-smoker	25A
Rubin 2013	Ever smoked versus non-smoker	25A
Ananthakrishnan 2016	Ever smoked versus non-smoker	25B
Carrat 2017	Active smoking versus not active smoking	25B

Supplementary Table 25C: Definitions used in studies used in pooled analysis

Supplementary file 26A-B Appendectomy

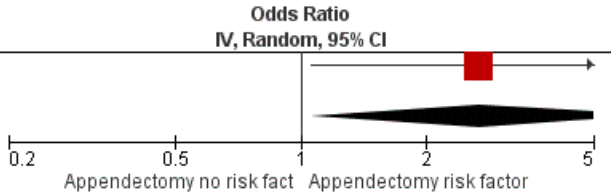
Supplementary Figure 26A: Forest plot of Univariable analysis OR

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
9.1.1 Cohort					
Cosnes 2002	-0.677	1.4522	6.3%	0.51 [0.03, 8.75]	2002
Florin 2004	1.505	0.8399	14.7%	4.50 [0.87, 23.36]	2004
Lakatos 2006	0.1901	1.0649	10.5%	1.21 [0.15, 9.75]	2006
Gordillo 2015	0.9352	0.4352	28.6%	2.55 [1.09, 5.98]	2015
Subtotal (95% CI)			**60.1%**	**2.36 [1.18, 4.71]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 3 (P = 0.54); I² = 0%					
Test for overall effect: Z = 2.44 (P = 0.01)					
9.1.2 Case-control					
Siegel 2006	-1.4194	0.8043	15.6%	0.24 [0.05, 1.17]	2006
Radford-Smith 2011	1.0332	1.1196	9.7%	2.81 [0.31, 25.22]	2011
Picazo-Ferrera 2011	0.7351	0.842	14.7%	2.09 [0.40, 10.86]	2011
Subtotal (95% CI)			**39.9%**	**1.02 [0.21, 4.97]**	
Heterogeneity: Tau² = 1.12; Chi² = 4.70, df = 2 (P = 0.10); I² = 57%					
Test for overall effect: Z = 0.03 (P = 0.98)					
Total (95% CI)			**100.0%**	**1.57 [0.72, 3.41]**	
Heterogeneity: Tau² = 0.36; Chi² = 9.13, df = 6 (P = 0.17); I² = 34%					
Test for overall effect: Z = 1.14 (P = 0.25)					
Test for subgroup differences: Chi² = 0.90, df = 1 (P = 0.34), I² = 0%					



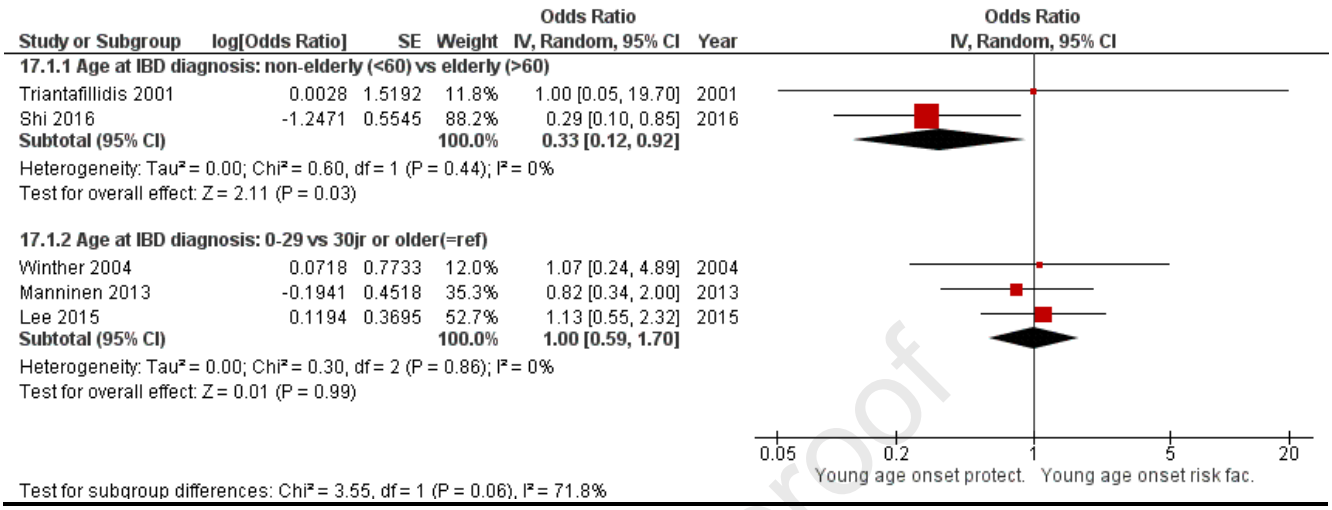
Supplementary Figure 26B: Forest plot of Multivariable OR cohort study

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Gordillo 2015	0.9783	0.4694	100.0%	2.66 [1.06, 6.67]
Total (95% CI)			**100.0%**	**2.66 [1.06, 6.67]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.08 (P = 0.04)				

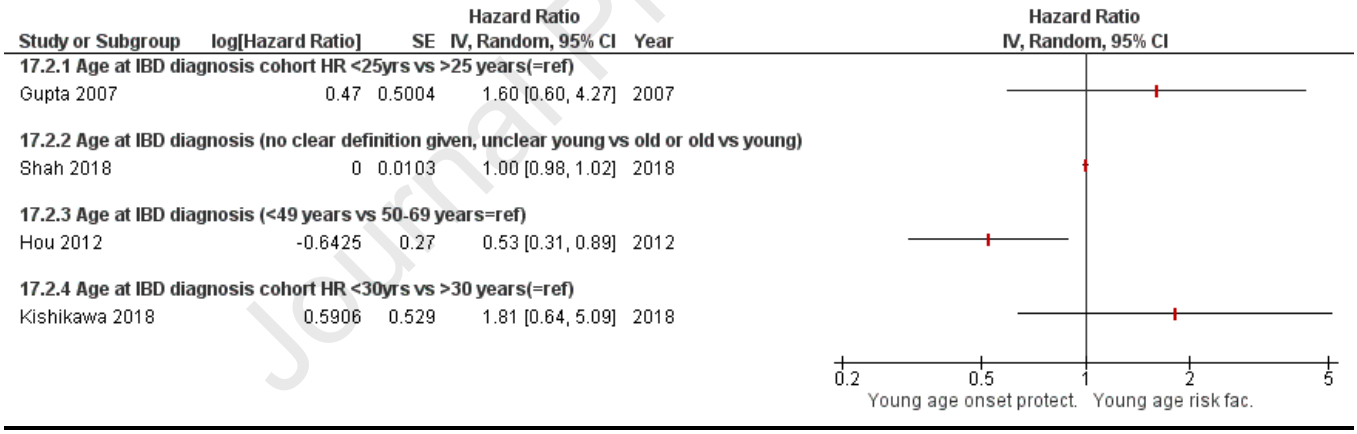


Supplementary file 27A-G Age at IBD diagnosis

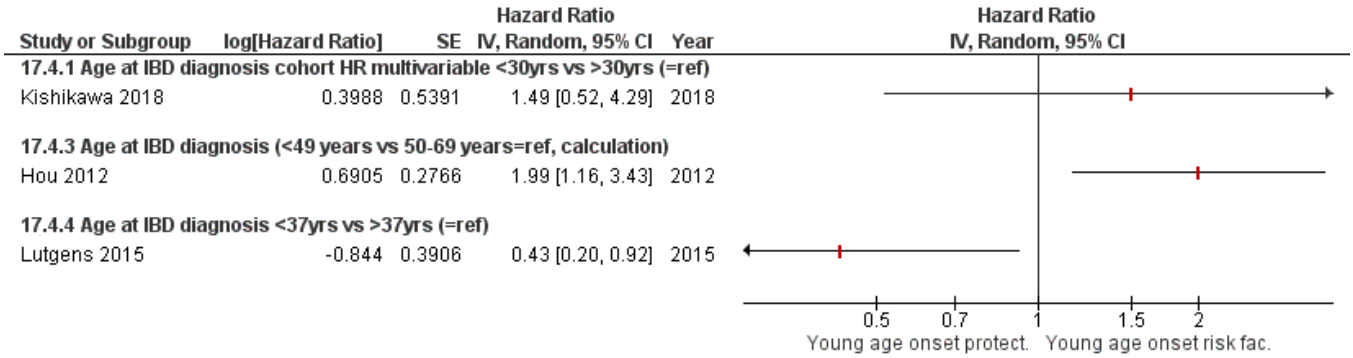
Supplementary Figure 27A: Forest plot of Univariable analysis OR, cohort studies



Supplementary Figure 27B: Forest plot of Univariable analysis HR, cohort studies

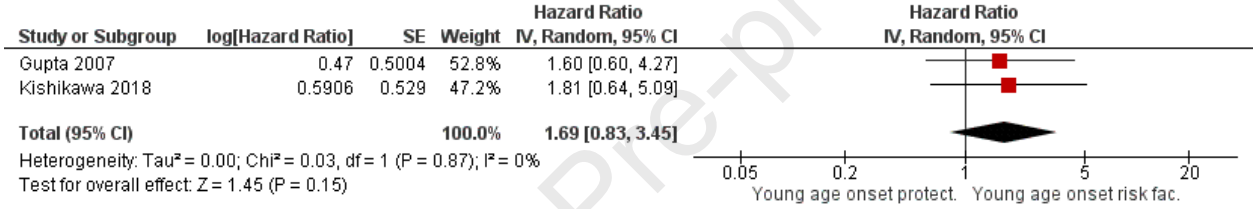


Supplementary Figure 27C: Forest plot of Multivariable analysis HR , cohort studies



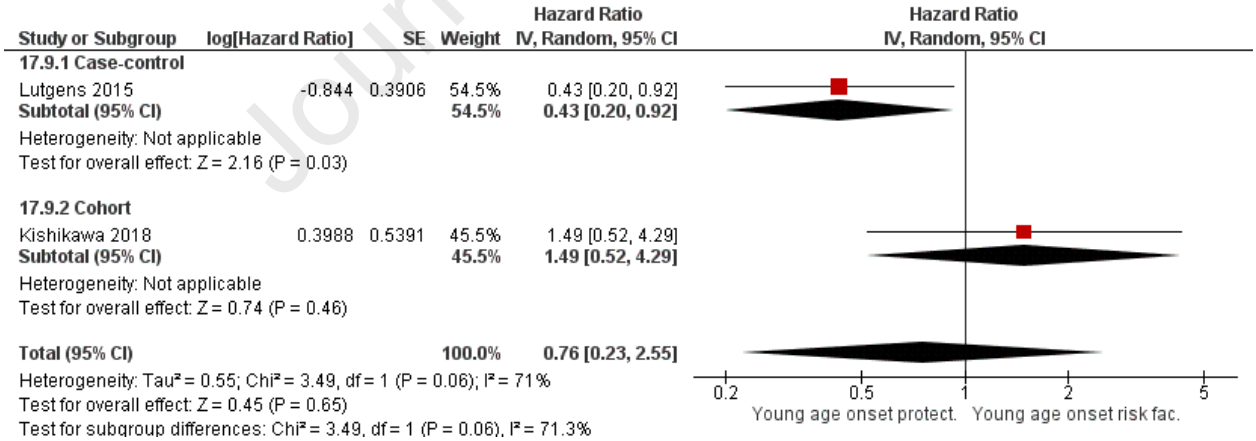
Supplementary Figure 27D: Forest plot of Univariable analysis HR cohort studies

(definition: <25/30 years versus >25/30 years, see definitions above)

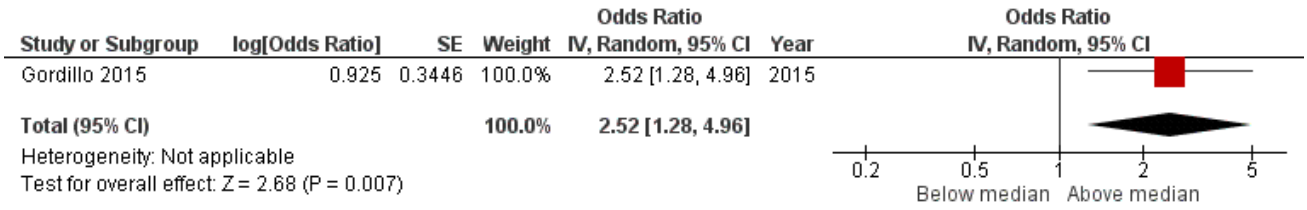


Supplementary Figure 27E: Forest plot of Multivariable analysis HR studies

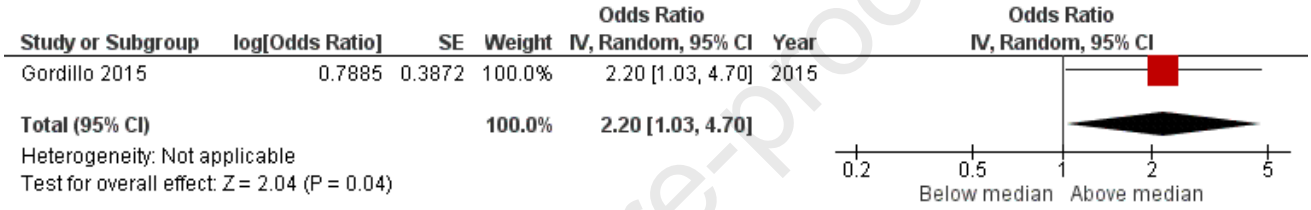
(definition: <30/37 years versus >30/37 years, see definitions above)



Supplementary Figure 27F: Forest plot of age at UC diagnosis above versus below median of study (univariable)



Supplementary Figure 27G: Forest plot of age at UC diagnosis above versus below median of study (multivariable)

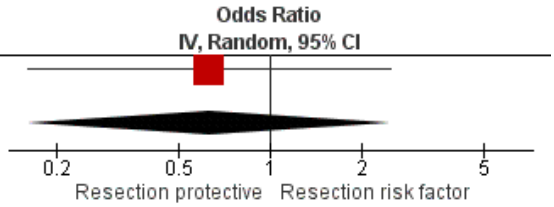


Supplementary file 28A-D Colon segment resection

Supplementary Figure 28A: Forest plot of Univariable OR case-control studies

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Siegel 2006	-0.462	0.6993	100.0%	0.63 [0.16, 2.48]	2006
Total (95% CI)			**100.0%**	**0.63 [0.16, 2.48]**	

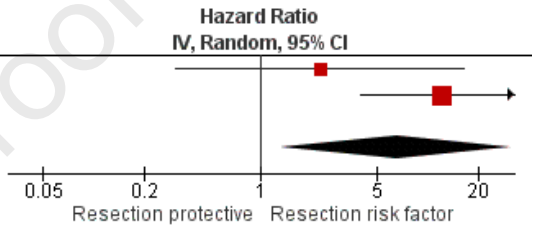
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



Supplementary Figure 28B: Forest plot of Univariable HR cohort studies

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Van Schaik 2012	0.8198	1.0158	37.5%	2.27 [0.31, 16.62]	2012
Scharl 2018	2.4929	0.574	62.5%	12.10 [3.93, 37.26]	2018
Total (95% CI)			**100.0%**	**6.46 [1.32, 31.61]**	

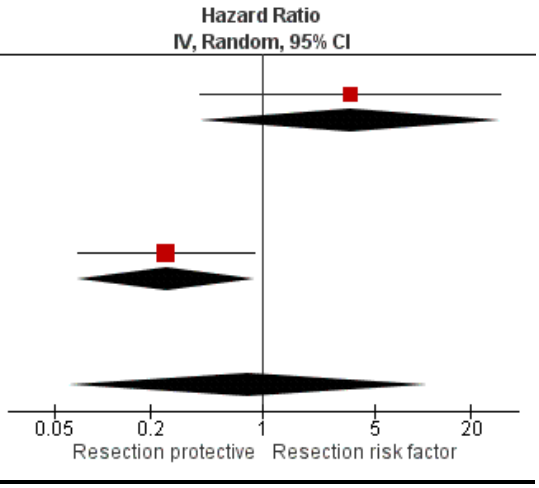
Heterogeneity: Tau² = 0.72; Chi² = 2.06, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 2.30 (P = 0.02)



Supplementary Figure 28C: Forest plot of Multivariable analysis HR

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
18.4.1 Cohort multivariable analysis					
Van Schaik 2012	1.2641	1.0999	44.4%	3.54 [0.41, 30.57]	2012
Subtotal (95% CI)			**44.4%**	**3.54 [0.41, 30.57]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 1.15 (P = 0.25)					
18.4.2 Case-control multivariable analysis					
Bergeron 2010	-1.3863	0.6495	55.6%	0.25 [0.07, 0.89]	2010
Subtotal (95% CI)			**55.6%**	**0.25 [0.07, 0.89]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 2.13 (P = 0.03)					
Total (95% CI)			**100.0%**	**0.81 [0.06, 10.71]**	

Heterogeneity: Tau² = 2.70; Chi² = 4.31, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Chi² = 4.31, df = 1 (P = 0.04), I² = 76.8%

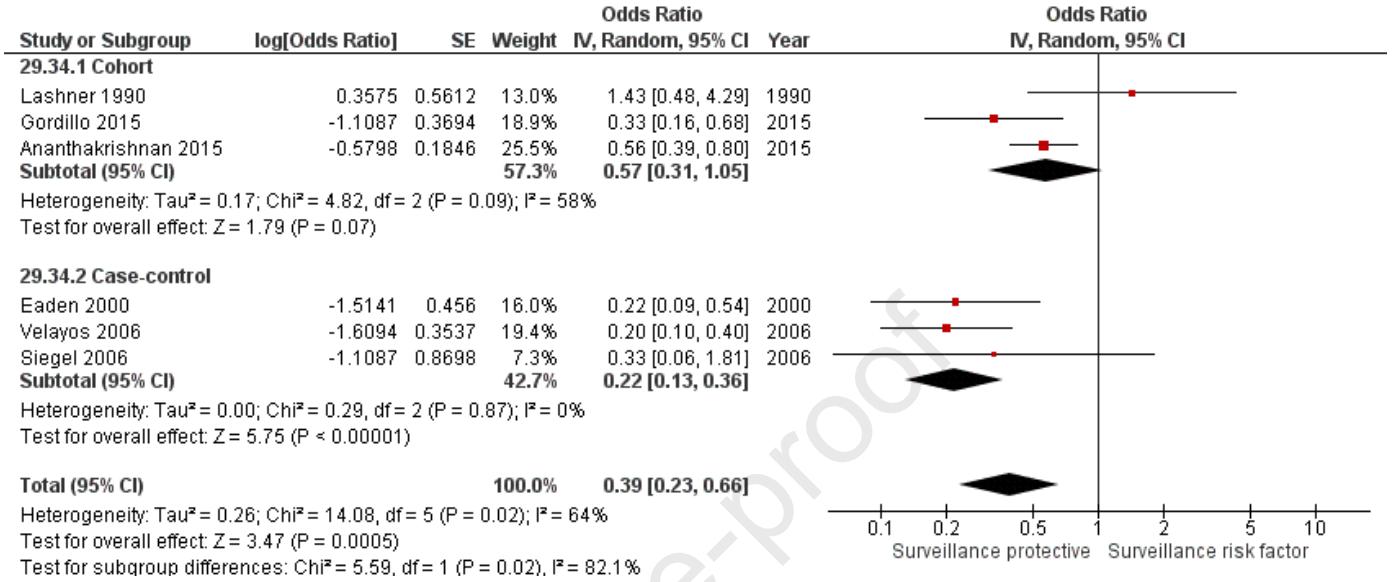


Supplementary table 28D: Definitions used in studies used in pooled analysis

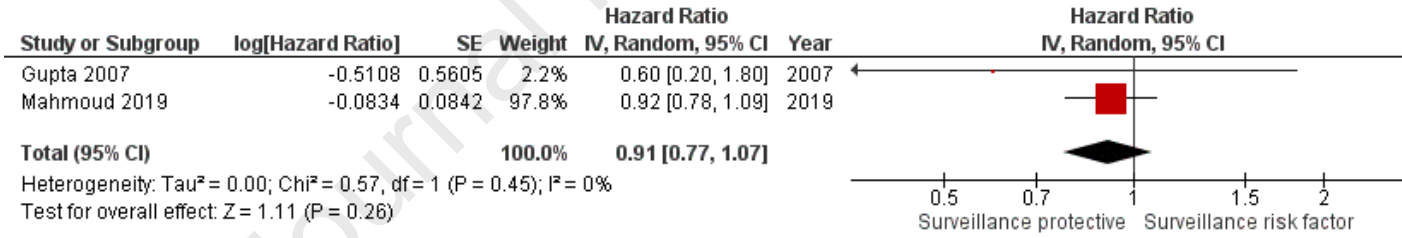
Study, year	Definition	Supplementary figure
Siegel 2006	Prior partial colonic resection could be any amount of colon, but patients had to have at least one third of their colon intact to be included in this study. Not specified which operation indication. Crohn colitis patients.	28A
Van Schaik 2012	History of partial colonic resection, not specified which operation indication (patients with a previous subtotal or total colectomy were excluded). IBD patients.	28B, 28C
Scharl 2018	Intestinal surgery not specified which operation indication; Patients who had non-CRC related colectomy were excluded from at risk population for CRC development. HR based on UC/IBD-U patients	28B
Bergeron 2010	Previous segmental colectomy during the course of the disease before diagnosis of neoplasia or date of censoring (IBD pancolitis patients)	28C

Supplementary file 29A-F Surveillance colonoscopies

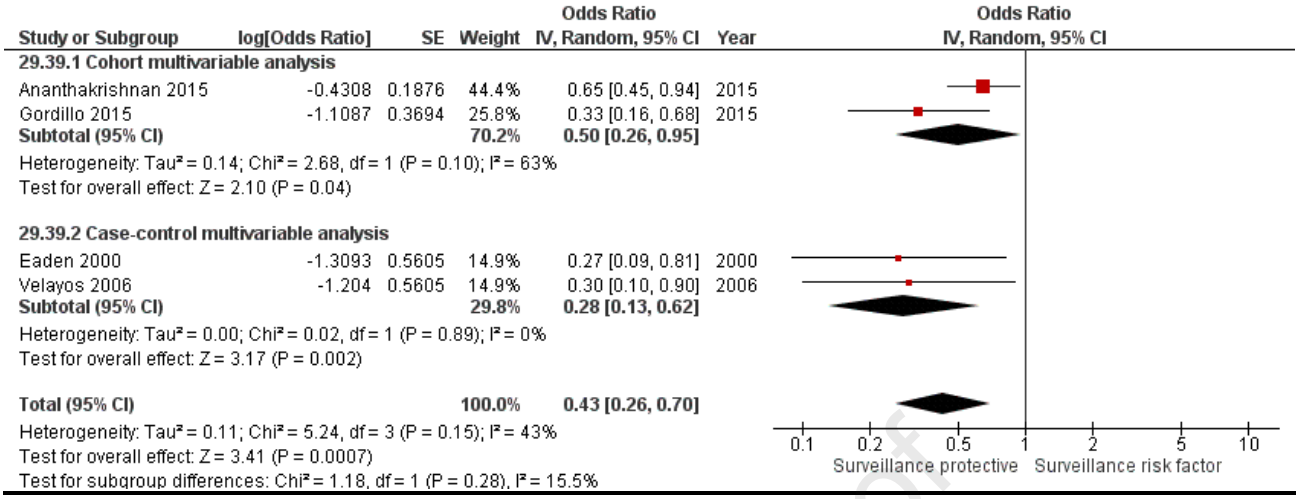
Supplementary Figure 29A: Forest plot of Univariable analysis OR



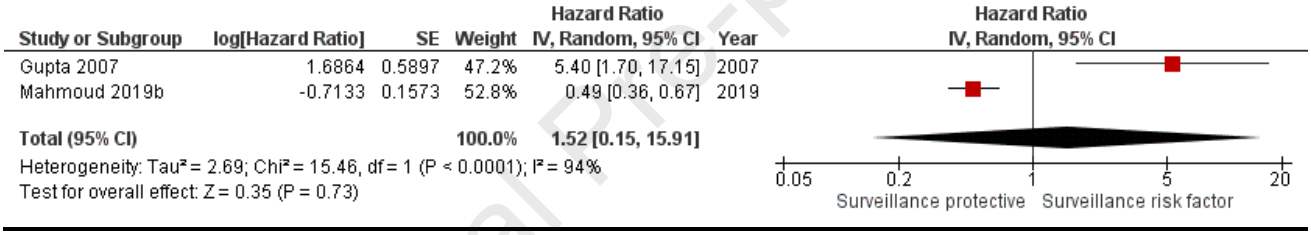
Supplementary Figure 29B: Forest plot of Univariable analysis HR cohort



Supplementary Figure 29C: Forest plot of Multivariable analysis OR



Supplementary Figure 29D: Forest plot of Multivariable analysis HR cohort studies



Supplementary Table 29E: Definitions used in studies used in pooled analysis

Study, year	Definition	Supplementary figure
Lashner 1990	Surveillance versus no surveillance	29A
Eaden 2000	1 to 2 colonoscopies during FU (compared to none)	29A
Eaden 2000	1-2 colonoscopies after diagnosis versus <1	29C
Siegel 2006	Prior surveillance colonoscopy	29A
Velayos 2006	Surveillance colonoscopy > 2 case-control	29A, 29C
Gupta 2007	One or more colonoscopies per year	29B, 29D
Ananthakrishnan 2015	Colonoscopy < 3 yrs cohort	29A, 29C
Gordillo 2015	Surveillance versus no surveillance	29A, 29C
Mahmoud 2019	Number of adequate surveillance colonoscopies	29B
Mahmoud 2019b	Number of adequate surveillance colonoscopies	29D

Supplementary Table 29F: Other definitions used, data not pooled

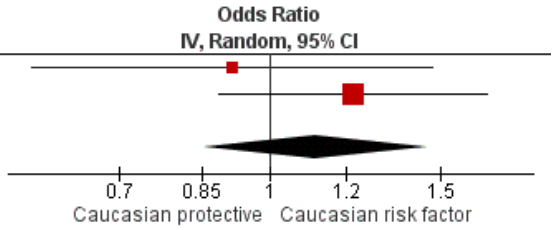
Study, year	Study design	Univariable or multivariable analysis?	Definition	Effect size [95% CI]
Siegel 2006	Case-control	Univariable OR	Colonoscopy indication surveillance	0.21 [0.04, 1.10]
Siegel 2006	Case-control	Univariable OR	Colonoscopy indication change in symptoms case-control	4.67 [1.30, 16.78]
Terdiman 2007	Case-control	Univariable OR	Colonoscopy 61-365 days before index date case-control	0.76 [0.58, 1.00]
Gong 2012	Cohort	Univariable OR	Colonoscopy follow up	1.86 [0.94, 3.69]
Stolwijk 2013	Cohort	Univariable HR	Age at 1st surveillance, yrs	1.00 [0.97, 1.03]
Stolwijk 2013	Cohort	Multivariable HR	Age at 1st surveillance, yrs	1.01 [0.98, 1.04]
Ten Hove 2019	Cohort	Univariable OR	1 negative colonoscopy (no neoplasia or other abnormalities) versus 1 positive colonoscopy	0.11 [0.01, 0.88]

Supplementary file 30A- D Race

Supplementary Figure 30A: Forest plot of Univariable analysis OR (Caucasian versus other races)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Ananthakrishnan 2015	-0.0907	0.2427	31.1%	0.91 [0.57, 1.47]
Bansal 1996	0.1961	0.1629	68.9%	1.22 [0.88, 1.67]
Total (95% CI)			**100.0%**	**1.11 [0.85, 1.45]**

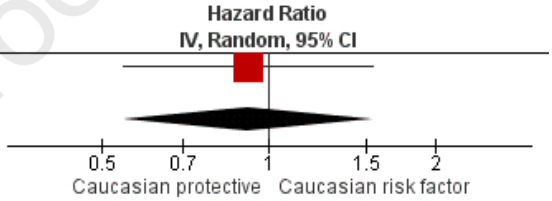
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)



Supplementary Figure 30B: Forest plot of Univariable analysis HR (Caucasian versus African-American)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Hou 2012	-0.0866	0.2645	100.0%	0.92 [0.55, 1.54]	2012
Total (95% CI)			**100.0%**	**0.92 [0.55, 1.54]**	

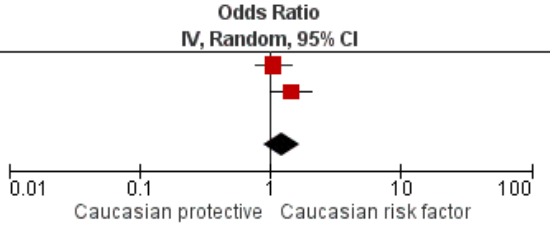
Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)



Supplementary Figure 30C: Forest plot of Multivariable analysis OR (Caucasian versus other races)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Bansal 1996	0.0488	0.1649	53.2%	1.05 [0.76, 1.45]	1996
Ananthakrishnan 2016	0.3709	0.1841	46.8%	1.45 [1.01, 2.08]	2016
Total (95% CI)			**100.0%**	**1.22 [0.89, 1.67]**	

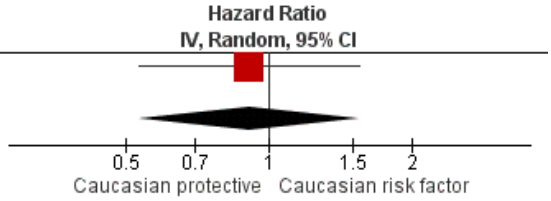
Heterogeneity: Tau² = 0.02; Chi² = 1.70, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 1.24 (P = 0.21)



Supplementary Figure 30D: Forest plot of Multivariable analysis HR (Caucasian versus African-American)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Hou 2012	-0.0954	0.2705	100.0%	0.91 [0.53, 1.54]	2012
Total (95% CI)			**100.0%**	**0.91 [0.53, 1.54]**	

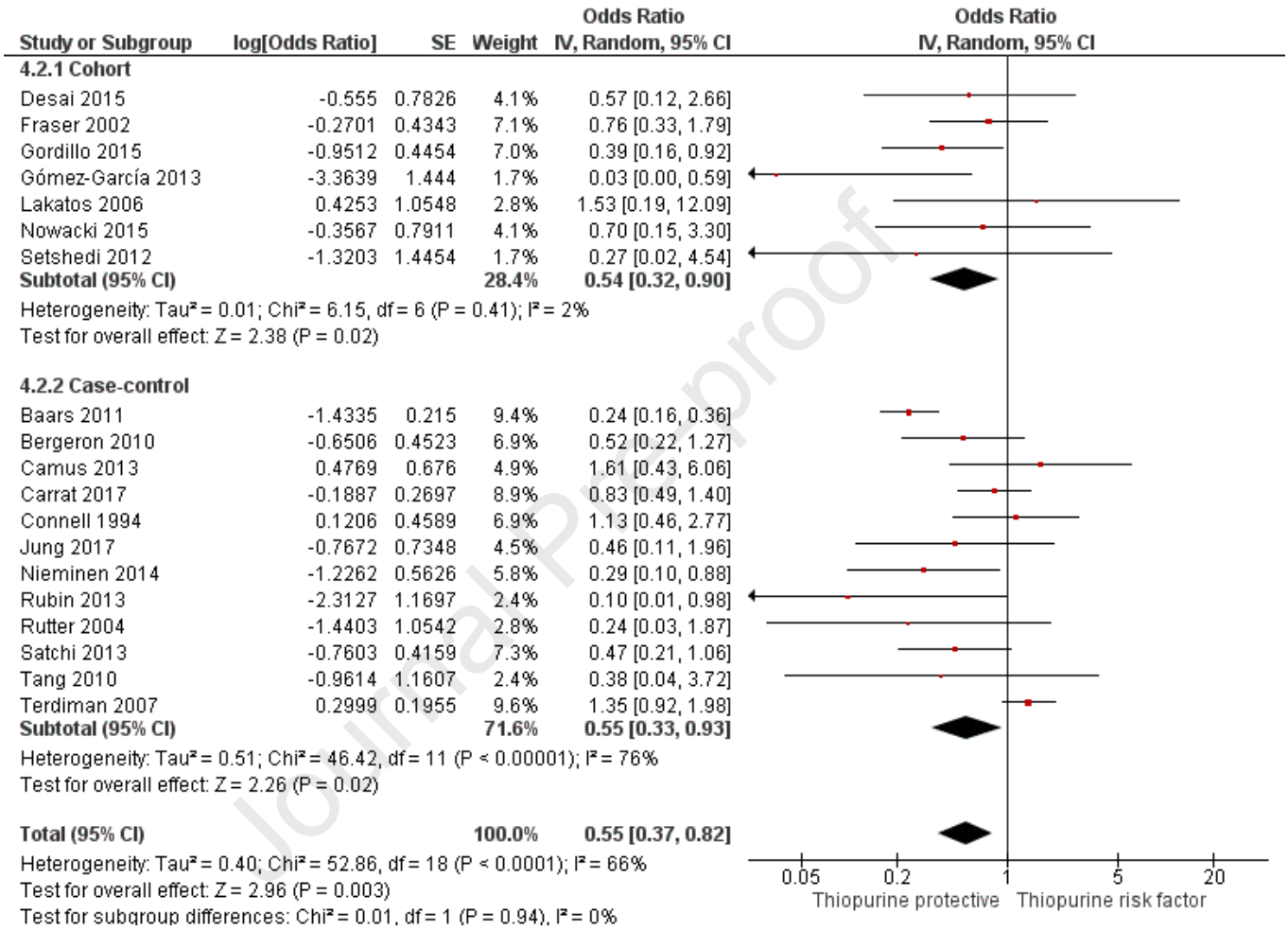
Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.72)



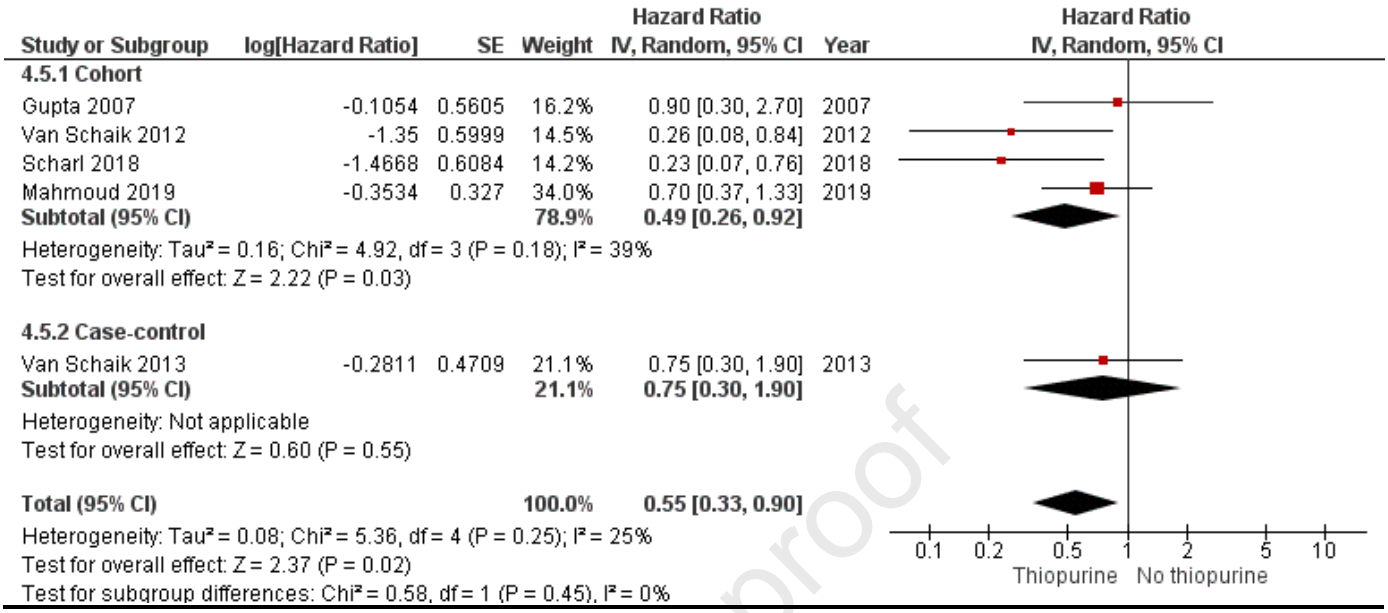
MEDICATION

Supplementary file 31A-E Thiopurines

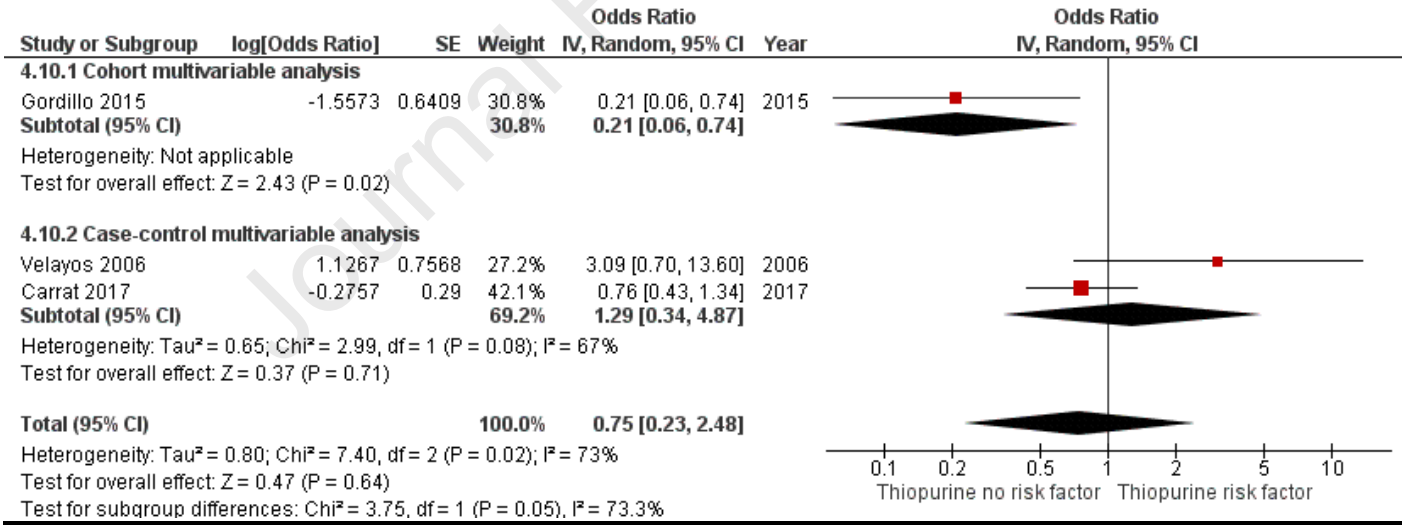
Supplementary Figure 31A: Forest plot of Univariable analysis OR



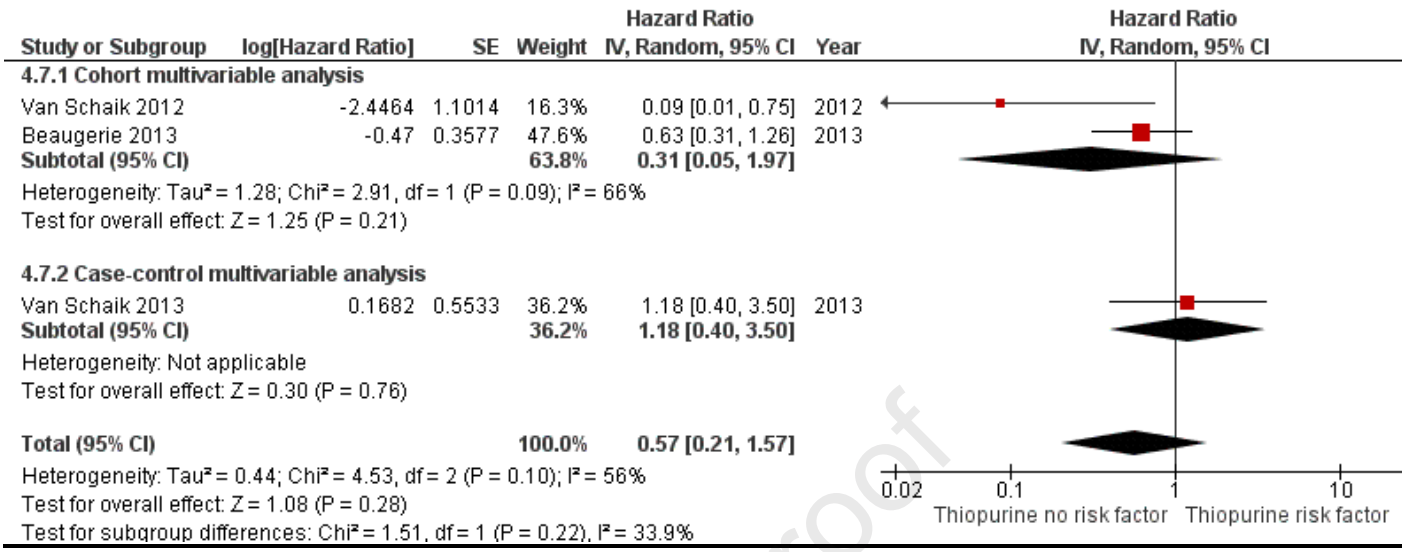
Supplementary Figure 31B: Forest plot of Univariable analysis HR



Supplementary Figure 31C: Forest plot of Multivariable analysis OR



Supplementary Figure 31D: Forest plot of Multivariable analysis HR

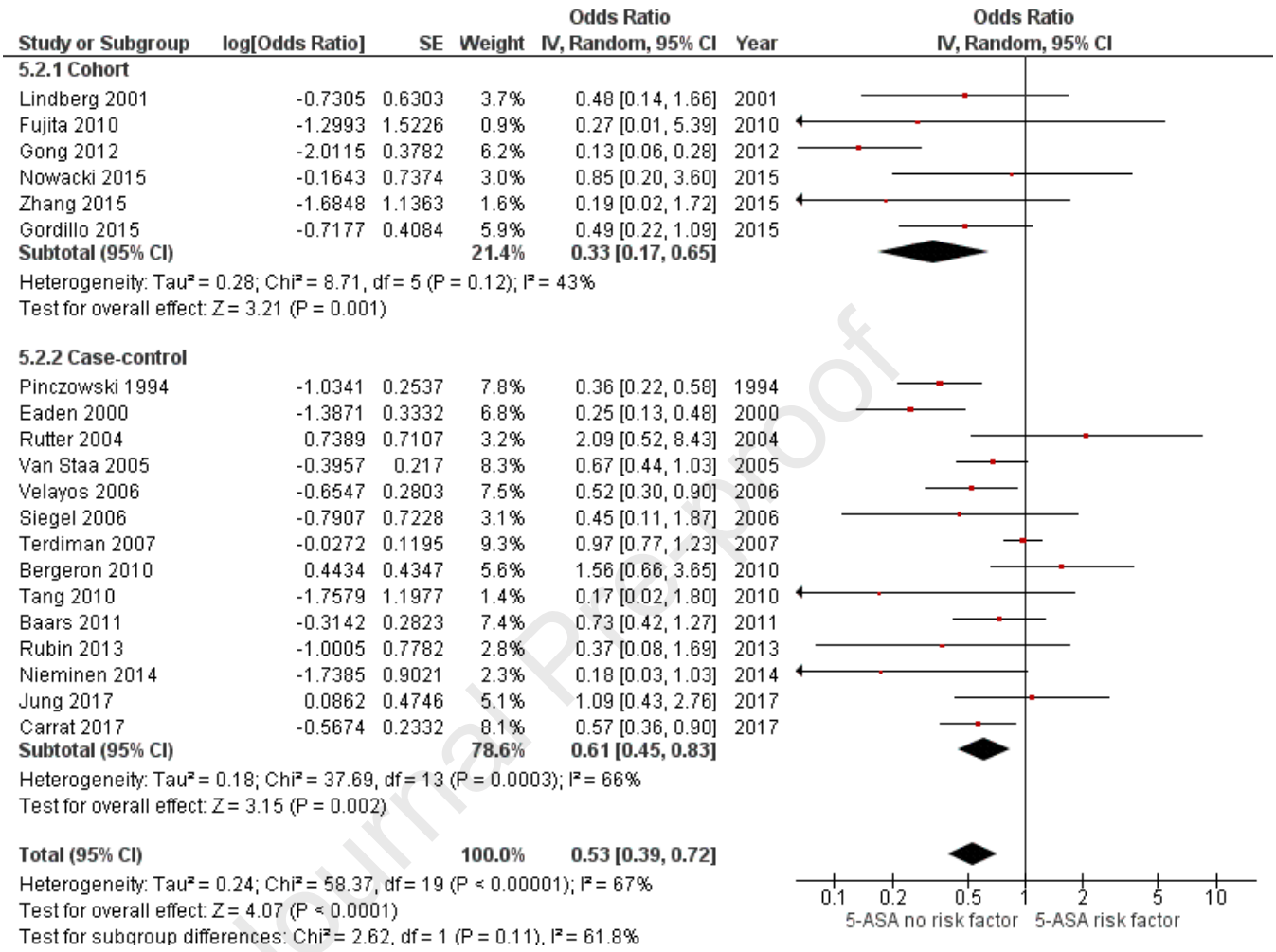


Supplementary Table 31E: Definitions used in studies used in pooled analysis

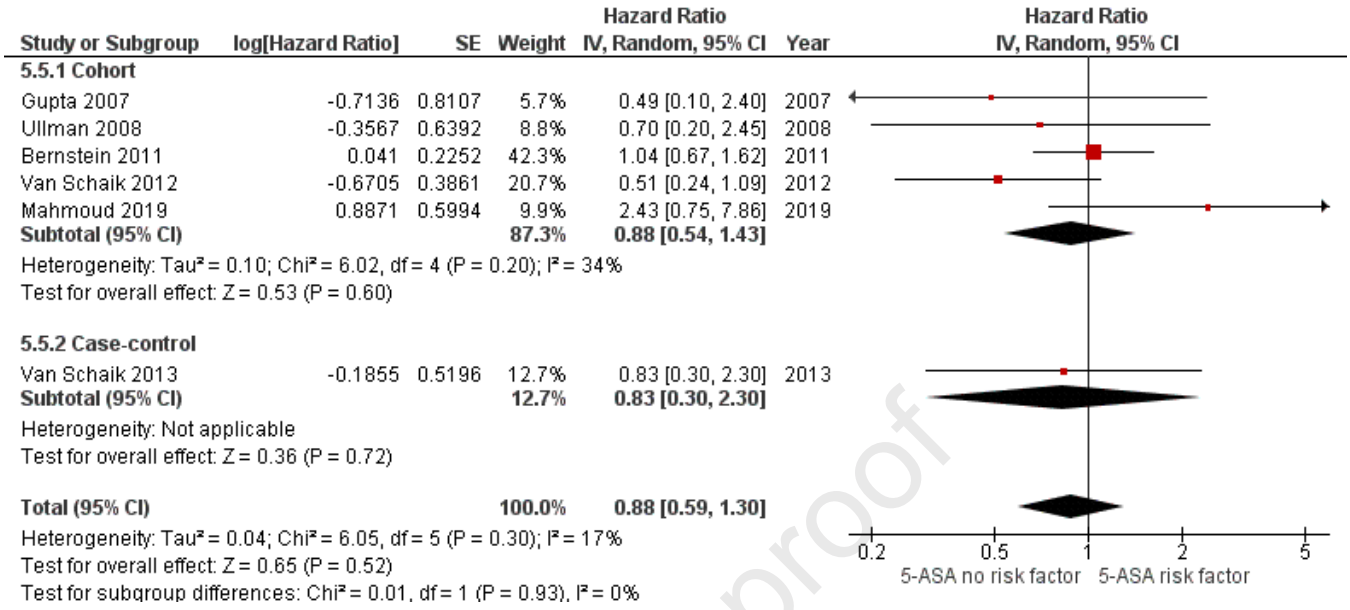
Study, year	Definition thiopurines	Supplementary figure
Desai 2015	Use of azathioprine	31A
Fraser 2002	Use of azathioprine	31A
Gordillo 2015	Use of any thiopurine	31A & 31C
Gómez-Garcia 2013	Use of azathioprine or mercaptopurine	31A
Lakatos 2006	Use of azathioprine	31A
Nowacki 2015	Use of any thiopurine	31A
Setshedi 2012	Use of azathioprine or mercaptopurine	31A
Baars 2011	Use of any thiopurine	31A
Bergeron 2010	Use of azathioprine or 6-mercaptopurine greater than 1 or 0.5 mg / kg per day, respectively, during the 5 years before neoplasia or censoring	31A
Camus 2013	Use of azathioprine	31A
Carrat 2017	Exposure to thiopurines during the year of cancer diagnosis	31A & 31C
Connell 1994	Use of azathioprine	31A
Jung 2017	Use of azathioprine or mercaptopurine	31A
Nieminen 2014	Use of azathioprine or mercaptopurine	31A
Rubin 2013	Any use of azathioprine, 6-mercaptopurine, or methotrexate	31A
Rutter 2004	Use of azathioprine	31A
Satschi 2013	Use of mercaptopurine	31A
Tang 2010	Use of azathioprine or mercaptopurine	31A
Terdiman 2007	Use of immunomodulators	31A
Gupta 2007	Use of azathioprine or mercaptopurine	31B
Van Schaik 2012	Use of azathioprine or mercaptopurine	31B & 31D
Scharl 2018	Use of azathioprine	31B
Mahmoud 2019	Use of azathioprine or mercaptopurine	31B
Van Schaik 2013	Use of azathioprine or mercaptopurine	31B & 31D
Velayos 2006	Use of azathioprine or mercaptopurine	31C
Beaugerie 2013	Use of any thiopurine	31D

Supplementary file 32A-E 5-Aminosalicylates (5-ASA)

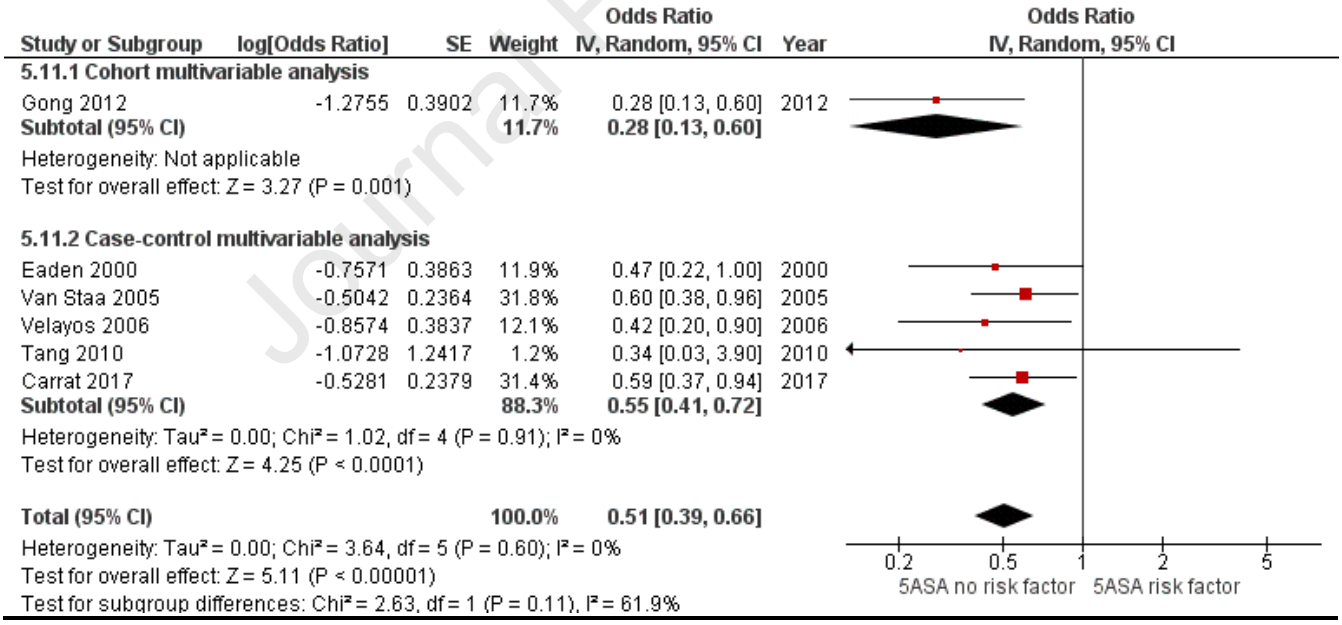
Supplementary Figure 32A: Forest plot of Univariable analysis OR



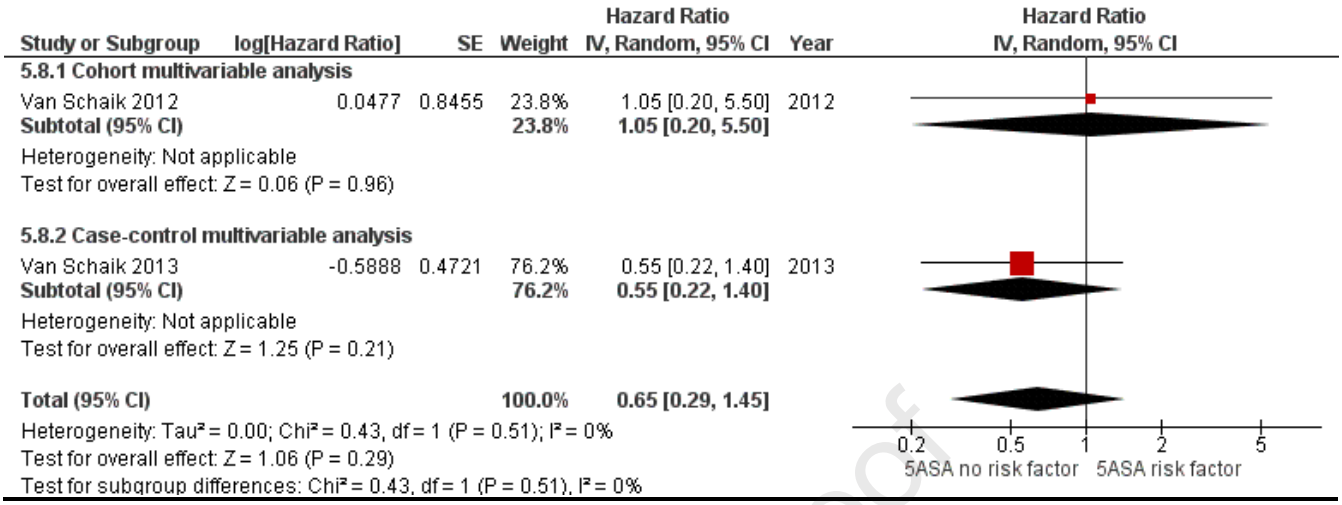
Supplementary Figure 32B: Forest plot of Univariable analysis HR



Supplementary Figure 32C: Forest plot of Multivariable analysis OR



Supplementary Figure 32D: Forest plot of Multivariable analysis HR



Supplementary Table 32E: Definitions used in studies used in pooled analysis

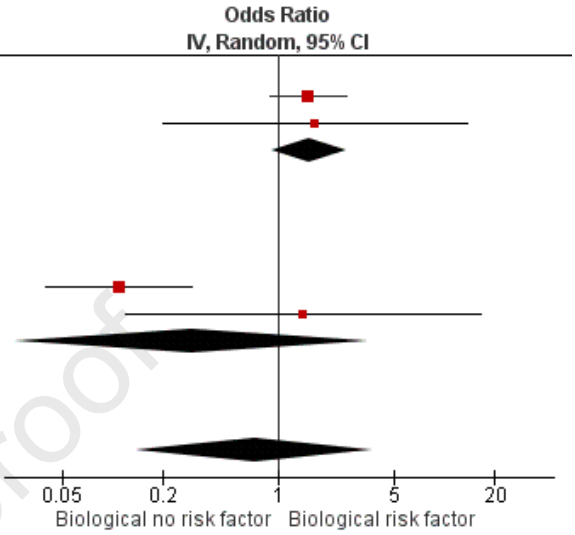
Study, year	Definition 5-aminosalicylates	Supplementary figure
Lindberg 2001	Use of 5-ASA or sulfasalazine for at least 6 months	32A
Fujita 2010	Use of 5-ASA	32A
Gong 2012	Use of 5-ASA or sulfasalazine	32A
Nowacki 2015	Use of 5-ASA	32A
Zhang 2015	Use of 5-ASA	32A
Gordillo 2015	Use of 5-ASA	32A
Pinczowski 1994	Use of sulfasalazine	32A
Eaden 2000	Regular use of mesalazine at a dose of 1.2g/day or greater	32A & 32C
Rutter 2004	Use of sulfasalazine > 3 months up to 10 years	32A
Van Staa 2005	Any 5-ASA (mesalazine, balsalazide, olsalazine, sulfasalazine)	32A & 32C
Velayos 2006	Use of sulfasalazine > 3 months up to 10 years	32A & 32C
Siegel 2006	Use of 5-ASA	32A
Terdiman 2007	Use of at least 1 prescription of mesalamine or sulfasalazine or balsalazide	32A
Tang 2010	Use of sulfasalazine, olsalazine, mesalazine klysma, mesalazine rectal suppository	32A & 32C
Bergeron 2010	Use of 5-ASA, mean dose greater dan 1g/day during the 5 years before event	32A
Baars 2011	Use of 5-ASA	32A
Rubin 2013	Use of sulfasalazine (results for non-sulfasalazine were similar)	32A
Nieminen 2014	Use of 5-ASA	32A
Carrat 2017	Use of mesalamine, sulfasalazine, olsalazine and balsalazide	32A & 32C
Jung 2017	Use of 5-ASA at least 1 month	32A
Gupta 2008	Use of mesalamine-based agents	32B
Ullman 2008	Use of mesalamine, dose 2.0 g/day (or an equivalent dose of balsalazide or sulfasalazine or olsalazine)	32B
Bernstein 2011	Use of 5-ASA > 1 year	32B
Van Schaik 2012	Use of mesalazine at a dose of at least 1.2 g/day during 6 monthas, or an equivalent dos of sulfasalazine or olsalazine	32B & 32D

Mahmoud 2019	Use of 5-ASA	32B & 32D
Van Schaik 2013	Use of 5-ASA	32B
Gong 2012	Use of 5-ASA ≥1.5 g/day or sulfasalazine ≥2g/day	32C

Supplementary file 33A-E Tumor necrosis factor alpha inhibitors

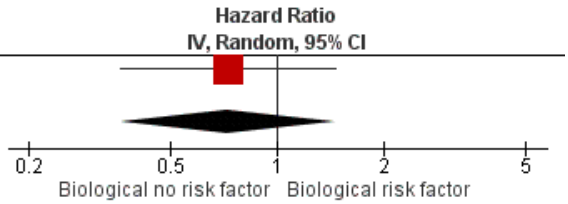
Supplementary Figure 33A: Forest plot of Univariable analysis OR

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
6.2.1 Cohort				
Ananthakrishnan 2015	0.4116	0.2741	31.3%	1.51 [0.88, 2.58]
Nowacki 2015	0.5076	1.0801	21.0%	1.66 [0.20, 13.80]
Subtotal (95% CI)			**52.4%**	**1.52 [0.90, 2.56]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%				
Test for overall effect: Z = 1.57 (P = 0.12)				
6.2.2 Case-control				
Baars 2011	-2.2114	0.514	28.9%	0.11 [0.04, 0.30]
Jung 2017	0.3385	1.2545	18.8%	1.40 [0.12, 16.40]
Subtotal (95% CI)			**47.6%**	**0.30 [0.03, 3.51]**
Heterogeneity: Tau² = 2.33; Chi² = 3.54, df = 1 (P = 0.06); I² = 72%				
Test for overall effect: Z = 0.96 (P = 0.34)				
Total (95% CI)			**100.0%**	**0.71 [0.14, 3.67]**
Heterogeneity: Tau² = 2.16; Chi² = 20.79, df = 3 (P = 0.0001); I² = 86%				
Test for overall effect: Z = 0.41 (P = 0.69)				
Test for subgroup differences: Chi² = 1.59, df = 1 (P = 0.21), I² = 37.2%				



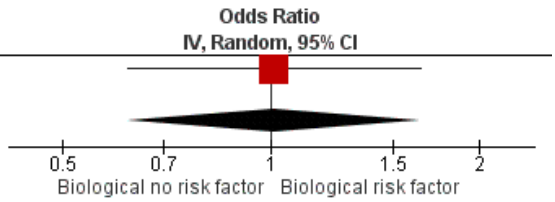
Supplementary Figure 33B: Forest plot of Univariable HR cohort studies

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Shah 2018	-0.3216	0.3572	100.0%	0.72 [0.36, 1.46]
Total (95% CI)			**100.0%**	**0.72 [0.36, 1.46]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.90 (P = 0.37)				

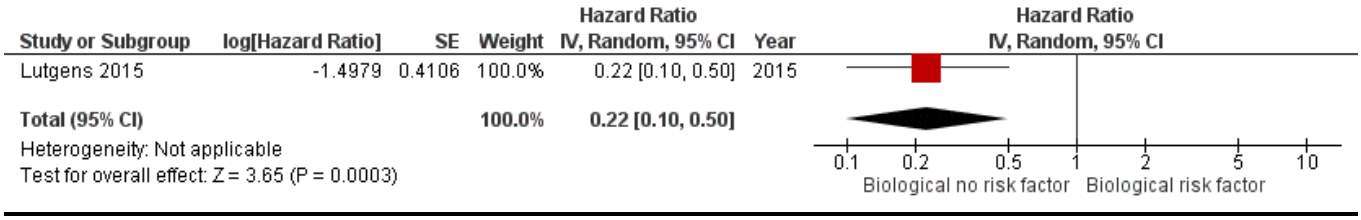


Supplementary Figure 33C: Forest plot of Multivariable OR cohort studies

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Ananthakrishnan 2016	0.01	0.249	100.0%	1.01 [0.62, 1.65]	2016
Total (95% CI)			**100.0%**	**1.01 [0.62, 1.65]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					



Supplementary Figure 33D: Forest plot of Multivariable HR cohort studies

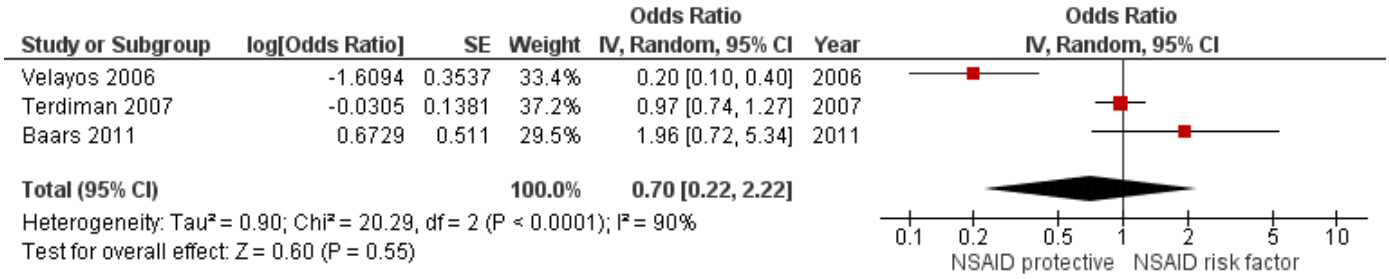


Supplementary Table 33E: Definitions used in studies used in pooled analysis

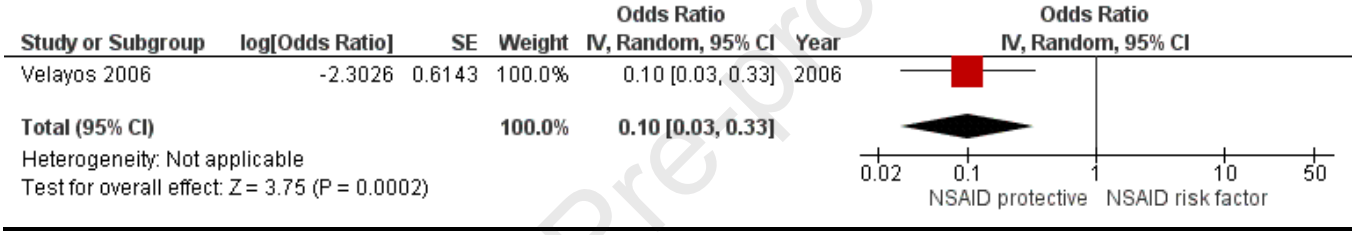
Study, year	Definition biologic	Supplementary figure
Ananthakrishnan 2015	Use of infliximab, adalimumab, and certolizumab	33A
Nowacki 2015	Use of anti-TNF	33A
Baars 2011	Use of anti-TNF	33A
Jung 2017	Use of infliximab or adalimumab	33A
Shah 2018	Use of biologics	33B
Ananthakrishnan 2016	Use of infliximab, adalimumab, and certolizumab	33C
Lutgens 2015	Use of anti-TNF	33D

Supplementary file 34A-C NSAIDs

Supplementary Figure 34A: Forest plot of Univariable OR case-control studies



Supplementary Figure 34B: Forest plot of Multivariable OR case-control studies



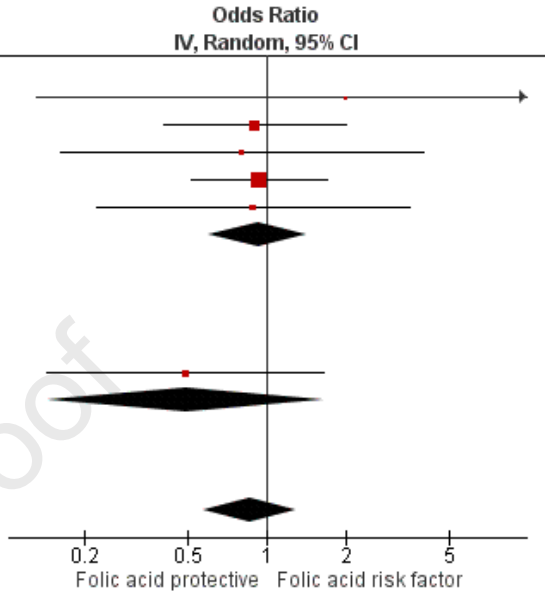
Study, year	Definition NSAID	Supplementary figure
Velayos 2006	Use of NSAIDs noted on at least 2 office visits	34A & 34B
Terdiman 2007	Ever use of NSAID	34A
Baars 2011	Ever use of NSAID	34A

Supplementary Table 34C: Definitions used in studies used in pooled analysis

Supplementary file 35A-D Folic acid

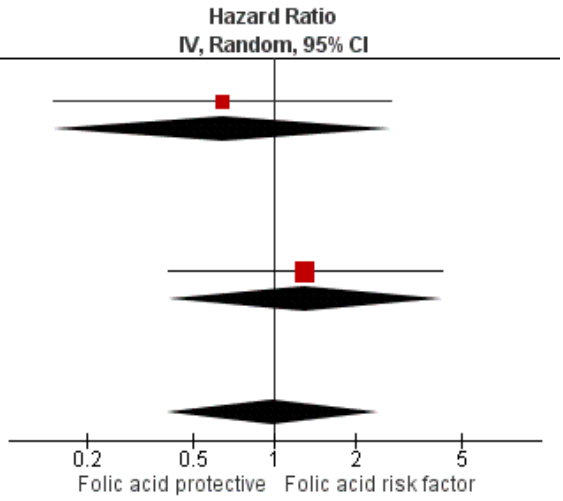
Supplementary Figure 35A: Forest plot of Univariable analysis OR

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
27.2.1 Case-control					
Rutter 2004	0.6931	1.3946	2.2%	2.00 [0.13, 30.77]	2004
Velayos 2006	-0.1054	0.4137	25.4%	0.90 [0.40, 2.02]	2006
Siegel 2006	-0.2231	0.8212	6.4%	0.80 [0.16, 4.00]	2006
Baars 2011	-0.0726	0.3065	46.2%	0.93 [0.51, 1.70]	2011
Rubin 2013	-0.1278	0.7073	8.7%	0.88 [0.22, 3.52]	2013
Subtotal (95% CI)			**88.9%**	**0.92 [0.60, 1.42]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 4 (P = 0.99); I² = 0%					
Test for overall effect: Z = 0.36 (P = 0.72)					
27.2.2 Cohort					
Lashner 1989	-0.7168	0.6251	11.1%	0.49 [0.14, 1.66]	1989
Subtotal (95% CI)			**11.1%**	**0.49 [0.14, 1.66]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 1.15 (P = 0.25)					
Total (95% CI)			**100.0%**	**0.86 [0.57, 1.29]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 5 (P = 0.94); I² = 0%					
Test for overall effect: Z = 0.72 (P = 0.47)					
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.34), I² = 0%					

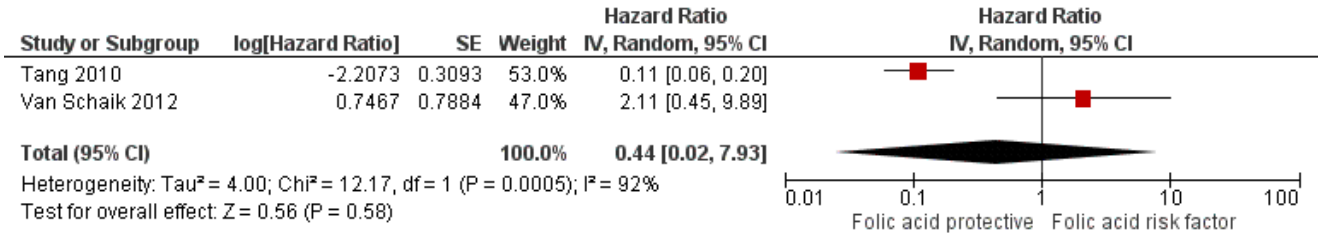


Supplementary Figure 35B: Forest plot of Univariable analysis HR

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
27.1.1 Cohort				
Van Schaik 2012	-0.4463	0.7402	39.8%	0.64 [0.15, 2.73]
Subtotal (95% CI)			**39.8%**	**0.64 [0.15, 2.73]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.60 (P = 0.55)				
27.1.2 Case-control				
Gupta 2007	0.2624	0.6014	60.2%	1.30 [0.40, 4.23]
Subtotal (95% CI)			**60.2%**	**1.30 [0.40, 4.23]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.44 (P = 0.66)				
Total (95% CI)			**100.0%**	**0.98 [0.39, 2.45]**
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%				
Test for overall effect: Z = 0.04 (P = 0.97)				
Test for subgroup differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%				



Supplementary Figure 35C: Forest plot of Multivariable HR cohort studies

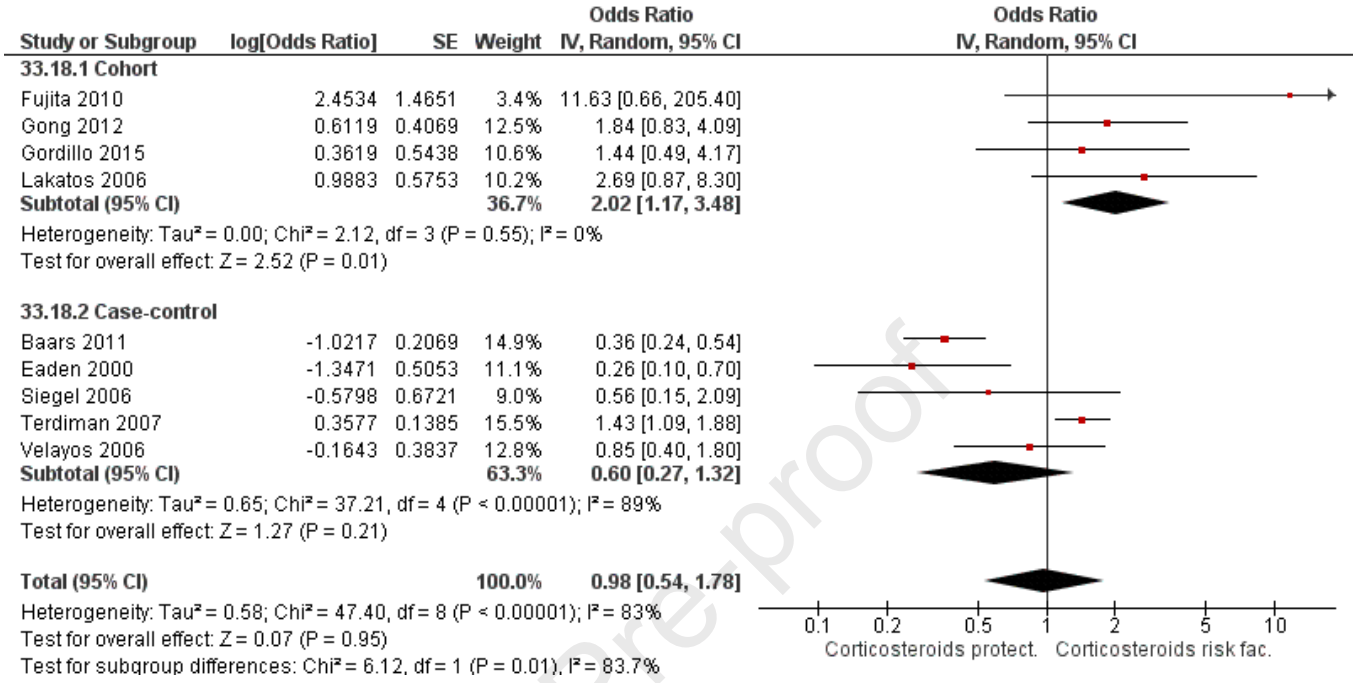


Supplementary Table 35D: Definitions used in studies used in pooled analysis

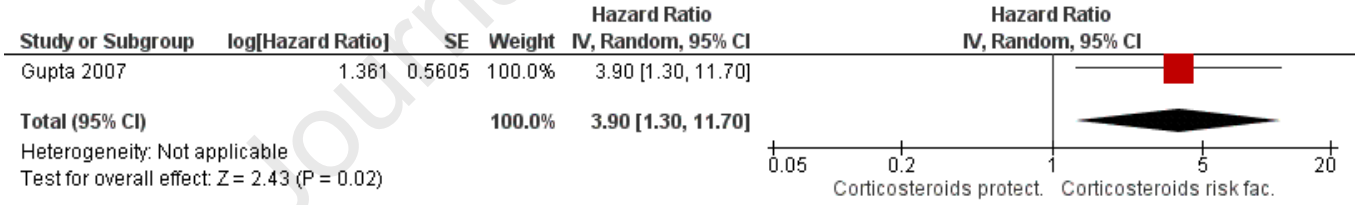
Study, year	Definition folic acid	Supplementary figure
Rutter 2004	Ever use of folic acid	35A
Velayos 2006	Use of folic acid, noted on at least 2 office visits	35A
Siegel 2006	Ever use of folic acid	35A
Baars 2011	Ever use of folic acid	35A
Rubin 2013	Ever use of folic acid	35A
Van Schaik 2012	Concurrent use of folic acid	35B & 35C
Gupta 2007	Ever use of folic acid	35B
Tang 2010	Ever use of folic acid	35C

Supplementary file 36A-D Corticosteroids

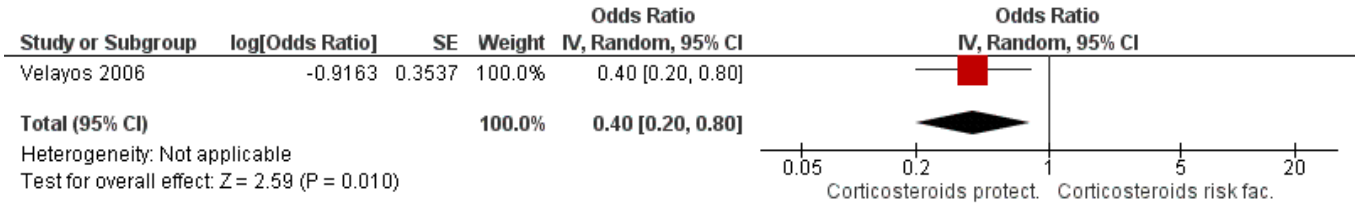
Supplementary Figure 36A: Forest plot of Univariable analysis OR



Supplementary Figure 36B: Forest plot of Univariable analysis HR cohort study



Supplementary Figure 36C: Forest plot of Multivariable analysis OR case-control study

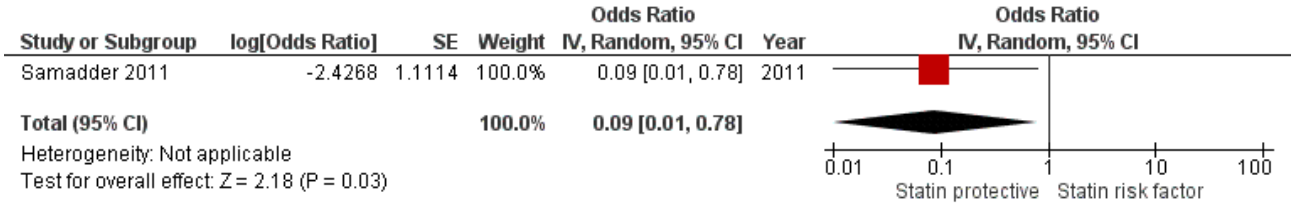


Study, year	Definition corticosteroids	Supplementary figure
Fujita 2010	Use of steroids	36A
Gong 2012	Use of steroids	36A
Gordillo 2015	Use of systemic steroids	36A
Lakatos 2006	Use of steroids	36A
Baars 2011	Use of steroids	36A
Eaden 2000	Use of systemic or local steroids	36A
Siegel 2006	Use of steroids	36A
Terdiman 2007	Use of steroids	36A
Velayos 2006	Use of steroids >1 year	36A & 36B
Gupta 2007	Use of steroids	36B

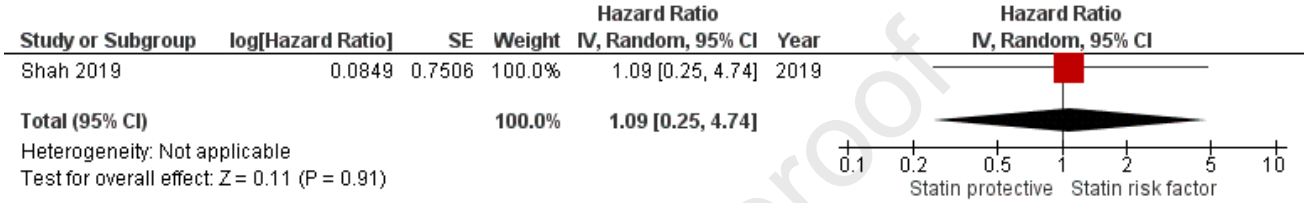
Supplementary Table 36D: Definitions used in studies used in pooled analysis

Supplementary file 37A-E Statins

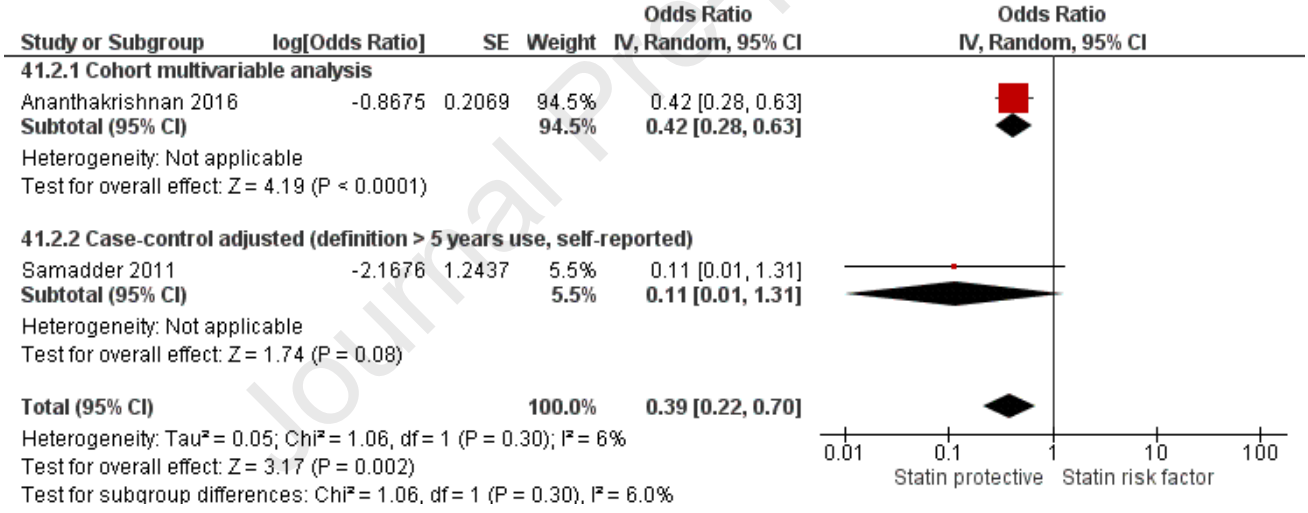
Supplementary Figure 37A: Forest plot of Univariable analysis OR case-control (definition > 5 years use, self-reported)



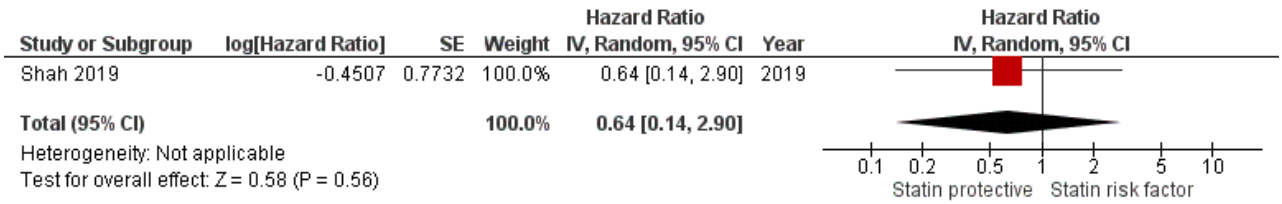
Supplementary Figure 37B: Forest plot of Univariable analysis HR cohort



Supplementary Figure 37C: Forest plot of Multivariable analysis OR



Supplementary Figure 37D: Forest plot of Multivariable analysis HR cohort

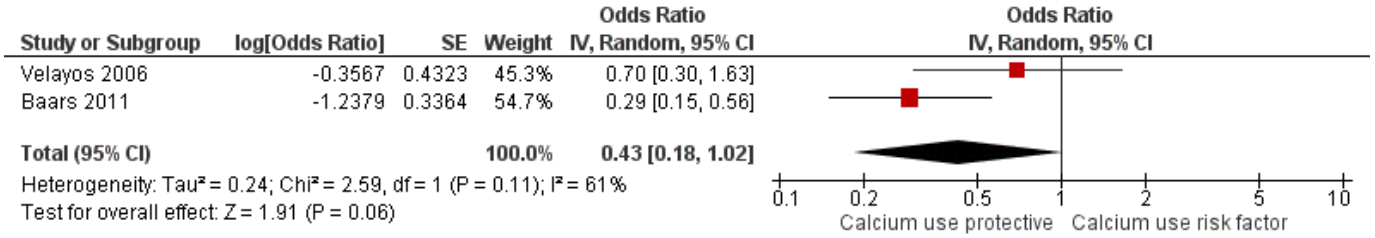


Supplementary Table 37E: Definitions used in studies used in pooled analysis

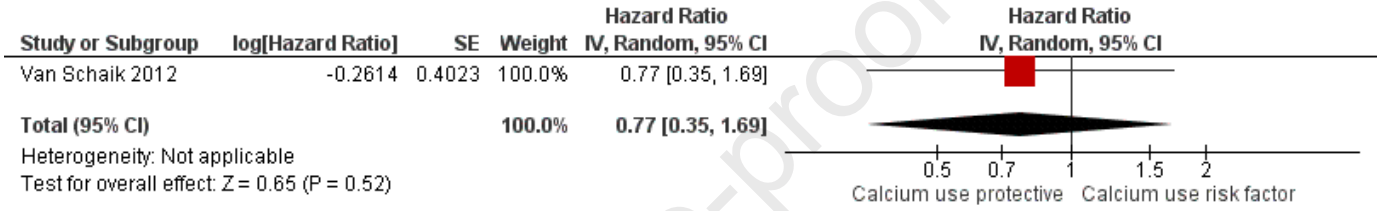
Study, year	Definition statin use	Supplementary figure
Samadder 2011	Statin use at least 5 years (as recalled by the patient)	37A & 37C
Shah 2019	Statin use at least 3 months	37B & 37D
Ananthakrishnan 2016	Statin use at least 6 months	37C

Supplementary file 38A-D Calcium supplements

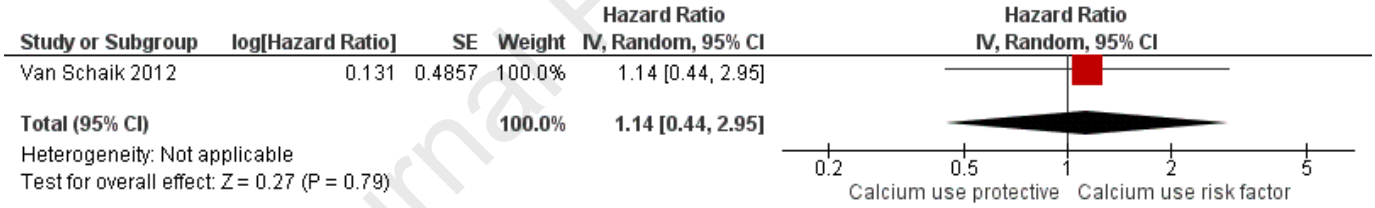
Supplementary Figure 38A: Forest plot of Univariable analysis OR case-control



Supplementary Figure 38B: Forest plot of Univariable analysis HR cohort



Supplementary Figure 38C: Forest plot of Multivariable analysis HR cohort



Study, year	Definition calcium supplements	Supplementary figure
Velayos 2006	Use of calcium, noted on at least 2 office visits	38A
Baars 2011	Use of calcium	38A
Van Schaik 2012	Concurrent use of calcium	38B & 38C

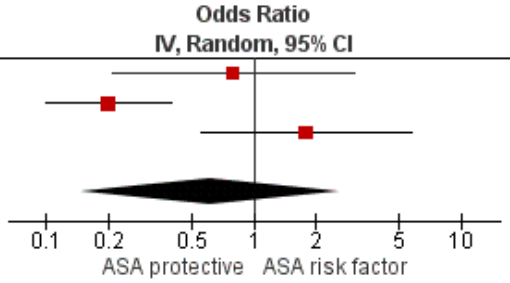
Supplementary Table 38D: Definitions used in studies used in pooled analysis

Supplementary file 39A-C Acetylsalicylic acid (ASA)

Supplementary Figure 39A: Forest plot of Univariable analysis OR case-control

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Eaden 2000	-0.2231	0.6824	30.2%	0.80 [0.21, 3.05]	2000
Velayos 2006	-1.6094	0.3537	37.4%	0.20 [0.10, 0.40]	2006
Baars 2011	0.5798	0.5933	32.3%	1.79 [0.56, 5.71]	2011
Total (95% CI)			**100.0%**	**0.62 [0.15, 2.59]**	

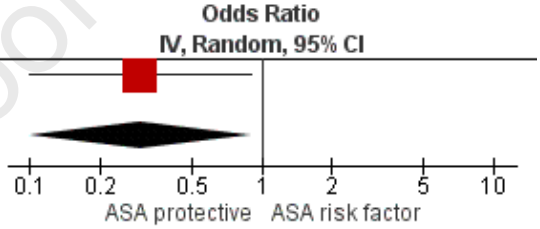
Heterogeneity: Tau² = 1.30; Chi² = 11.23, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 0.66 (P = 0.51)



Supplementary Figure 39B: Forest plot of Multivariable analysis OR case-control

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Velayos 2006	-1.204	0.5605	100.0%	0.30 [0.10, 0.90]
Total (95% CI)			**100.0%**	**0.30 [0.10, 0.90]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.15 (P = 0.03)

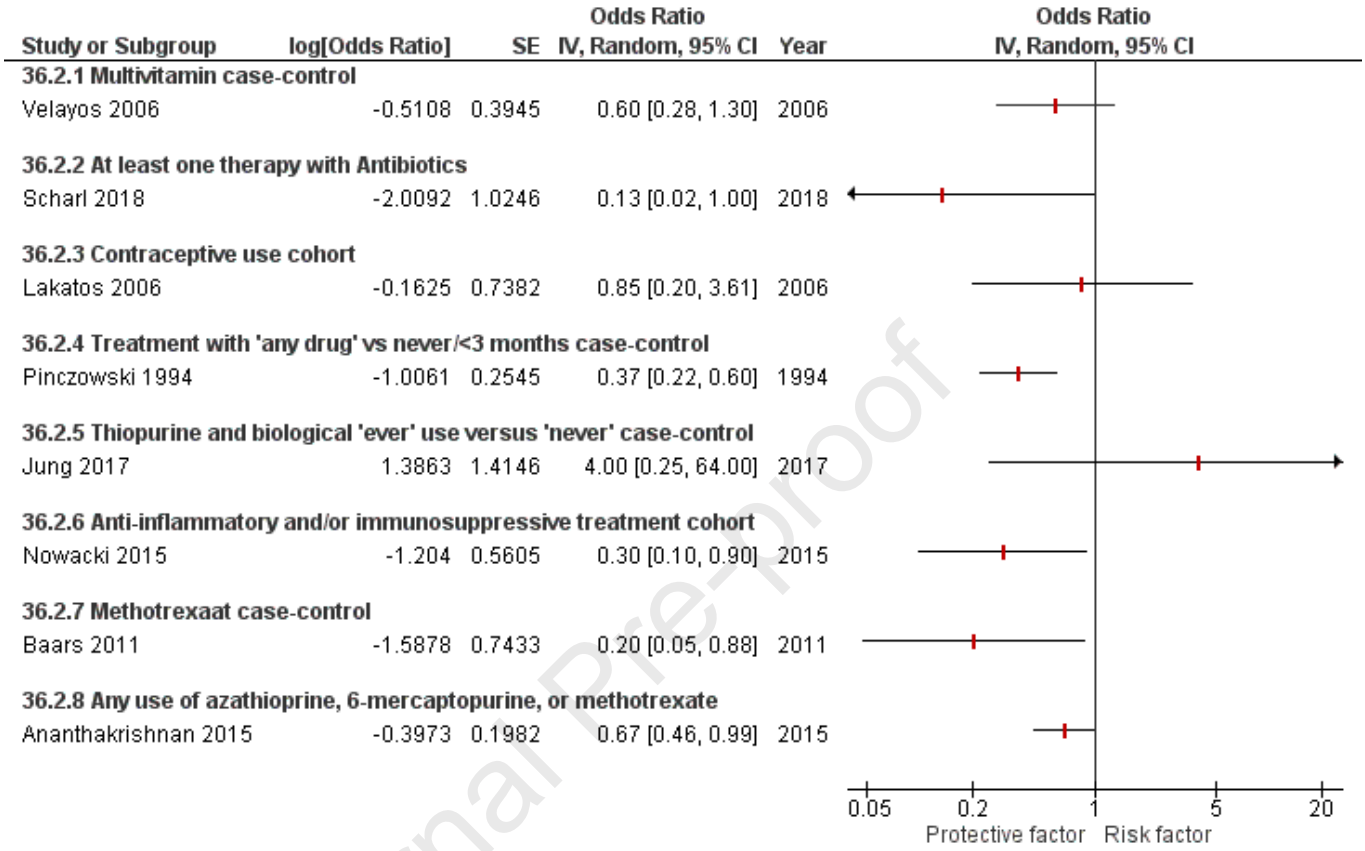


Study, year	Definition ASA	Supplementary figure
Eaden 2000	Use of ASA	39A
Velayos 2006	Use of ASA, noted on at least 2 office visits	39A & 39B
Baars 2011	Use of ASA	39A

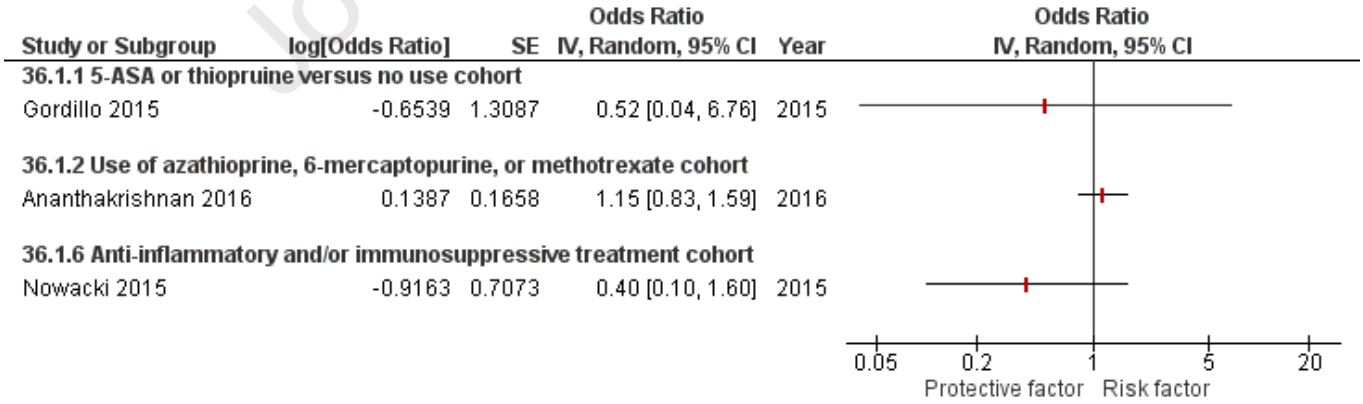
Supplementary Table 39C: Definitions used in studies used in pooled analysis

Supplementary file 40A-L Other prognostic factors

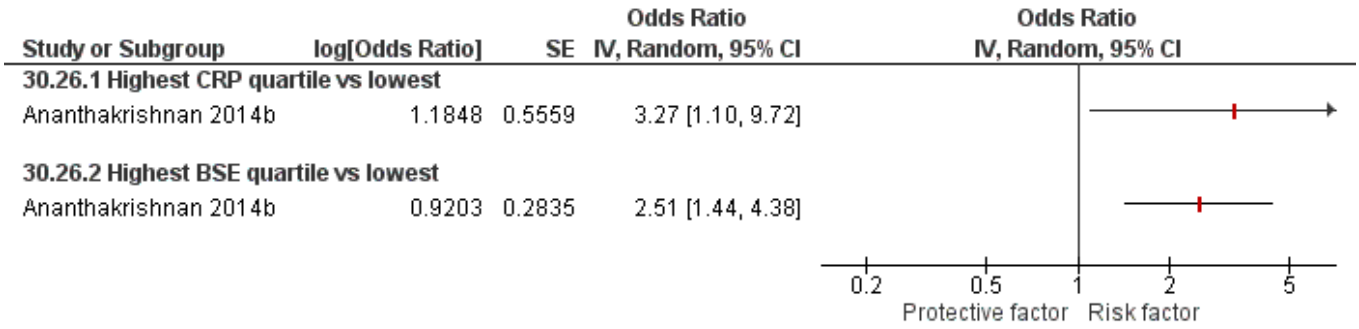
Supplementary Figure 40A: Medication other, univariable OR



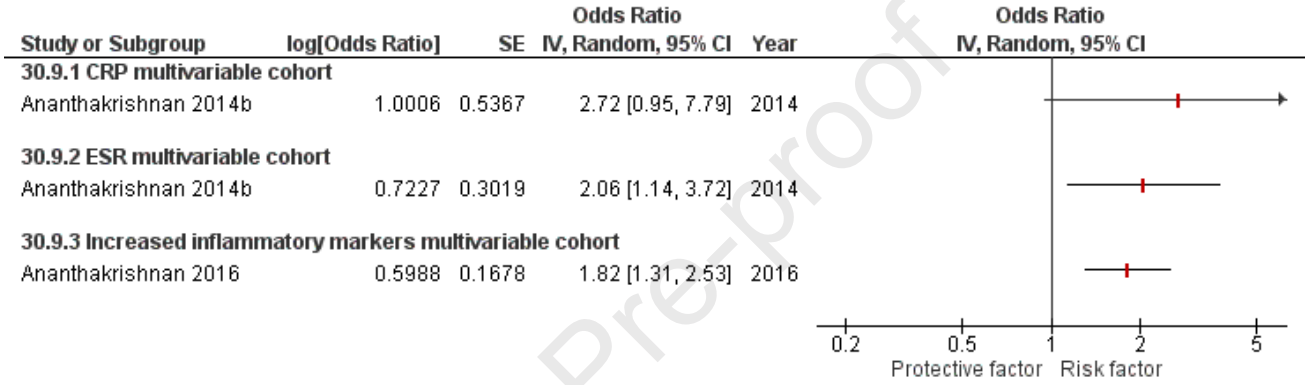
Supplementary Figure 40B: Medication other, multivariable OR



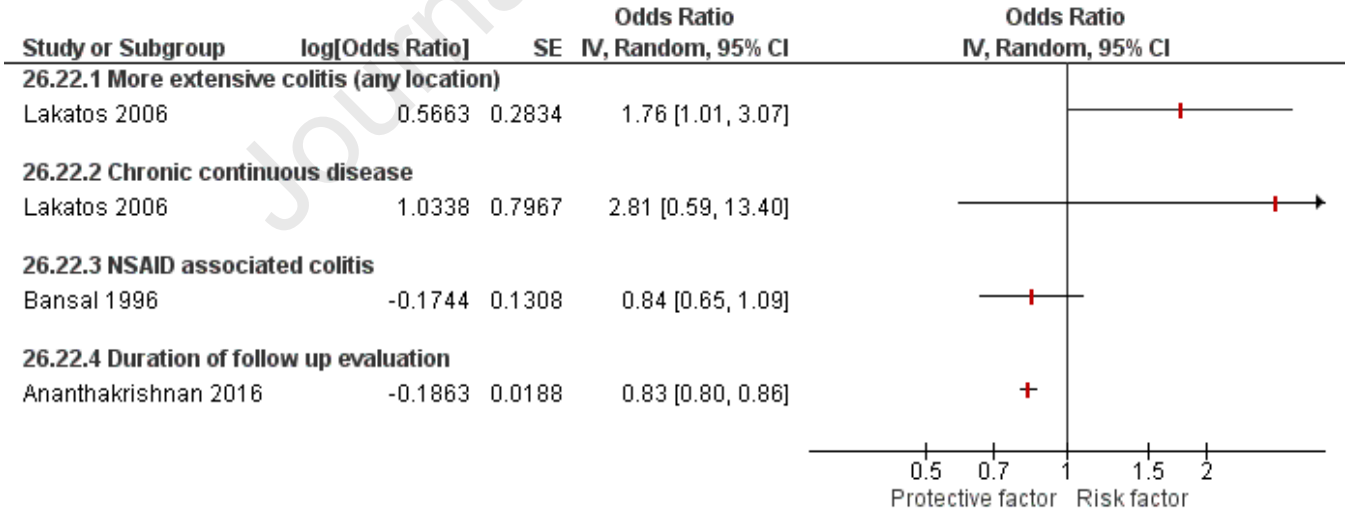
Supplementary Figure 40C: Inflammatory markers, univariable OR cohort



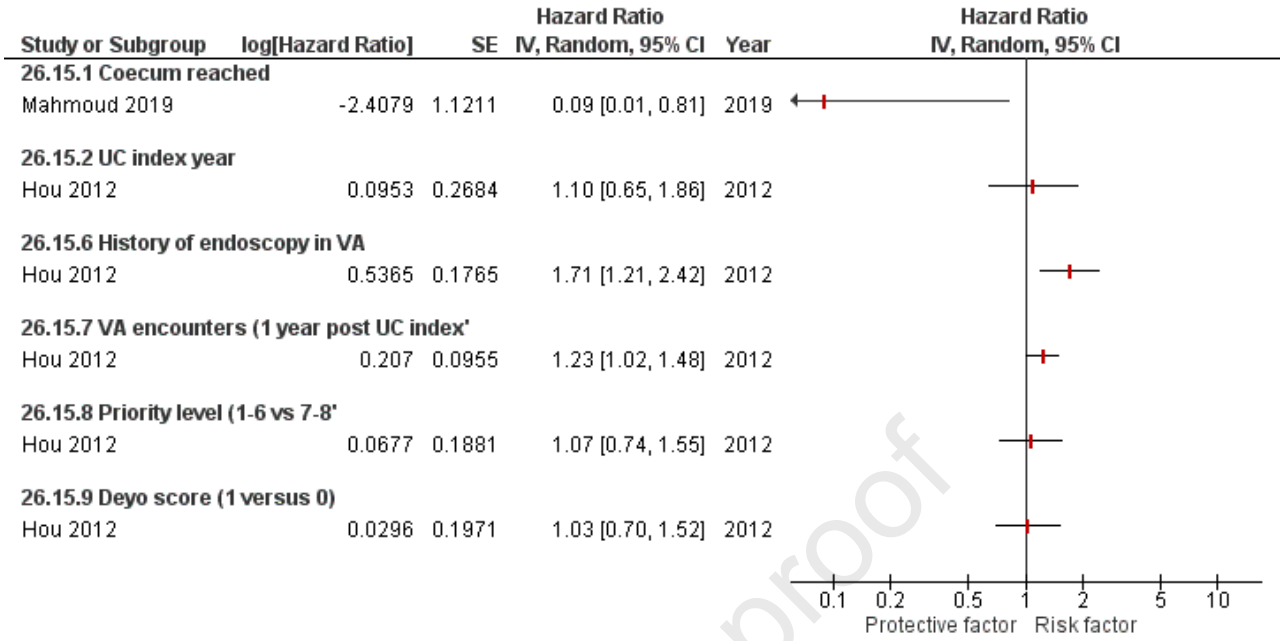
Supplementary Figure 40D: Inflammatory markers, multivariable OR



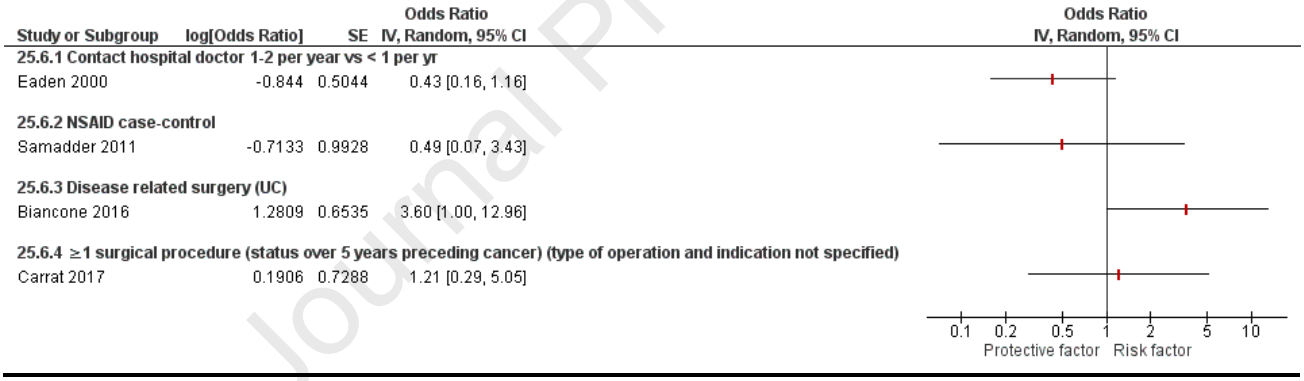
Supplementary Figure 40E: Cohort multivariable analysis OR



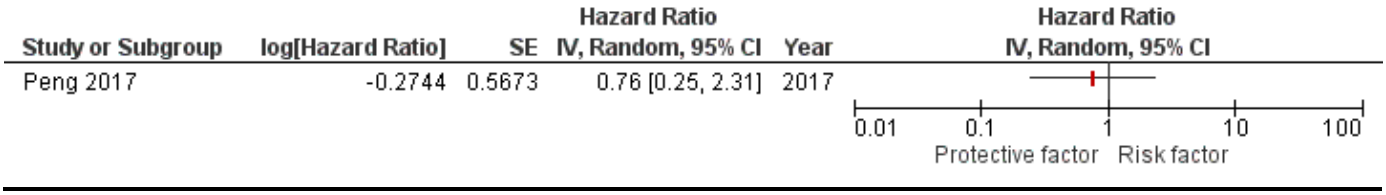
Supplementary Figure 40F: Cohort multivariable analysis HR



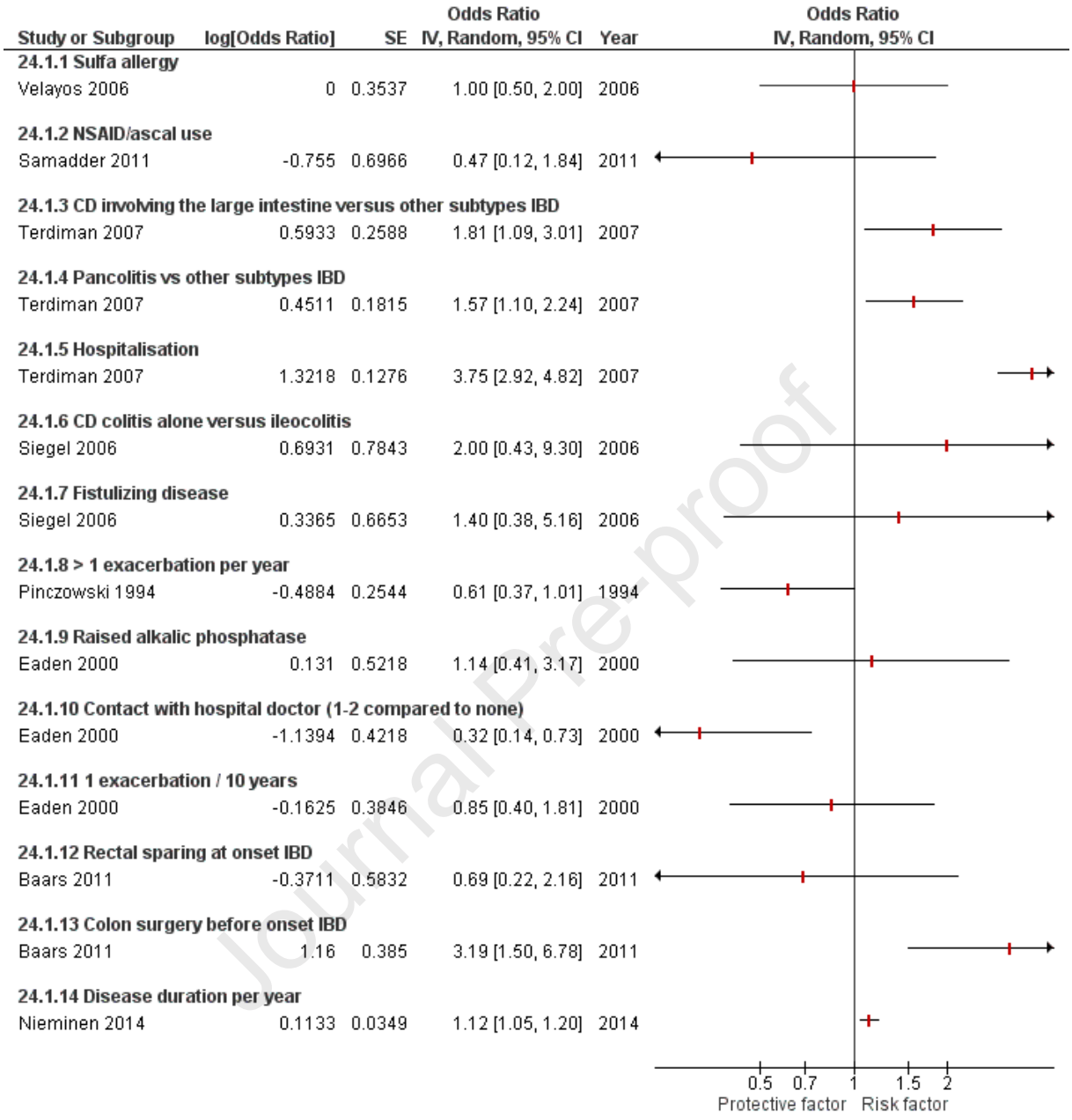
Supplementary Figure 40G: Case-control multivariable analysis OR



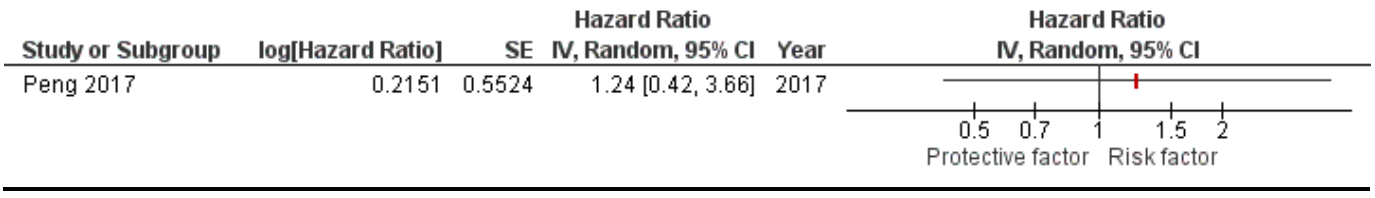
Supplementary Figure 40H: Case-control multivariable analysis HR



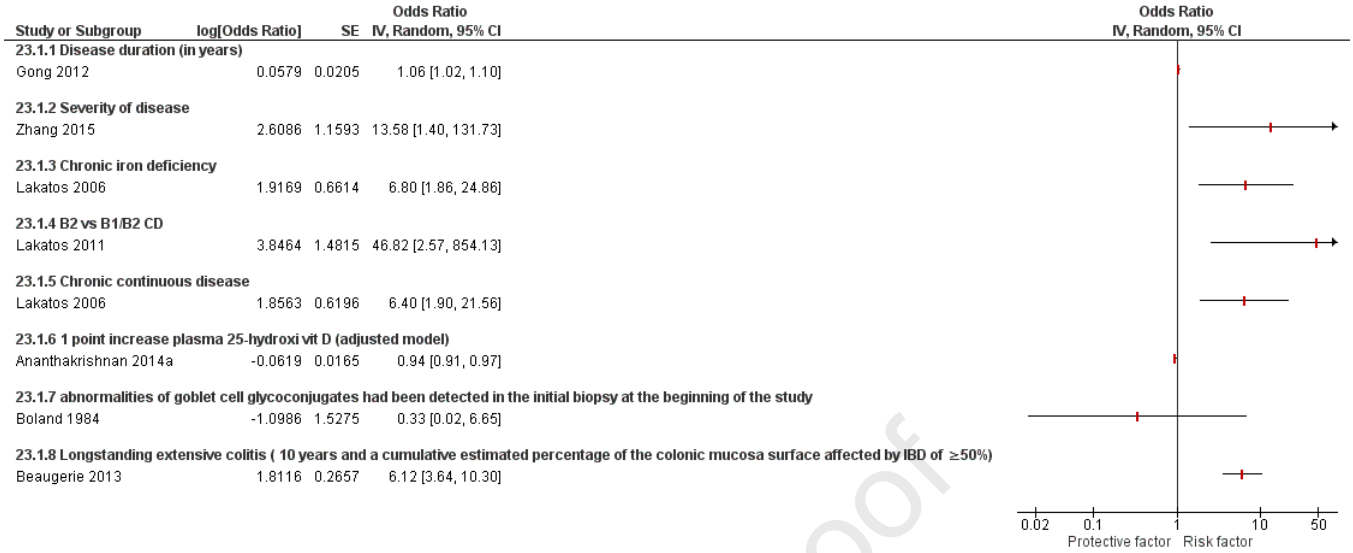
Supplementary Figure 40I: Case-control univariable analysis OR



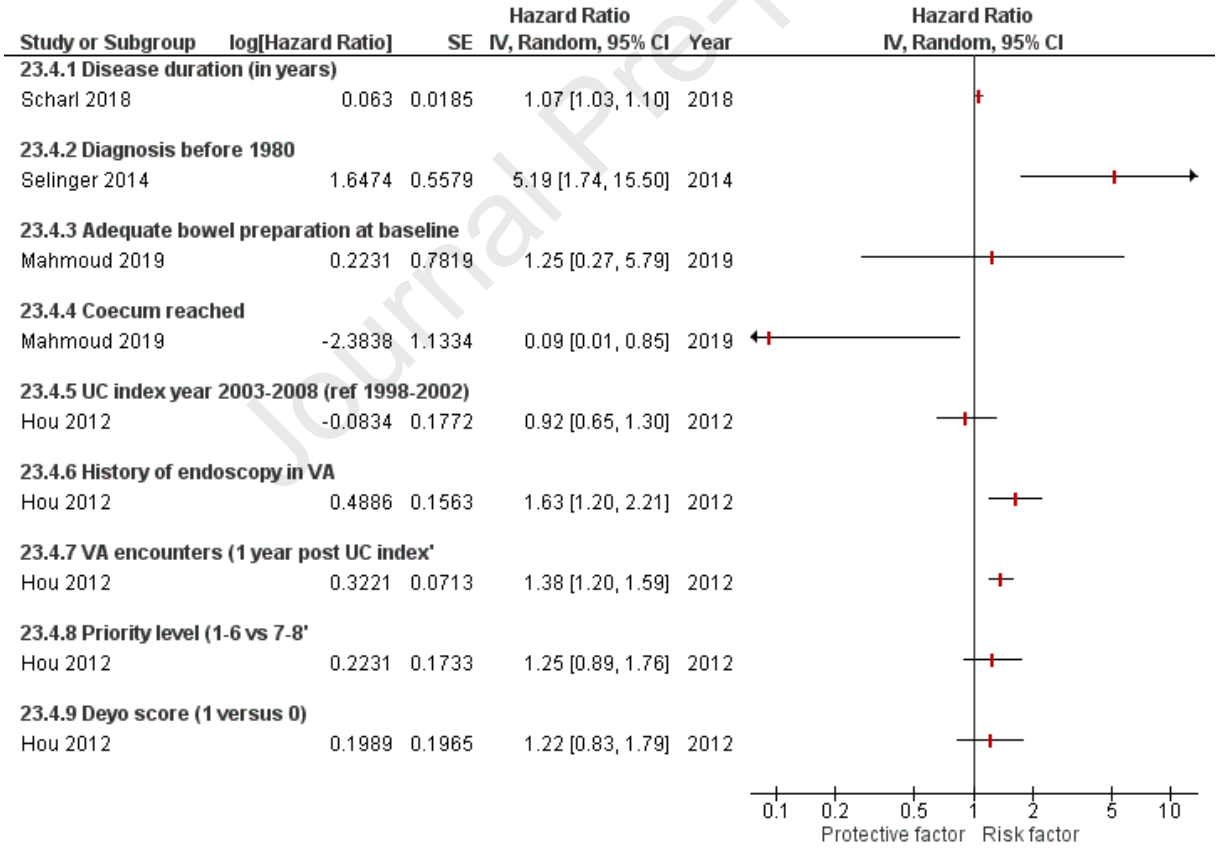
Supplementary Figure 40J: Case-control univariable analysis HR



Supplementary Figure 40K: Cohort univariable analysis OR

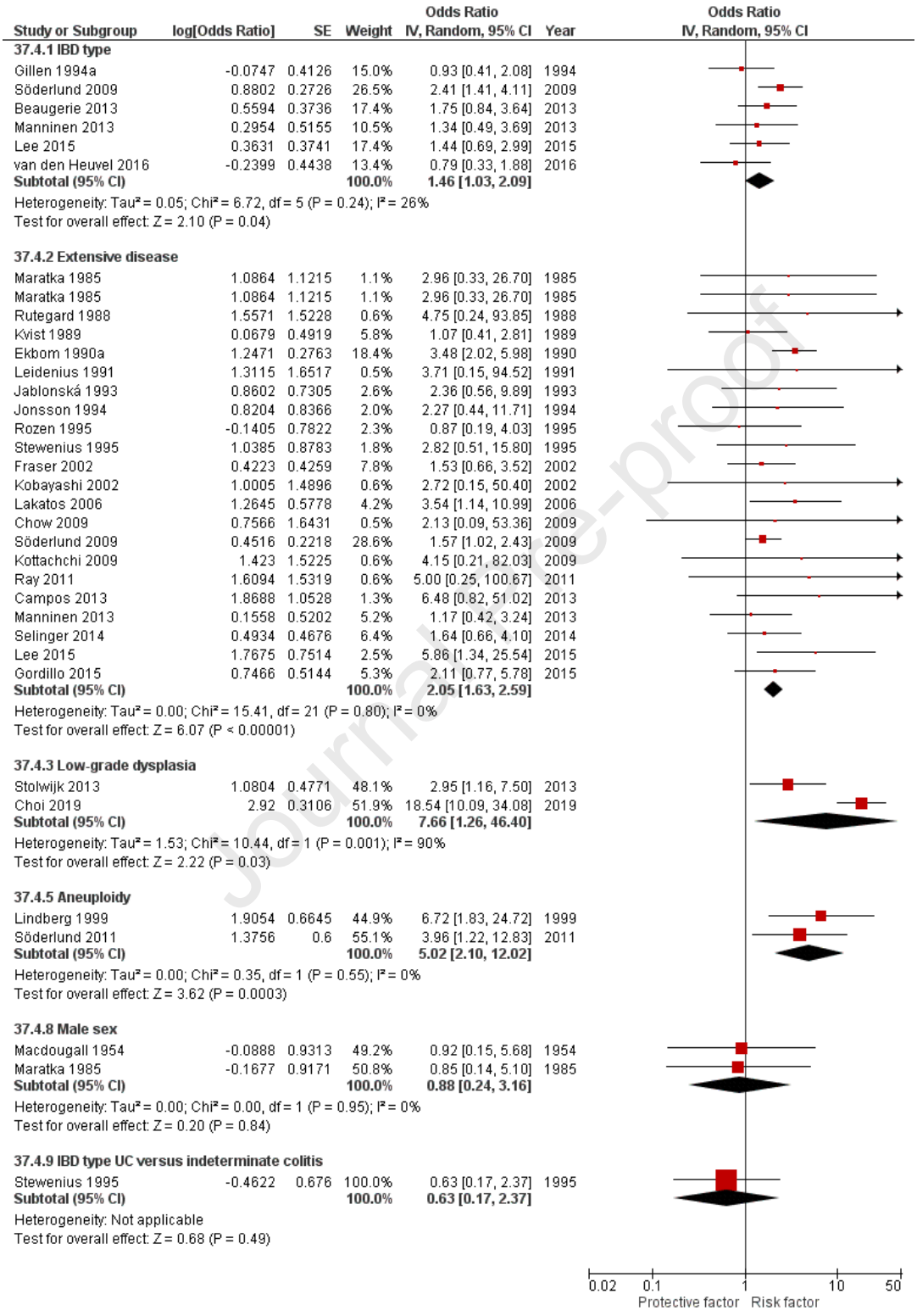


Supplementary Figure 40L: Cohort univariable analysis HR

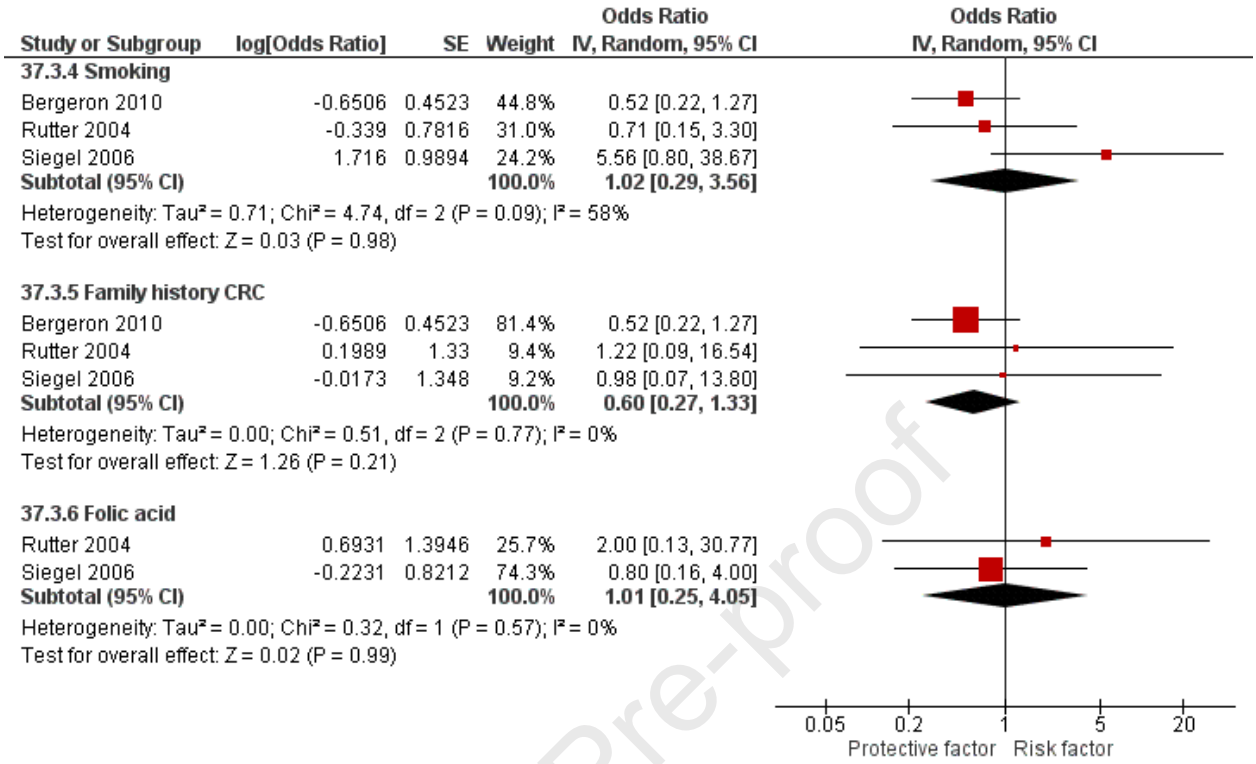


Supplementary file 41A-H: Good quality synthesis

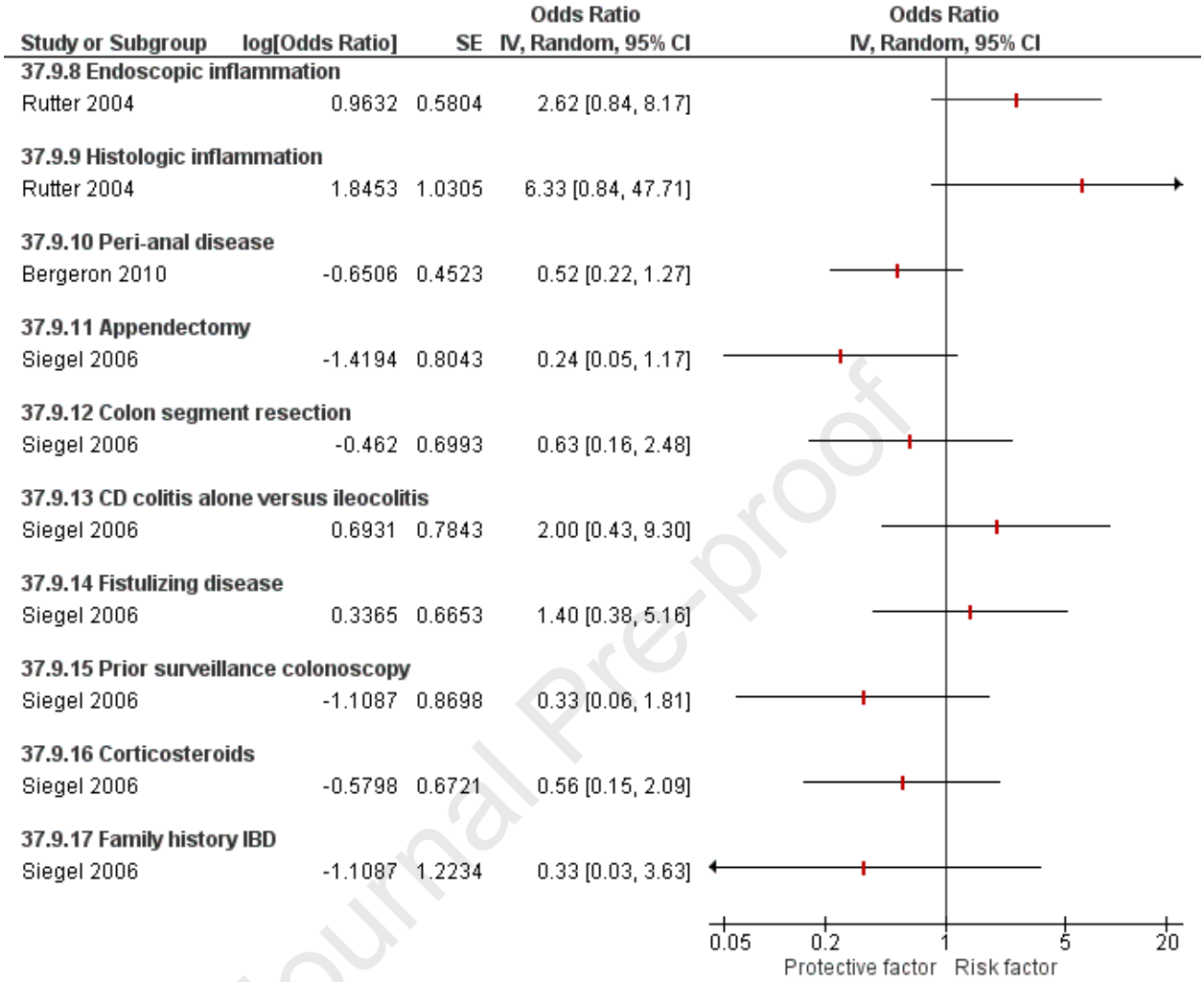
Supplementary Figure 41A: Forest plot of univariable OR cohort studies



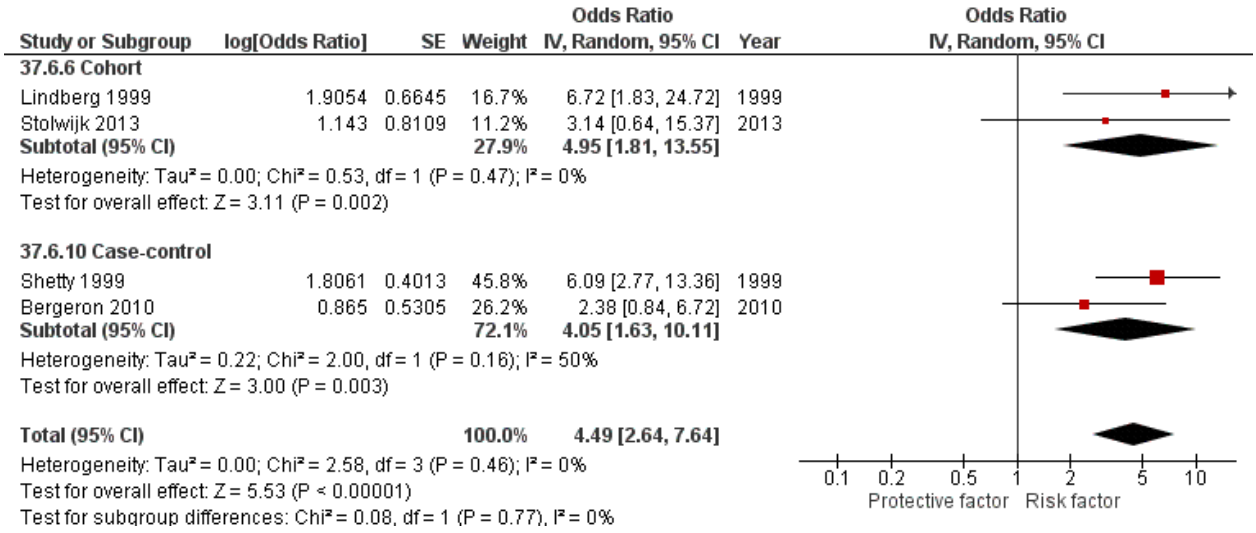
Supplementary figure 41B.1: Forest plot of univariable OR case-control studies, pooled analysis possible



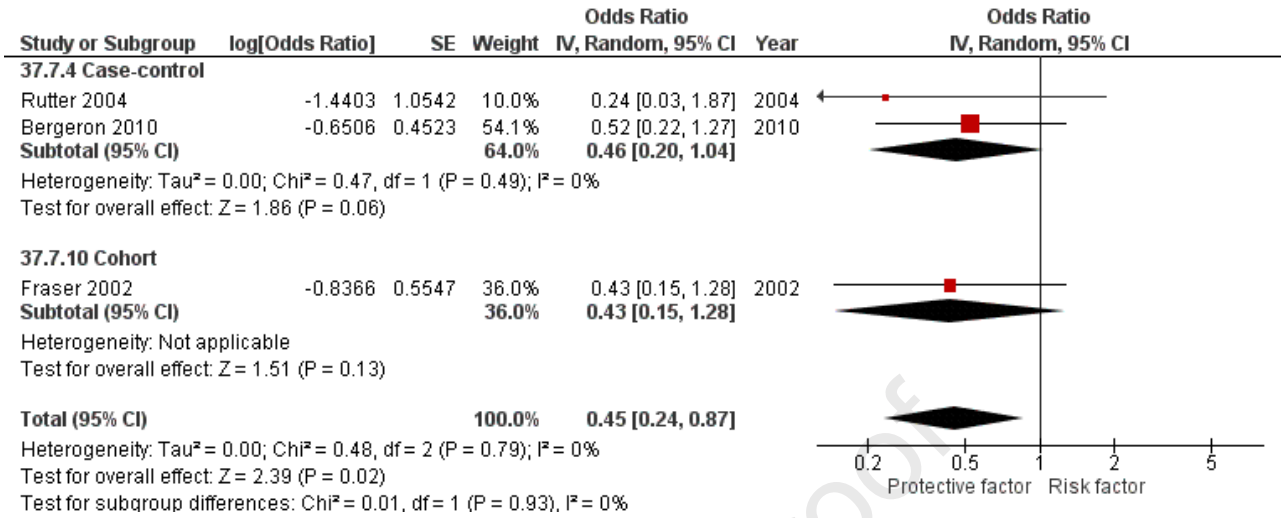
Supplementary figure 41B.2: Forest plot of univariable OR case-control studies, no pooled analysis



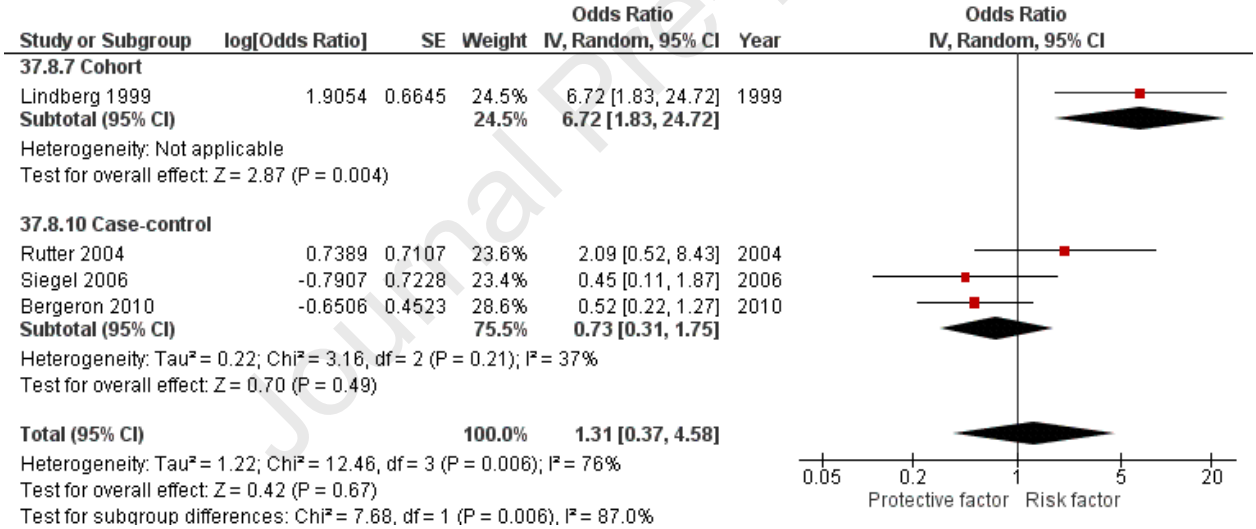
Supplementary figure 41C.1: Forest plot PSC of univariable OR cohort and case-control studies pooled



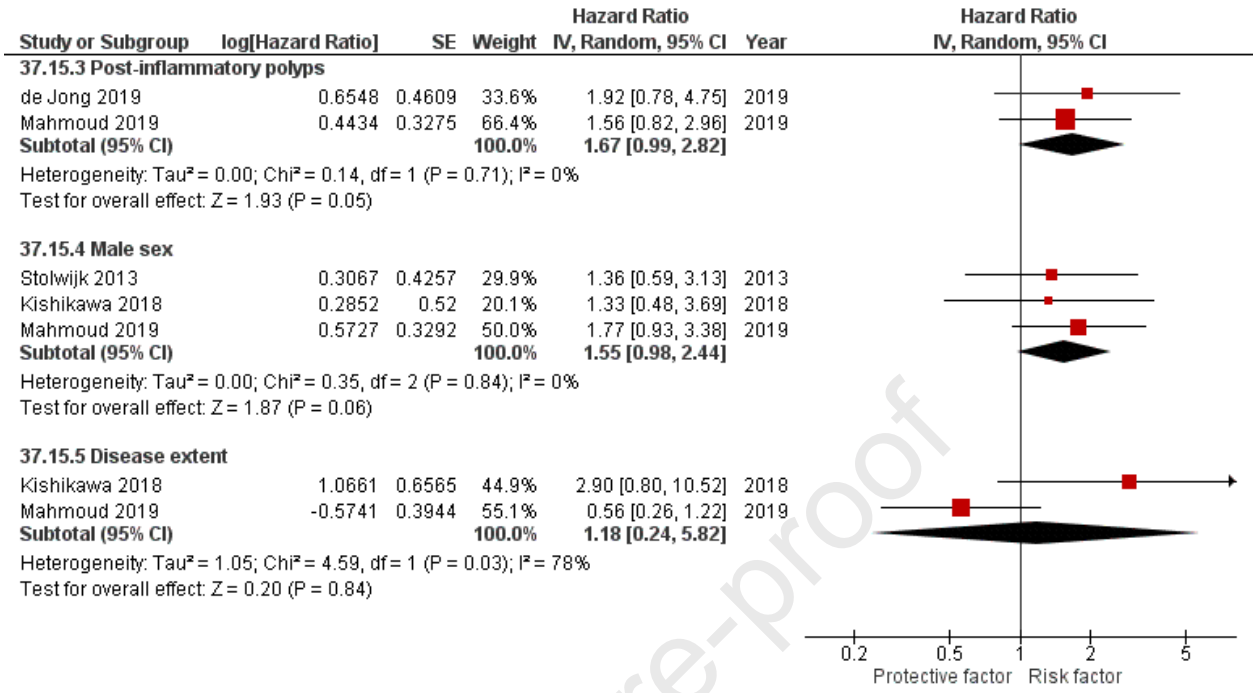
Supplementary figure 41C.2: Forest plot Thiopurines of univariable OR cohort and case-control studies pooled



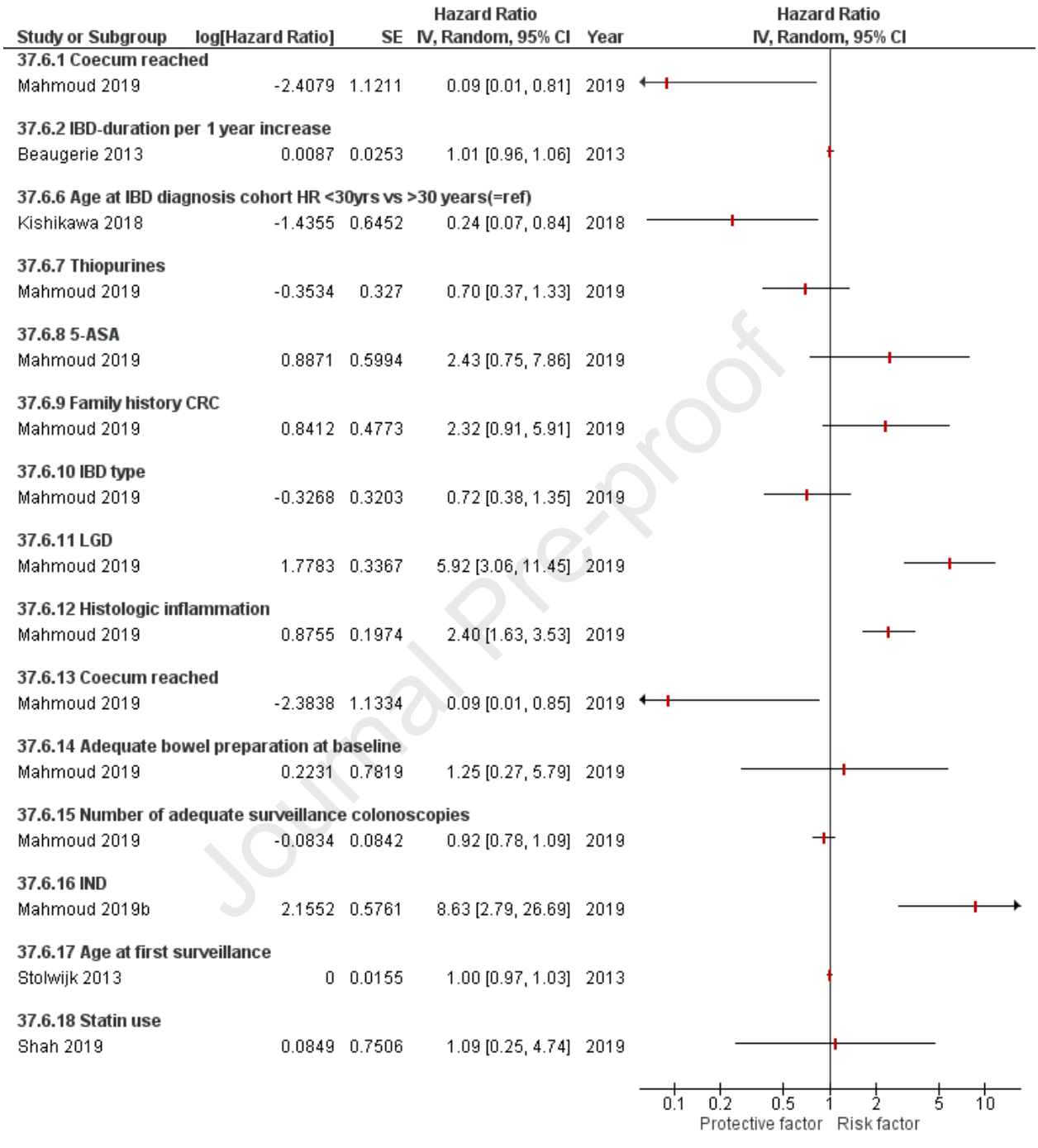
Supplementary figure 41C.3: Forest plot 5-ASA of univariable OR cohort and case-control studies pooled



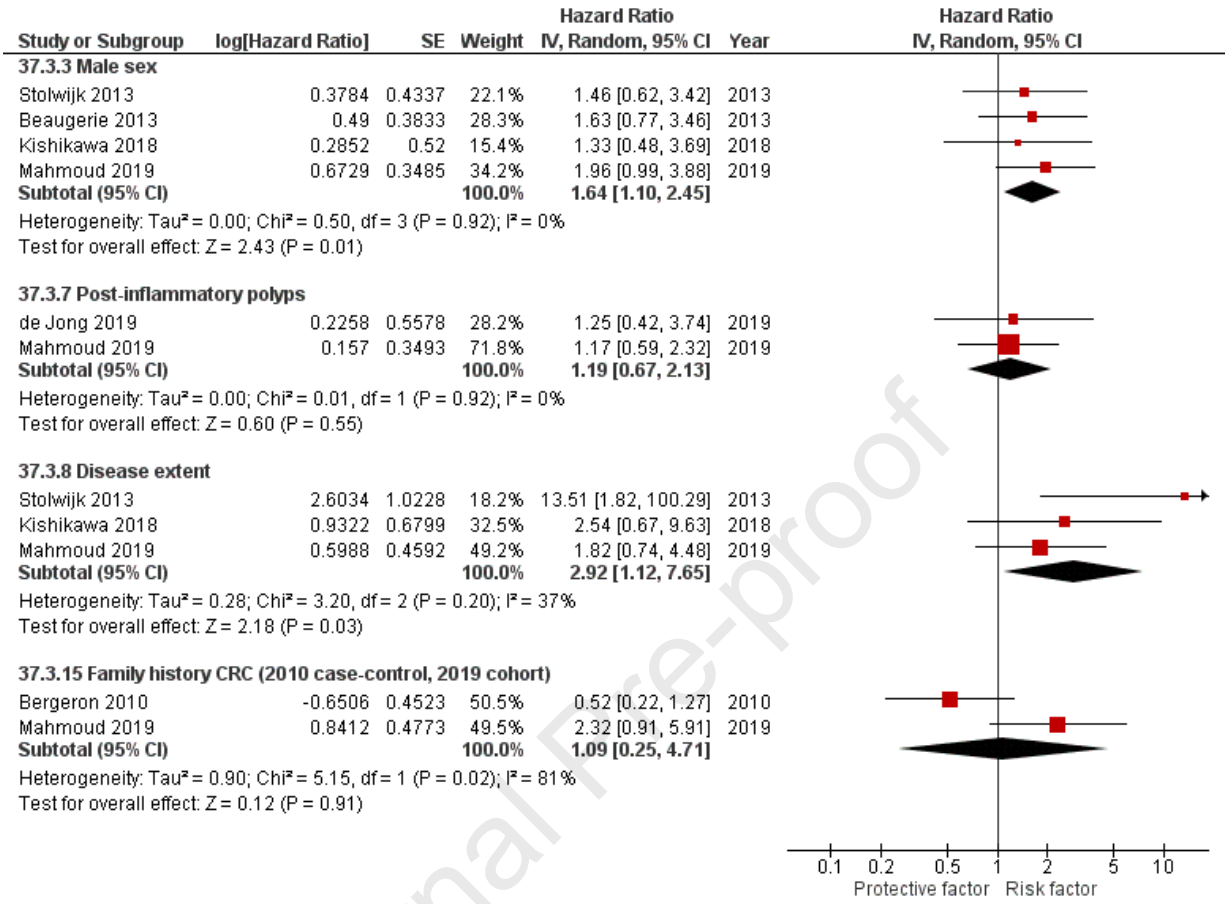
Supplementary figure 41D: Forest plot of univariable HR cohort studies, pooled analysis



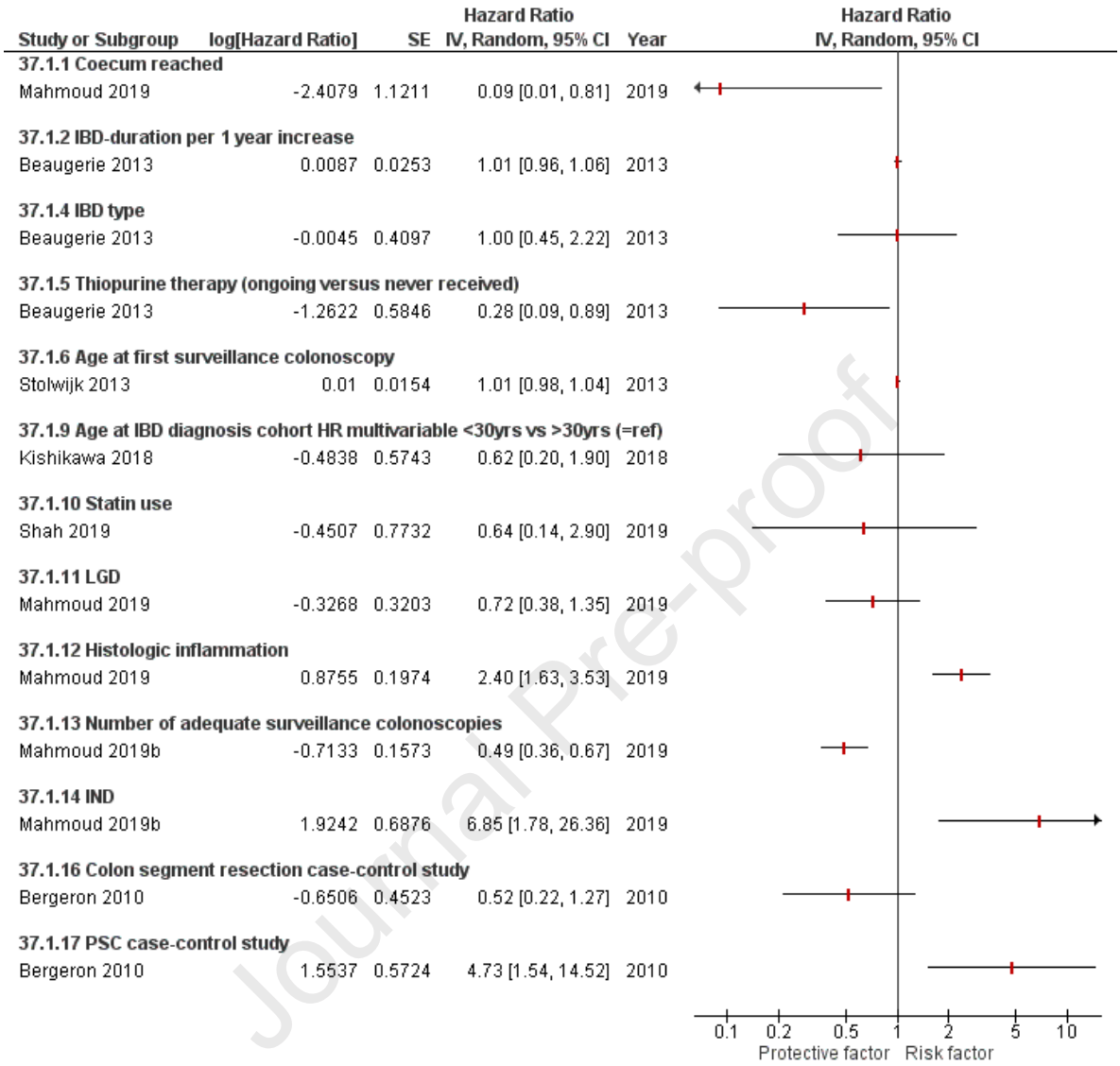
Supplementary figure 41E: Forest plot of univariable HR cohort studies, no pooled analysis



Supplementary figure 41E: Forest plot of multivariable HR cohort (and case-control study if mentioned), pooled analysis possible



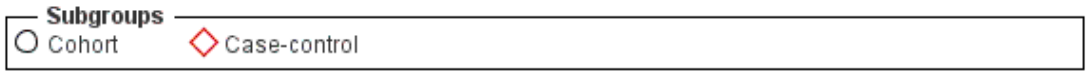
Supplementary figure 41F: Forest plot of multivariable HR cohort and case-control studies, no pooled analysis

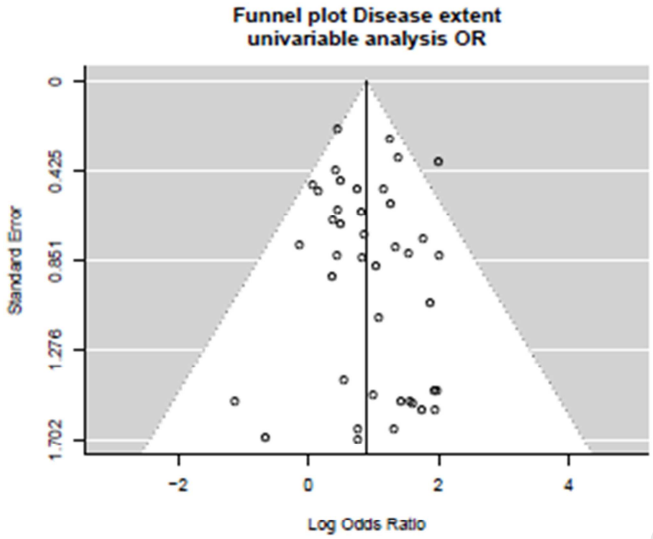


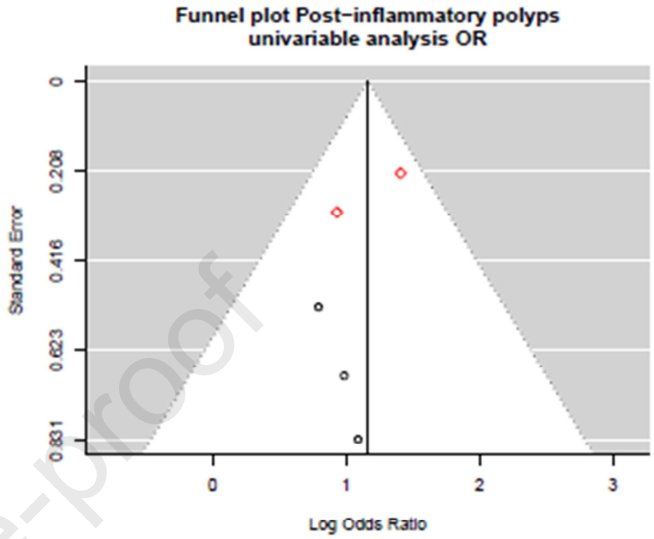
Supplementary file 42: Egger's regression test univariable analysis OR (≥ 10 studies)

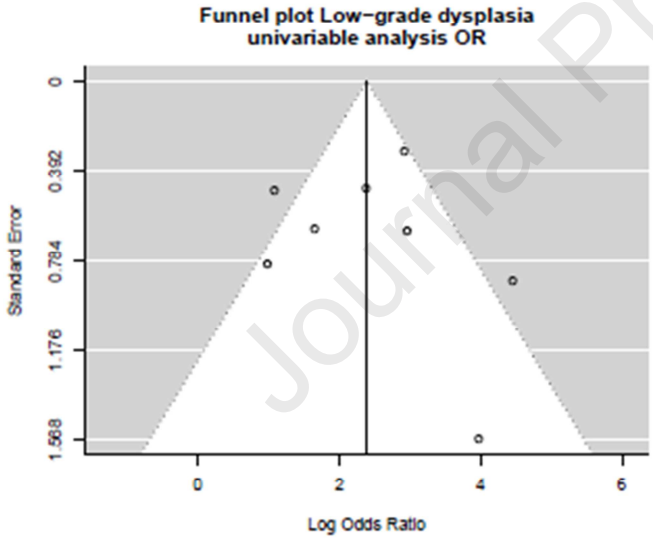
Prognostic factor	Index	Reference	N of studies	P-value Egger	N of cohorts	N of case-controls
PSC	PSC	No PSC	32	0.268	15	17
Sex	Male sex	Female sex	60	0.196	58	2
Thiopurine	Thiopurines	No thiopurines	20	0.141	8	12
5-ASA	5-ASA use	No 5-ASA use	20	0.336	6	14
Smoking	Smoking	No smoking	13	0.923	5	8
Family history CRC	Positive family history CRC	No family history CRC	15	0.558	6	9
Disease extent	Extensive disease	No extensive disease	41	0.667	41	0

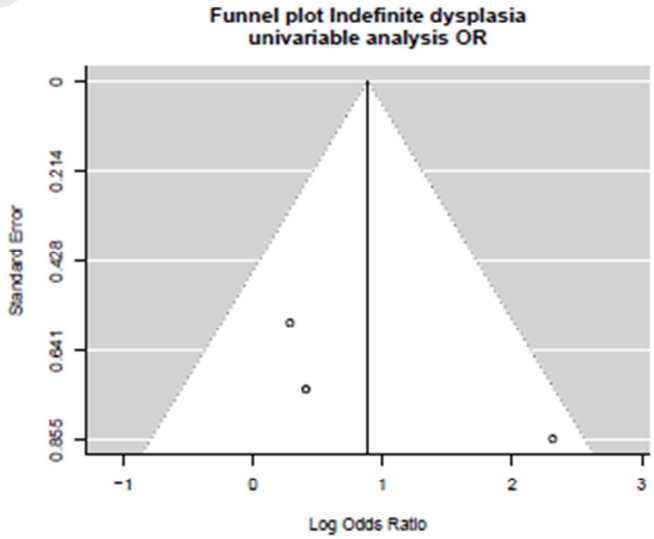
Supplementary file 43: Funnel plot univariable OR analyses

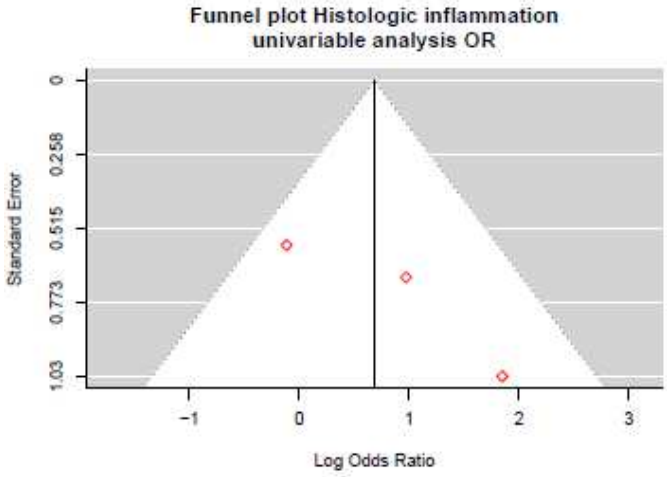


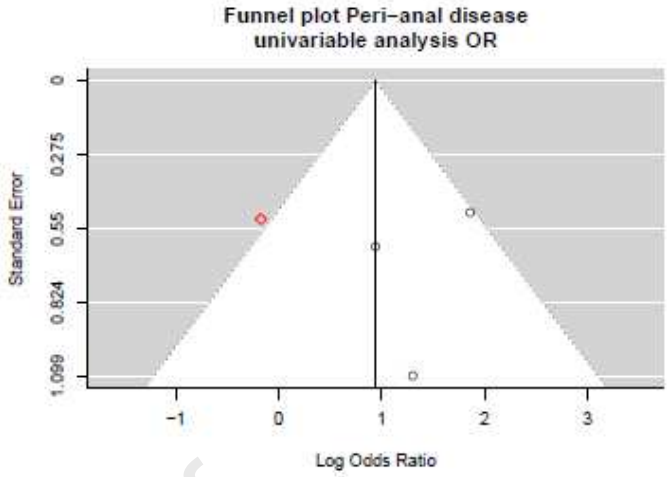


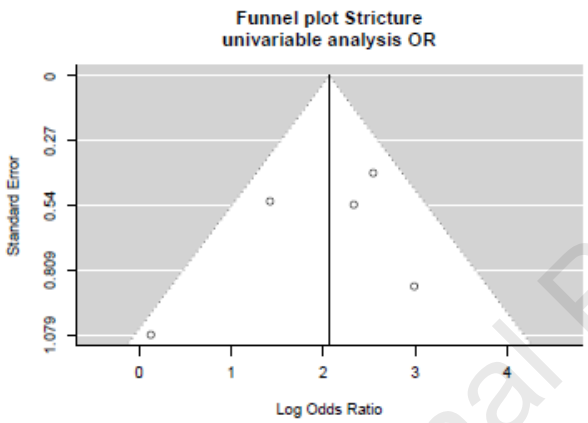


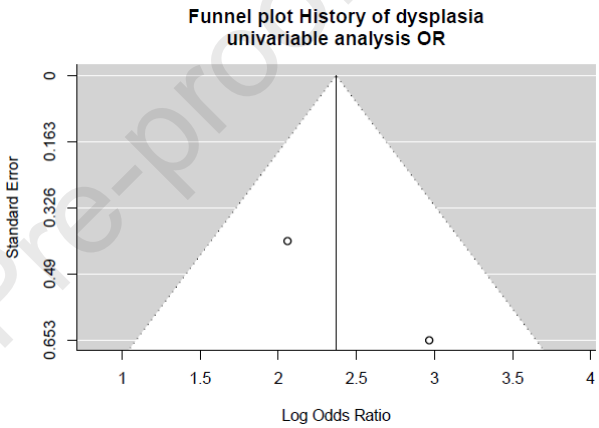


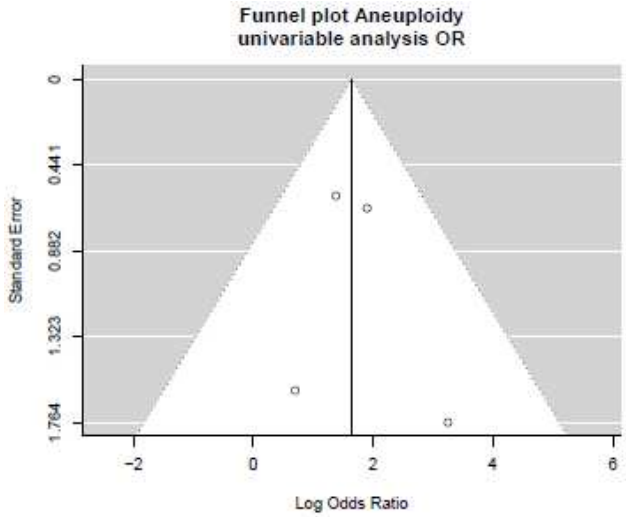


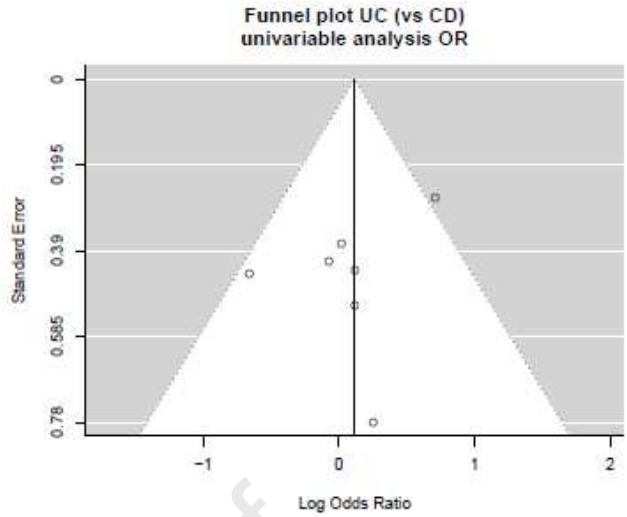


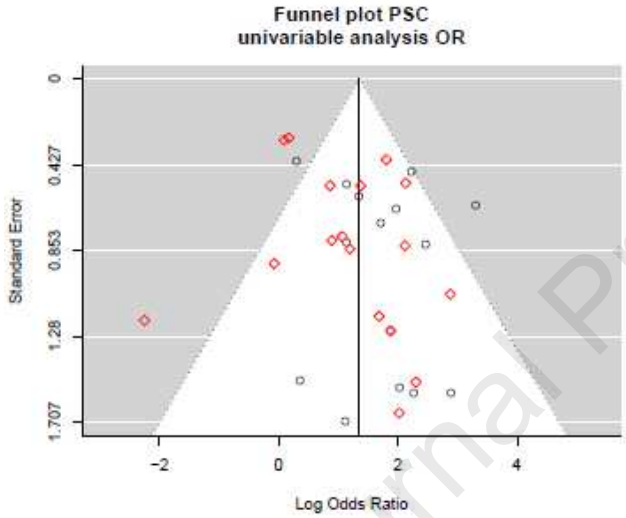


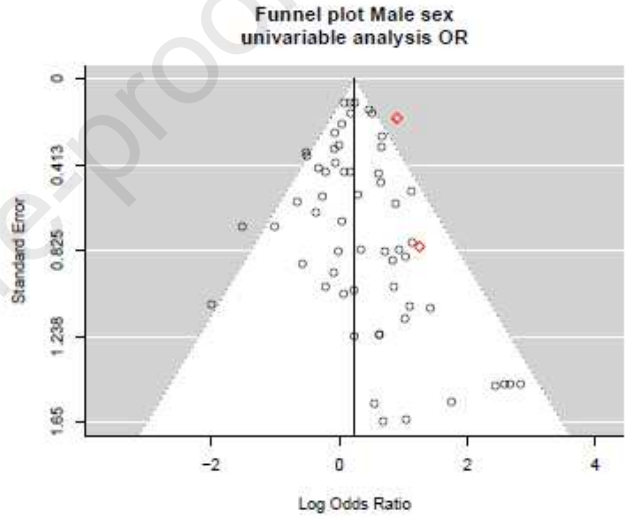


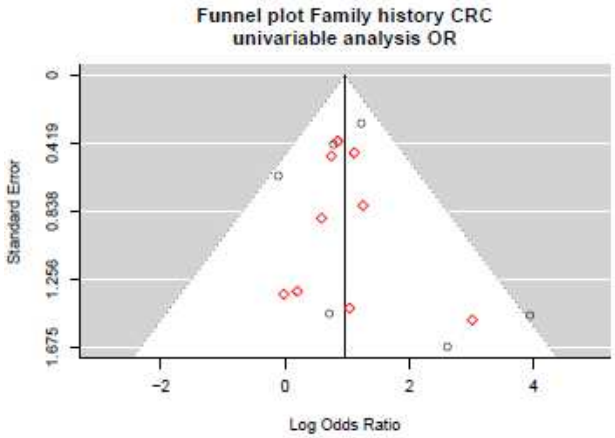


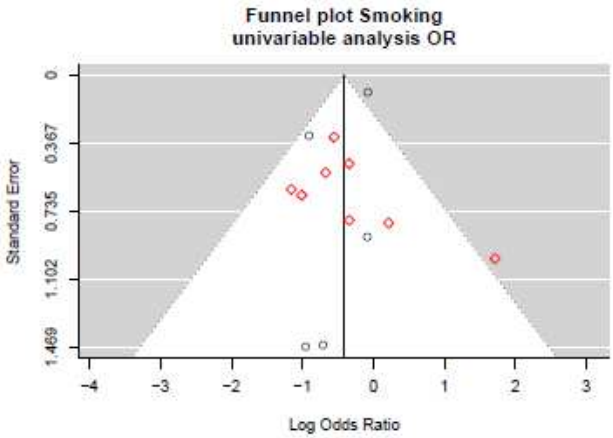


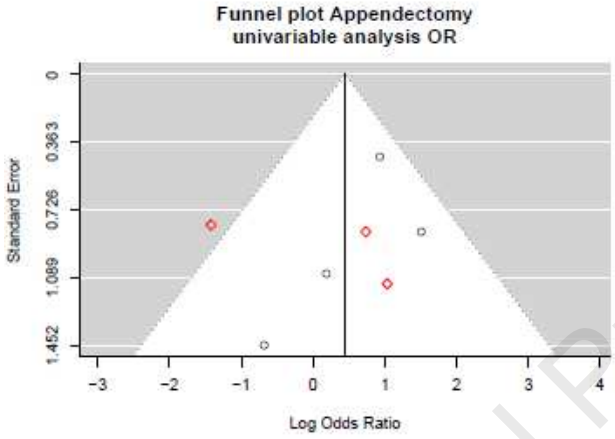


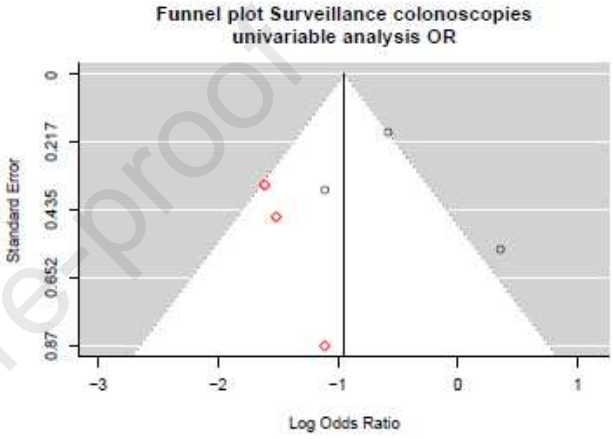


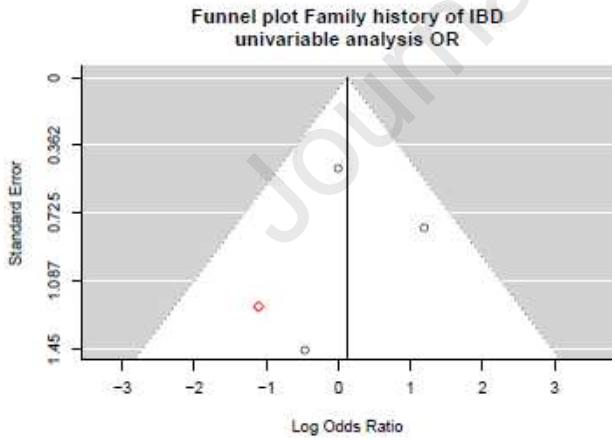


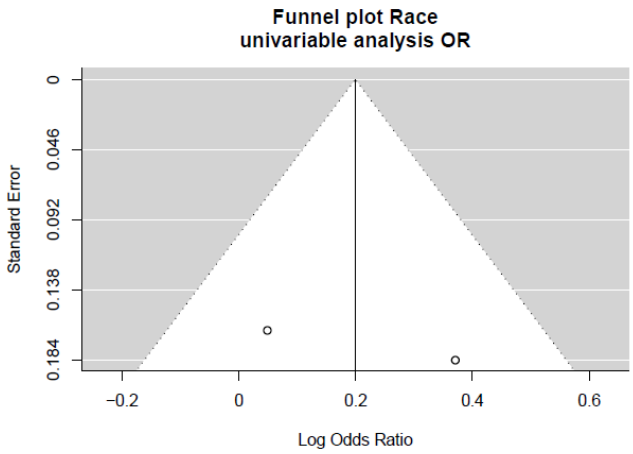


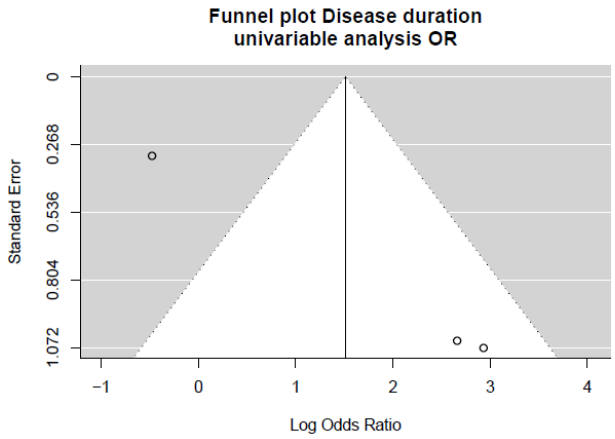


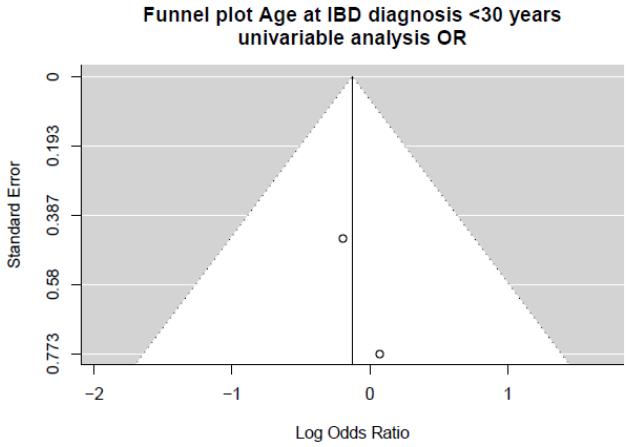


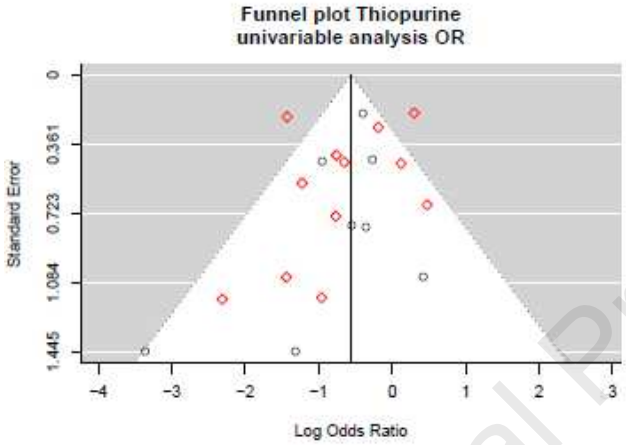


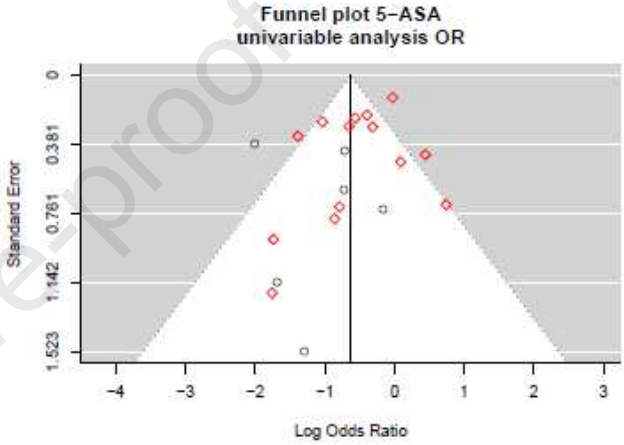


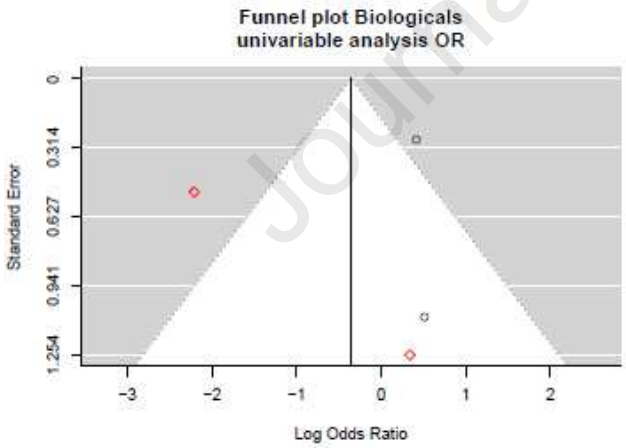


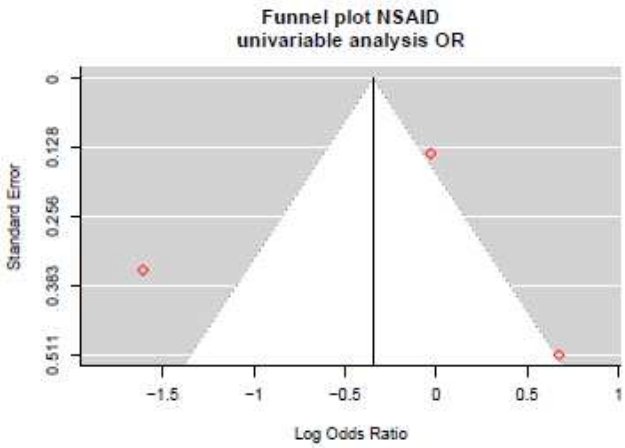


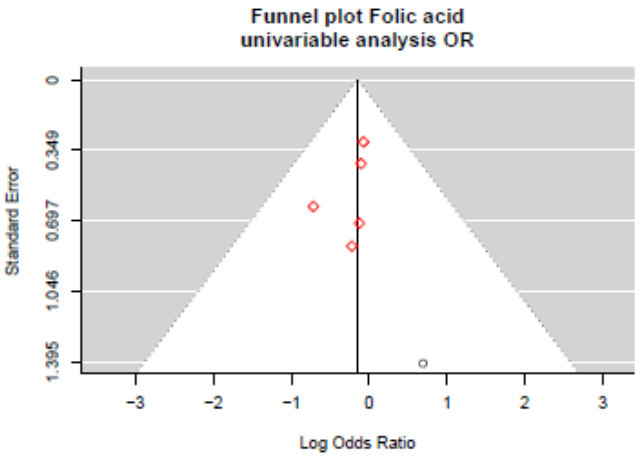


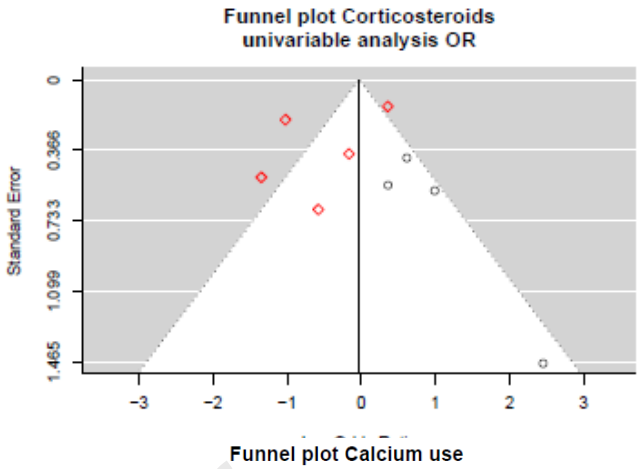


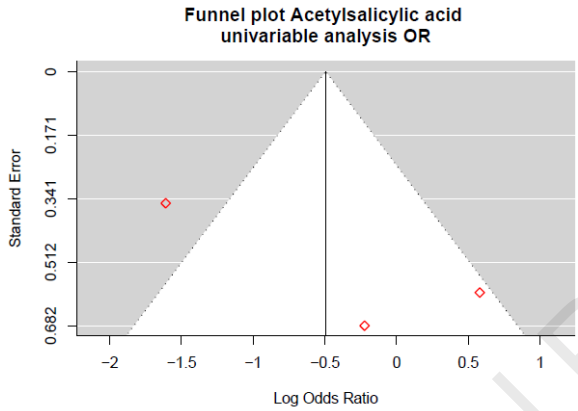


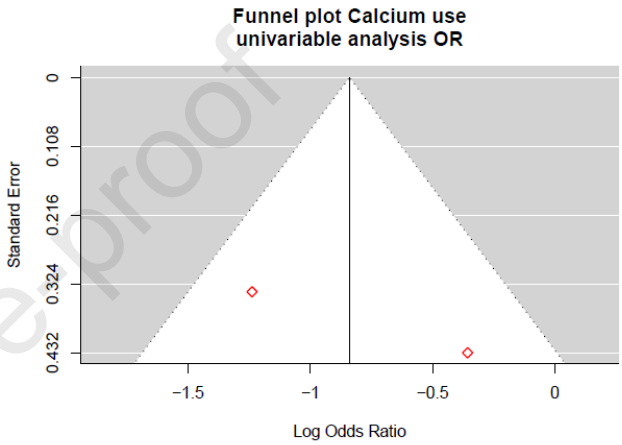












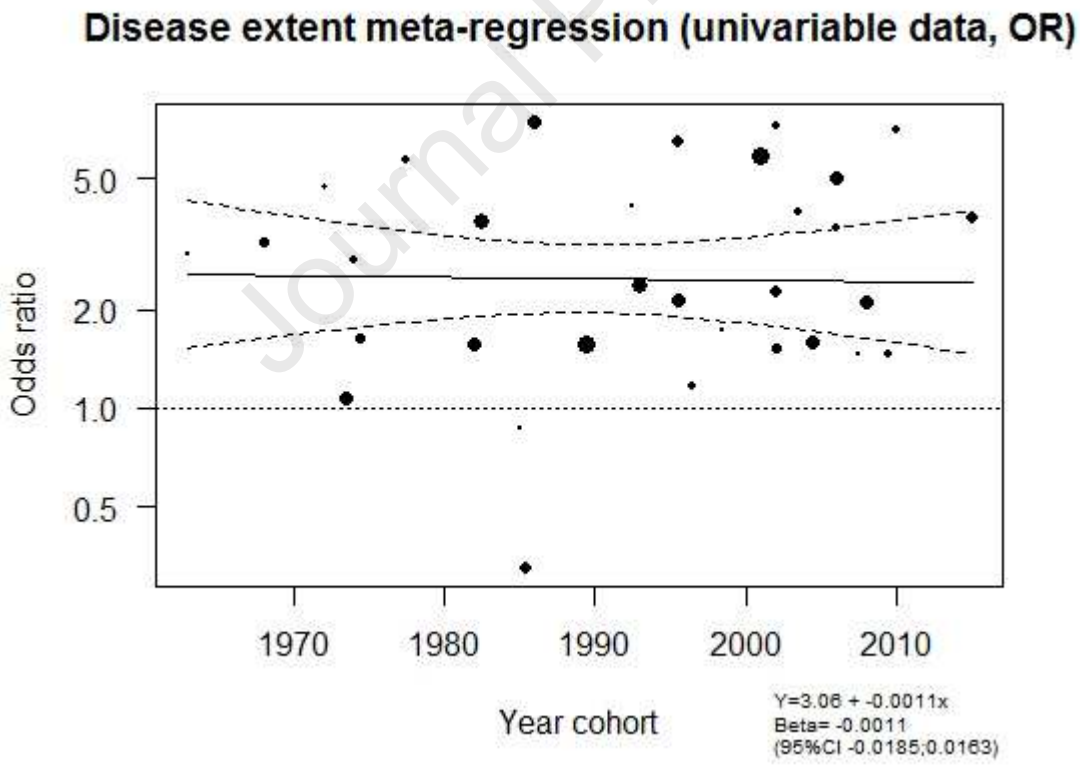
Supplementary file 44A-C: Meta-regression (univariable OR analyses)

Supplementary Table 44A: Results meta-regression of calendar time

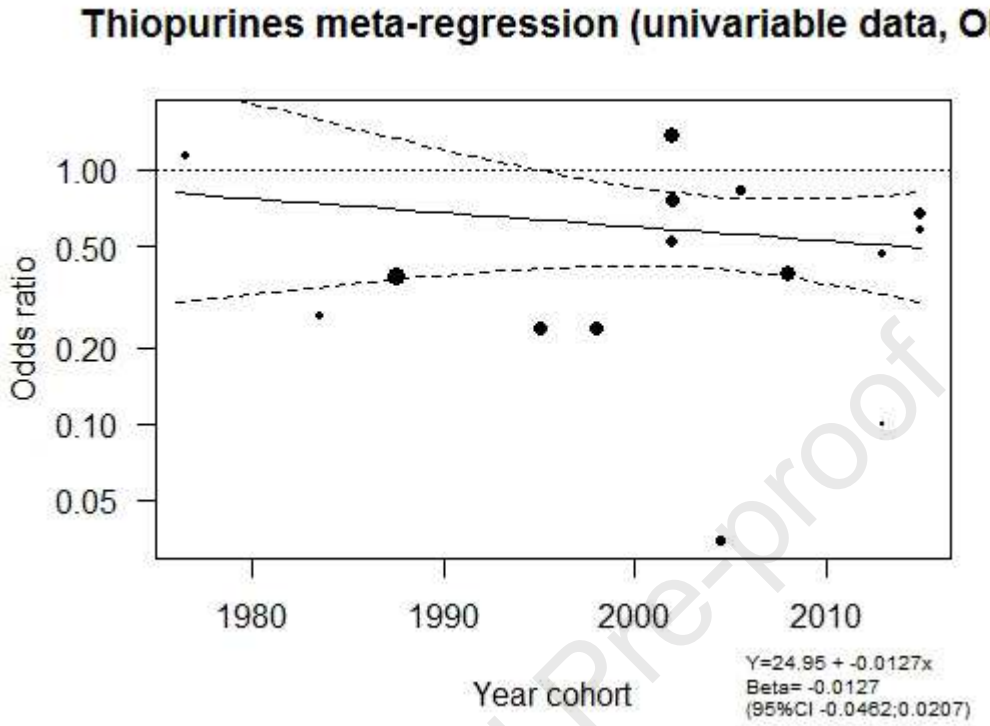
Prognostic factor	Test of moderators	Test for residual heterogeneity	Z-value meta-regression model (p-value, 95% CI)
Disease extent	p .90	p .52	-0.12 (p .90, 95%CI -0.019-0.016)
Thiopurines	p .46	p < .01	-0.75 (p .46, 95%CI -0.046-0.021)
5-ASA	p .95	p < .01	-0.06 (p .95, 95%CI -0.049-0.046)

Based on the test of moderators (omnibus test) and meta-regression analyses, we conclude that none of the evaluated prognostic factors displayed statistically significant temporal changes in effect size (supplementary table 44A). Scatterplots in which each study was proportionally sized to the precision of the study indicated a possible reduced risk over time for thiopurines (supplementary figure 44B). The test for residual heterogeneity was significant for thiopurines and 5-ASA, indicating a role for other moderator variables influencing the effect sizes of these prognostic factors.

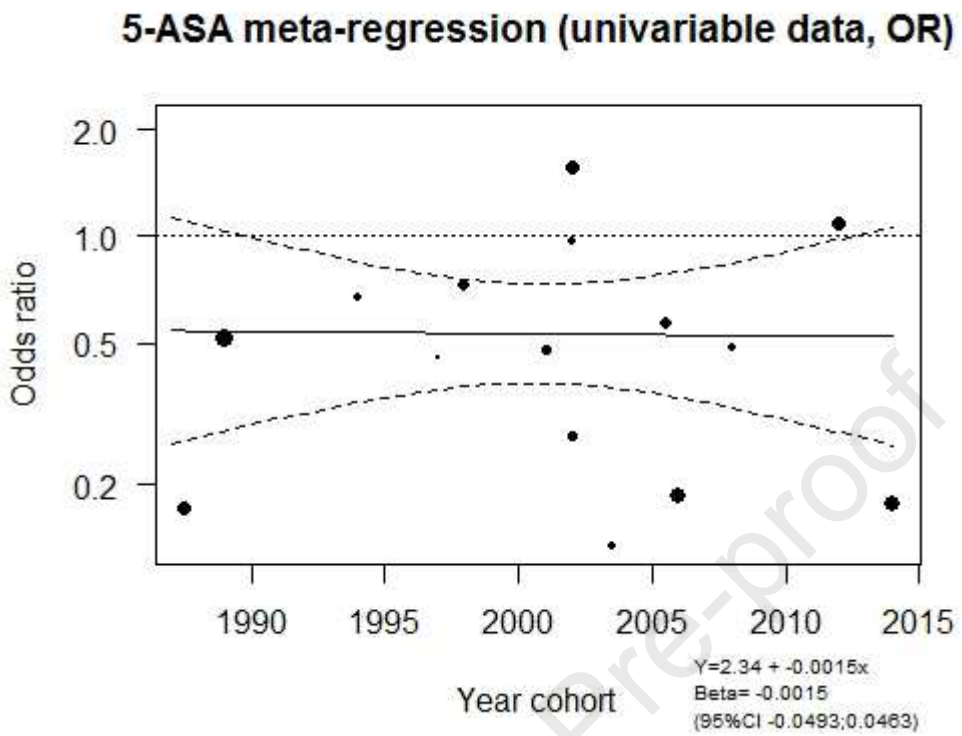
Supplementary Figure 44A: Disease extent meta-regression (extensive versus limited extent), moderator variable 'year cohort'



Supplementary Figure 44B: Thiopurines meta-regression (yes versus no), moderator variable 'year cohort'



Supplementary Figure 44C: 5-ASA meta-regression (yes versus no), moderator variable 'year cohort'



Supplementary file 45: Summary of identified protective factors for aCRN

We observed that thiopurines protected against the development of aCRN in univariable pooled analyses (OR and HR). This association was not observed in our pooled multivariable analyses (OR and HR). Two[1,2] out of 3 [1-3] previous meta-analyses on the impact of thiopurines showed similar results as our study. Also, the use of 5-ASA has a protective effect in both pooled univariable and multivariable analyses (OR), in line with two previous meta-analyses. [4,5] However, this effect was not observed in univariable and multivariable HR analyses. No previous meta-analysis evaluated the effect of TNF-alpha inhibitors on aCRN or CRC. Our pooled univariable OR analysis did not show a protective effect (OR 0.71, 95% CI 0.14-3.67). One study reported a protective effect in multivariable analysis (HR 0.22, 95% CI 0.10-0.50) [6] and one study did not find an association (OR 1.01, 95% CI 0.62-1.65). [7] The anti-inflammatory mechanisms of these medications may underlie the lower risk of aCRN. One can speculate that no protective effect was found for TNF-alpha inhibitors as a result of selection bias, as patients who use anti-TNF are generally the patients with a more severe disease.

One can speculate that the protective effect of smoking in the pooled univariable OR analysis (0.66, 95% CI 0.49-0.91) is related to the anti-inflammatory effect of smoking in UC patients.[8] In our pooled multivariable analysis we did not observe any association (OR 1.27, 95% CI 0.75-2.13).

In accordance with a recent meta-analysis reporting a lower CRC risk in IBD patients undergoing surveillance (OR 0.58, 95% CI 0.42-0.80)[9], we found surveillance colonoscopies to be protective for the development of aCRN (univariable OR 0.39,

95% CI 0.23-0.66). It should be noted that the definitions used in the included studies varied widely (supplementary file 15E).

In contrast to a previous meta-analysis (pooled OR 3.97, 95% CI 1.35-11.70)[10], we did not observe an association between appendectomy and subsequent development of aCRN in 7 studies (6 studies in UC patients). This difference may be explained by the different selection of studies. We identified additional studies and we excluded cohorts that included only patients who had received a proctocolectomy. We excluded 'proctocolectomy only' cohorts since these cohorts do not represent the general IBD population, but generally patients with more severe disease or patients who had severe dysplasia.

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Supplementary file 46: References from included studies (from supplementary file 3 and 5)

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