Risk of Cancers in Patients with Pediatric Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis

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Objectives We performed a systematic review and meta-analysis to evaluate the risk of the development of cancers in patients with pediatric-onset inflammatory bowel disease (IBD).

Study design A computerized literature search was performed. The primary outcome was the pooled incidence of cancer in studies reporting the risk as a standardized incidence ratio. The secondary outcomes were the pooled incidence rates of all cancers and site-specific cancers including colorectal cancer and hematologic cancers.

Results Sixty-six studies reporting outcomes in 38 092 patients were included. The pooled standardized incidence ratio for cancer was 2.39 ($P < .0001$, 95% CI 2.00-2.86) in IBD. The pooled incidence rates for cancer in patients with Crohn's disease (CD) and ulcerative colitis (UC) were 0.014 (95% CI 0.0087-0.021) and 0.031 (95% CI 0.018-0.052), respectively. The pooled incidence rate of colorectal cancer in CD and UC were 0.0075 (95% CI 0.0049-0.011) and 0.020 (95% CI 0.012-0.034), respectively. The pooled rates of hematologic cancers in CD and UC were 0.0061 (95% CI 0.0040-0.0090) and 0.0045 (95% CI 0.0026-0.0079), respectively. Cumulative meta-analyses showed a decreasing trend in the incidence of these cancers in both CD and UC.

Conclusions Patients with pediatric-onset IBD had an increased risk of cancer development compared with the general population, however, incidence appeared to be decreasing in recent years. *(J Pediatr 2021;229:102-17)*.

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The incidence of childhood-onset inflammatory bowel disease (IBD) is increasing,[1] therefore, understanding the risks of the disease complications, including cancer development, is essential in providing adequate care throughout the transition from pediatric to adult IBD.

Chronic inflammation is a known risk factor for the development of cancer in IBD. Beyond the recognized association between IBD and the increased risk of colorectal cancer (CRC),[2] recent data have expanded the concept to inflammation as a driver of tumor progression.[3] In addition, the increasingly widespread use of immunosuppressive therapies in the management of Crohn's disease (CD) and ulcerative colitis (UC) raises concerns about the risk of cancer development secondary to such therapies. Immunosuppressive therapies increase the risk of lymphoma and skin cancer in transplant recipients as well as patients with rheumatoid arthritis and psoriasis.[4]

There have been some reports that cancers were more likely to occur in patients with pediatric-onset IBD.[5,6] A previous meta-analysis provided an overview of patients with IBD diagnosed at pediatric age who developed cancer or suffered a fatal outcome at any point later in life.[7] However, the risk of cancer development in patients with pediatric-onset IBD remains largely unknown, in spite of the risk of cancer development including CRC[8,9] and lymphoma[10] in patients with adult-onset IBD has been previously identified. In addition, we sought to find out the frequency of cancer and the relationship with background factors of cancer in childhood-onset IBD, which have not been studied in detail in the previous meta-analysis. In the present systematic review and meta-analysis, we aimed to assess the risk of cancer development in patients with IBDs diagnosed in their childhood.

CD	Crohn's disease
CRC	Colorectal cancer
IBD	Inflammatory bowel disease
RCT	Randomized controlled trial
SEER	Surveillance, epidemiology, and end result
SIR	Standardized incidence ratio
TNF	Tumor necrosis factor
UC	Ulcerative colitis

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Methods

We performed this study according to a priori defined protocol and in accordance with the PRISMA guidelines and Meta-Analysis of Observational Studies in Epidemiology guidelines.[11,12] The protocol of this meta-analysis has been registered to International prospective register of systematic reviews (PROSPERO[13] CRD42017076264).

Data Sources

A computerized literature search was performed on PubMed/MEDLINE, Google Scholar, Scopus, EMBASE, and Cochrane Central Register of Controlled Trials (inception to June 30, 2018). An update literature search was undertaken on April 30, 2020 for PubMed/MEDLINE, Google Scholar, Scopus, and Cochrane Central Register of Controlled Trials. For Google Scholar, only the first 1000 articles were reviewed in each search, as it does not provide results beyond it. We also searched abstracts from medical conferences (Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, European Crohn's and Colitis Organisation, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, American Society of Hematology, European Hematology Association, American Society of Clinical Oncology, European Cancer Congress) and bibliographies of identified articles for additional references (inception to April 30, 2020).

Search Strategy and Study Selection

To be eligible for inclusion, we considered prospective and retrospective studies evaluating the risk of cancer development in patients with IBD diagnosed prior to age 18 years (further referred to as pediatric IBD).[14] Studies were eligible if the included subjects were of a pediatric population (age <18 years) or an adolescent (age ≤25 years) as well as childhood population with the majority of the included subjects less than age 18 years. Studies were required to report outcomes specifically for IBD, CD, UC, or indeterminate colitis. There were no restrictions regarding date of study, sex of the subjects, or duration of the study. We imposed no geographic or language restrictions and articles in languages other than English were translated if necessary. Two authors independently screened each of the potential titles, abstracts, and/or full-manuscripts to determine whether they were eligible for inclusion. Studies were initially excluded based on their title. Next, the abstract or full text were reviewed to assess eligibility. Areas of disagreement or uncertainty were resolved by consensus among the authors. The corresponding authors of studies were contacted to provide additional information on studies if required. Studies were identified with the terms: "inflammatory bowel disease," "Crohn's disease," or "ulcerative colitis." These were combined by using the set operator AND with studies identified with the terms: "pediatric*," "childhood," "cancer*," "malignancy*," "colorectal cancer*," "hematologic cancer*," "Hodgkin's lymphoma," "non-Hodgkin's lymphoma," "lymphoma," and "leukemia" (both as medical subject headings and free text terms). Details of PubMed/MEDLINE search is shown in **Table I** (available at www.jpeds.com), as one of the search strategies. PRISMA flow diagram, describing the number of studies identified from the search strategy and retained at each stage, is described in **Figure 1** (available at www.jpeds.com).

Data Extraction and Quality Assessment

All data were independently extracted in duplicate by 2 authors by using a data extraction form. The 2 authors' data extraction were found to be consistent. Data on the study characteristics, such as author name, year of publication, country, sample size, age of patients, comorbidity, outcome, and incidence of adverse effects, were collected. The Jadad score[15] and Cochrane Risk of Bias Assessment Instrument,[16] a scale that assesses the methodological quality of a clinical trial, were used to assess the quality of randomized controlled trials (RCTs). The Newcastle-Ottawa Scale was used to assess the quality of the observational studies.[17] Star rating of 0-9 was allocated to each study based on 3 parameters (selection, 0-4; comparability, 0-2; and outcome, 0-3). Studies receiving 6 or more stars are considered high quality.[18,19] The overall quality and the risk of bias level in this systematic review were assessed using the GRADE criteria (Grading of Recommendations Assessment, Development and Evaluation)[20] using GRADEpro.[21]

Outcome Assessment

The primary outcome of interest was the pooled risk of cancer development among studies that reported the risk as a standardized incidence ratio (SIR). The secondary outcome of interest was the pooled incidence rates of all cancers and site-specific cancers including CRC and hematologic cancers (Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia). We conducted subgroup meta-analyses for each assessment. In addition, we performed meta-regression analyses to evaluate whether incidences of cancer were influenced by medication type. We also assessed temporal trends in the risk of cancers by cumulative meta-analyses. The secondary outcomes except for the pooled incidence rates of all cancers and site-specific cancers deviated from the registered PROSPERO protocol: these outcomes were determined to be necessary for this study after registration to PROSPERO.

Statistical Analyses

Random-effects meta-analysis was performed to assess the risk of cancer development among patients with pediatric IBD. We evaluated the presence of heterogeneity across trials of each therapy by using the I^2 statistic. I^2 <25% indicates low heterogeneity, 25%-75% moderate heterogeneity, and >75% high heterogeneity.[22] Statistic Q (Q) was also used with a probability (P) value of <.10 as evidence of statistically significant heterogeneity.[23] We conducted subgroup meta-analyses, which were performed for both CD and UC, or meta-regression to examine potential sources of heterogeneity, where indicated, with factors such as age, sex, disease duration, and concomitant anti-tumor necrosis factor

(TNF) agents or immunomodulator use. Accompanying each meta-regression, we also did the analyses of variance to find whether the amount of total variance was more than we would expect based on within-study error or not.[24] To assess the potential for small-study effect and publication bias, we performed Begg and Egger tests and constructed funnel plots to visualize possible asymmetry when 3 or more studies were available.[25,26] In addition, we conducted cumulative meta-analysis ranked by year to explore the temporal trend of the summary estimate. The temporal change of the cumulative meta-analysis was assessed by univariate regression analyses to evaluate whether the change was significant. In addition, influence analyses, by removing individual studies from the meta-analyses to assess the influence of any particular study on the results, and meta-analyses excluding studies with less than 30 patients were performed to assess the robustness of our results. All statistical analyses were performed with Comprehensive Meta Analysis V2 (Biostat, Englewood, New Jersey). *P* values that were <.05 were considered statistically significant except for the *Q* statistic *P* value. All statistical tests were 2-sided.

Results

Study Characteristics

We identified 969 127 citations through literature search and excluded 968 806 citations after initial screening of titles and abstracts; 321 full-text studies were evaluated for eligibility. After final review, 66 full text articles, including 38 092 patients were included in our analysis (**Figure 1**). Among the 66 studies, 44 studies included patients with CD, 31 studies included patients with UC, and 5 studies reported data on patients with IBD with no distinction made between CD or UC. Fourteen studies included data on both CD and UC. Fifty (75.76%) of the studies included patients under 18 years at diagnosis of IBD, and the remainder of the studies included patients who were aged 18-24 years at diagnosis. Thirty studies specified that the cancer occurred in childhood. Among 62 observational studies, 14 studies received 6 or more stars in the assessment by the Newcastle-Ottawa Scale, but the rest of the studies received 2 to 5 stars. Among 4 RCTs, all RCTs received 3 or 2 points in the assessment by the Jadad score. The quality of RCTs was also assessed by Cochrane Risk of Bias Assessment Instrument (**Table II**; available at www.jpeds.com). There was no inter-rater disagreement for the extracted data between the two authors. The characteristics and outcomes of the included studies are summarized in **Table III**. A summary of findings table (**Table IV**; available at www.jpeds.com) was created and exported from GRADEpro.

Meta-Analysis of the Overall Risk of Cancer Reported as SIR among Patients with Pediatric IBD

Six retrospective observational studies including more than 17 450 patients reported the overall risk of cancer as an SIR. Four studies reported outcome in both CD and UC. Two studies did not differentiate between CD and UC and one of these reported outcomes separately for patients exposed to biologic therapy (anti-TNFα agents) or not. Among 17 450 patients from 6 retrospective observational studies where SIR was reported, at least 125 patients developed malignancy, though 1 paper did not report the specific number of patients with malignancies. As shown in **Figure 2**, A, 4 studies included patients with CD and demonstrated a 2.4-fold increased risk of cancers (pooled SIR 2.42, $P < .0001$, 95% CI 1.90-3.06) with low heterogeneity ($I^2 = 0\%$). Five studies included patients with UC and also demonstrated a 2.1-fold increased risk of cancers (pooled SIR 2.10, $P < .0001$, 95% CI 1.51-2.90) with moderate heterogeneity ($I^2 = 41.54\%$).

The pooled SIR including all patients with pediatric IBD was 2.39 ($P < .0001$, 95% CI 2.00-2.86) with low heterogeneity ($I^2 = 0\%$) (**Figure 2**, A). Visual inspection of the funnel plot demonstrated no asymmetry and there were no small-study effects or publication biases as assessed by the Begg and Egger tests ($P = .35, .30$, respectively; **Figure 2**, B).

Meta-Analysis of Incidence Rates of Overall Cancer Development among Patients with Pediatric IBD

The pooled incidence rate of cancer occurrence was analyzed from 9 prospective and 44 retrospective studies (1 study included both study designs) with a total of 32 417 patients with pediatric IBD.

As shown in **Figure 3**, A, the pooled incidence rate of overall cancers in CD was 0.014 (95% CI 0.0087-0.021) with high heterogeneity ($I^2 = 78.90\%$). The pooled incidence rate of cancers in patients with UC was 0.031 (95% CI 0.018-0.052) with high heterogeneity ($I^2 = 91.59\%$) (**Figure 3**, A). The pooled incidence rate of overall cancers among all included studies was 0.018 (95% CI 0.013-0.025) with high heterogeneity ($I^2 = 89.10\%$) (**Figure 3**, A). Meta-regression showed that there was a positive correlation between the follow-up duration of the studies and the risk of overall malignancy (regression coefficient 0.014, 95% CI 0.0011-0.017, $P < .0001$) (**Figure 3**, B). Analyses of variance showed that *Qe* was not statistically significant ($Qe = 46.01$, $P = .050$), indicating that heterogeneity was largely explained by this factor, and that there remained no statistically significant heterogeneity once follow-up duration has been taken into consideration. According to meta-regression analyses, the risk of overall cancer development was not particularly affected by the history of concomitant medications such as steroid, immunomodulator and anti-TNF agents (**Tables V-VII**; available at www.jpeds.com). There were small-study effects or publication biases as assessed by the Begg and Egger tests ($P = .00072, .00060$, respectively), but visual inspection of the funnel plot appeared to show no asymmetry (**Figure 3**, C). Funnel plots of the studies reporting the risk of overall cancers among patients with CD and UC were also shown in **Figure 4**, B, D, respectively (available at www.jpeds.com).

Table III. Characteristics of studies for cancer development in pediatric IBD

Diseases	Author	Year (reference*)	Study design	Patient numbers (n)	Age at diagnosis (y)	Age at diagnosis or onset (y, mean)	Age at study (y, mean)	Age at diagnosis of cancers (y, median) †	Follow-up duration (mean, mo)	Concomitant medications (%)			Numbers of patients with overall cancers (n)	SIR of overall cancers (95% CI)	Numbers of patients with CRC	Numbers of patients with hematologic cancer (n)				Newcastle-Ottawa scale‡	Jadad score
										Steroids	AZA, 6 MP	Anti-TNFα				Overall	HL	NHL	Leukemia		
CD	Weedon et al[1]	1973	Retrospective	449	1-21§	14.9	NA	NA (34 at diagnosis of CRC)	NA	NA	NA	NA	12	NA	8	NA	NA	NA	NA	2 (S:1, C:0, 0:1)	NA
	Postuma et al[2]	1985	Retrospective	33	6-16	13.0	NA	12	28.2	48	NA	NA	1	NA	0	1	NA	NA	0	5 (S:2, C:0, 0:3)	NA
	Verhave et al[3]	1990	Retrospective	12	11-16§	NA	14.0	-	24	NA	100	NA	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	NA
	Gold et al[4]	1993	Retrospective	15	5.5-22.5§	NA	15.5¶	-	NA	NA	NA	NA	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	NA
	Gillen et al[5]	1994	Retrospective	113	15-25	NA	NA	40	NA	NA	NA	NA	NA	NA	4	NA	NA	NA	NA	1 (S:1, C:0, 0:0)	NA
	Gryboski et al[6]	1994	Retrospective	40	≤10	7.5	NA	NA	78	95	NA	NA	1	NA	0	0	0	0	0	2 (S:0, C:0, 0:2)	NA
	Langholz et al[7]	1997	Retrospective	23	<15	11.0	NA	-	NA	NA	NA	NA	0	NA	0	0	0	0	0	3 (S:3, C:0, 0:0)	NA
	Markowitz et al[8]	2008	Prospective (RCT)	55	<18§	NA	13.0	-	18**	100	49	NA	0	NA	0	0	0	0	0	NA	3
	Stephens et al[9]	2003	Retrospective	82	5-23§	NA	15.3	-	NA	49	95	100	0	NA	0	0	0	0	0	4 (S:3, C:0, 0:1)	NA
	de Ridder et al[10]	2004	Retrospective	30	2.7-16.8	11.4	NA	-	25.3	60	90	100	0	NA	0	0	0	0	0	6 (S:3, C:0, 0:3)	NA
	Hyams et al[11]	2007	Prospective (RCT)	112	6-17§	NA	13.3	-	11.0	35	89	100	0	NA	0	0	0	0	0	NA	2
	de Ridder et al[12]	2008	Retrospective	66	<19§	12.2	NA	-	41.3	12	64	100	0	NA	0	0	0	0	0	4 (S:2, C:0, 0:2)	NA
	Vernier-Massouille et al[13]	2008	Retrospective	404	<17	14.0	NA	-	84.0	85	61	24	0	NA	0	0	0	0	0	6 (S:3, C:0, 0:3)	NA
	Duricova et al[14]	2009	Retrospective	82	8-18	NA	14.5	-	33.0	NA	91	100	0	NA	0	0	0	0	0	5 (S:2, C:0, 0:3)	NA
	Hyams et al[15]	2009	Prospective	128	NA	NA	12.7††	14	42.0	52	90	100	1	NA	0	1	1	0	0	5 (S:3, C:0, 0:2)	NA
	Jakobsen et al[16]	2009	Retrospective	9	<15	12.0	NA	-	NA	NA	0	0	0	NA	0	0	0	0	0	6 (S:2, C:2, 0:2)	NA
	Ruemmele et al[17]	2009	Prospective (RCT)	40	7-17	NA	13.9	-	14.0	100	93	100	0	NA	0	0	0	0	0	NA	2
	Viola et al[18]	2009	Prospective	23	9-20	12.0	16.1	-	12.0	78	48	100	0	NA	0	0	0	0	0	2 (S:0, C:0, 0:2)	NA
	Pigneur et al[19]	2010	Retrospective	206	<16	13.0	NA	NA	NA	96	72	26	5	NA	3	NA	NA	NA	NA	4 (S:3, C:0, 0:1)	NA
	Sinitsky et al[20]	2010	Retrospective	16	1.8-17.5§	NA	13.0††	-	28.0	44	94	100	0	NA	0	0	0	0	0	4 (S:1, C:0, 0:3)	NA
	Crombé et al[21]	2011	Retrospective	120	<17	14.5	NA	30	32.0	82	38	100	1	NA	0	0	0	0	0	5 (S:2, C:0, 0:3)	NA
	Hyams et al[22]	2011	Prospective	60	6-17	NA	13.2	-	23.0	37	90	100	0	NA	0	0	0	0	0	3 (S:1, C:0, 0:2)	NA
	Kelsen et al[23]	2011	Retrospective	20	≤7	NA	6.2¶,††	-	NA	NA	NA	100	0	NA	0	0	0	0	0	2 (S:1, C:0, 0:1)	NA
	Ashworth et al[24]	2012	Retrospective	791	≤21‡‡	12.4	NA	12	NA	NA	73	30	NA	NA	NA	1	0	1	0	6 (S:3, C:0, 0:3)	NA
	De Greef et al[25]	2012	Prospective§§, retrospective	104	≤17	13.2	NA	-	45.0	NA	75	100	0	NA	0	0	0	0	0	4 (S:2, C:0, 0:2)	NA
	Hyams et al[26]	2012	Prospective (RCT)	188	6-17	NA	13.6	-	12.0¶¶	38	62	100	0	NA	0	0	0	0	0	NA	3
	Kierkus et al[27]	2012	Prospective	66	NA	8.4	14.1	-	2.5	NA	NA	100	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	NA
	Assa et al[28]	2013	Retrospective	102	<18	11.3	NA	-	NA	NA	NA	100	0	NA	0	0	0	0	0	2 (S:0, C:0, 0:2)	NA
	Jess et al[29]	2013	Retrospective	115	≤19	NA	NA	NA	195.0	NA	NA	NA	13	2.17 (1.21-3.90)	NA	NA	NA	NA	NA	7 (S:2, C:2, 0:3)	NA
	Navas-López et al[30]	2013	Retrospective	16	NA	10.6	NA	17	NA	6	88	100	1	NA	0	1	0	1	0	2 (S:0, C:0, 0:2)	NA
	Peneau et al[31]	2013	Retrospective	538	<17	14.6	NA	15¶	134.0	36	NA	NA	6	2.50 (0.80-5.80)	1	1	0	0	1	7 (S:3, C:2, 0:2)	NA
	Kappelman et al[32]	2014	Retrospective	NA	≤19	NA	NA	NA	NA	NA	NA	NA	NA	2.30 (1.53-3.46)	NA	NA	NA	NA	NA	6 (S:2, C:2, 0:2)	NA
	Nuti et al[33]	2014	Retrospective	78	8-23	NA	15.0	-	36	NA	54	100	0	NA	0	0	0	0	0	3 (S:1, C:0, 0:2)	NA
	Rosh et al[34]	2014	Retrospective	192	NA***	NA	NA	-	NA	NA	NA	100	0	NA	0	0	0	0	0	2 (S:1, C:0, 0:1)	NA
	Vahabnezhad et al[35]	2014	Retrospective	157	≤21	11.0	NA	NA	60	36	21	100	1	NA	0	1	NA	NA	NA	3 (S:1, C:0, 0:2)	NA
	Fumery et al[36]	2015	Retrospective	27	<17	11.0	15.0	-	16.0	19	7	100	0	NA	0	0	0	0	0	5 (S:2, C:0, 0:3)	NA
	Hyams et al[37]	2017	Retrospective	4047	<17	9.9†††	12.3†††	NA	19.2†††	NA†††	67†††	67†††	12	2.43 (1.29-4.15)†††	0	7	1	4	2	7 (S: 4, C:1, 0:2)	NA
	Mallet et al[38]	2017	Retrospective	4	11-20	15.5	NA	-	3.8	75	100	NA	0	NA	0	0	0	0	0	4 (S:2, C:0, 0:2)	NA
	Olen et al[39]	2017	Retrospective	3768	<18	14.0	30.0	NA	NA	NA	28	8.4	153	NA	17	12	NA	NA	NA	8 (S:4, C:2, 0:2)	NA
	Choi et al[40]	2018	Retrospective	33	9.1-15.6	13.6	NA	-	NA	NA	100	100	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	NA

(continued)

Table III. Continued

Diseases	Author	Year (reference*)	Study design	Patient numbers (n)	Age at diagnosis (y)	Age at diagnosis or onset (y, mean)	Age at study (y, mean)	Age at diagnosis of cancers (y, median) †	Follow-up duration (mean, mo)	Concomitant medications (%)			Numbers of patients with overall cancers (n)	SIR of overall cancers (95% CI)	Numbers of patients with CRC	Numbers of patients with hematologic cancer (n)				Newcastle-Ottawa scale‡	Jadad score
										Steroids	AZA, 6 MP	Anti-TNFα				Overall	HL	NHL	Leukemia		
	Fang et al[41]	2018	Retrospective	39	0-6	1.2¶	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	0	0	NA	5 (S:2, C:0, 0:3)	NA
	Turner et al[42]	2018	Retrospective	881	6-17	NA	15.0	-	33.6	NA	43	57	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	NA
	Malham et al[43]	2019	Retrospective	2921	<18	14.0	NA	NA	114.0	NA	NA	NA	33	2.6 (1.8-3.7)	4	6	4	1	NA	8 (S:4, C:2, 0:2)	NA
	Olén et al[44] ‡‡‡	2020	Retrospective	1385	<18	NA	NA	NA	NA	NA	NA	NA	NA	NA	4	NA	NA	NA	NA	8 (S:4, C:2, 0:2)	NA
UC	Ladd et al[45]	1935	Retrospective	26	≤12	NA	NA	13	NA	NA	NA	NA	1	NA	1	0	0	0	0	0 (S:0, C:0, 0:0)	NA
	Lagercrantz et al[46]	1955	Retrospective	137	≤15	NA	NA	NA	NA	NA	NA	NA	NA	NA	6	NA	NA	NA	NA	2 (S:0, C:0, 0:2)	NA
	Holowach et al[47]	1956	Retrospective	18	<15	8.9§§§	NA	21	NA	NA	NA	NA	NA	NA	214	NA	NA	NA	NA	0 (S:0, C:0, 0:0)	NA
	Michener et al[48]	1961	Retrospective	427	≤13	11.1	NA	NA	NA	NA	NA	NA	NA	NA	46	NA	NA	NA	NA	1 (S:0, C:0, 0:1)	NA
	Hijmans et al[49]	1962	Retrospective	43	≤16	9.1	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	0 (S:0, C:0, 0:0)	NA
	Korelitz et al[50]	1962	Retrospective	134	≤15	11.0	NA	NA	NA	NA	NA	NA	9	NA	5	0	0	0	0	1 (S:0, C:0, 0:1)	NA
	Skyring et al[51]	1965	Retrospective	80	≤15	7.2§§	NA	NA (17 at diagnosis of CRC)	NA	NA	NA	NA	3	NA	2	0	0	0	0	1 (S:1, C:0, 0:0)	NA
	Devroede et al[52]	1971	Retrospective	396	<15	NA	NA	NA	NA	NA	NA	NA	52	NA	NA	NA	NA	NA	NA	0 (S:0, C:0, 0:0)	NA
	Patterson et al[53]	1971	Retrospective	43	<20§	14.0	NA	28	NA	72	NA	NA	2	NA	1	0	0	0	0	1 (S:0, C:0, 0:1)	NA
	Binder et al[54]	1972	Retrospective	44	<16§	10.0	NA	NA	60.8	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	2 (S:1, C:0, 0:1)	NA
	Michener et al[55]	1979	Retrospective	336	≤20	15.0§§	NA	NA	142.0¶¶¶	NA	NA	NA	10	NA	9	1	NA	NA	NA	3 (S:1, C:0, 0:2)	NA
	Verhave et al[3]	1990	Retrospective	9	3.5-17§	NA	14.0	-	24.0	NA	100	NA	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	NA
	Ahsgren et al[56]	1993	Retrospective	32	≤19	14.0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	2 (S:1, C:0, 0:1)	NA
	Gold et al[4]	1993	Retrospective	4	5.5-22.5§	NA	15.5¶	-	NA	NA	100	NA	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	NA
	Hyams et al[57]	1996	Retrospective	171	<18	11.1	NA	25	61.2	33	2	NA	2	NA	2	0	0	0	0	4 (S:1, C:0, 0:4)	NA
	Langholz et al[7]	1997	Retrospective	80	<15	10.0	NA	NA	NA	NA	NA	NA	1	NA	1	0	0	0	0	3 (S:3, C:0, 0:0)	NA
	Falcone et al[58]	2000	Retrospective	73	<18	11.3	NA	NA	48.4	NA	5	NA	NA	NA	0	NA	NA	NA	NA	4 (S:1, C:0, 0:2)	NA
	Gower-Rousseau et al[59]	2009	Retrospective	113	<17	14.0	NA	28	77.0	82	25	1	NA	NA	1	NA	NA	NA	NA	6 (S:3, C:0, 0:3)	NA
	Jakobsen et al[16]	2009	Retrospective	60	<15	11.0	NA	NA	NA	38	0	0	2	NA	2	0	0	0	0	6 (S:2, C:2, 0:2)	NA
	Hyams et al[60]	2010	Retrospective	52	<16	12.2	NA	-	30.0	90	42	100	0	NA	0	0	0	0	0	5 (S:3, C:0, 0:2)	NA
	Kelsen et al[23]	2011	Retrospective	4	≤7	NA	6.2¶,††	-	NA	NA	NA	100	0	NA	0	0	0	0	0	2 (S:1, C:0, 0:1)	NA
	Ashworth et al[24]	2012	Retrospective	535	≤21‡‡	12.7	NA	18	NA	NA	45	12	NA	NA	NA	1	1	0	0	6 (S:3, C:0, 0:3)	NA
	Jess et al[29]	2013	Retrospective	153	≤19	NA	NA	NA	225.0	NA	NA	NA	9	1.16 (0.57-2.37)	NA	NA	NA	NA	NA	7 (S:2, C:2, 0:3)	NA
	Peneau et al[31]	2013	Retrospective	160	<17	14.5	NA	15¶	139.0	27	NA	NA	3	4.60 (0.90-13.50)	1	0	0	0	0	7 (S:3, C:2, 0:2)	NA
	Kappelman et al[32]	2014	Retrospective	NA	≤19	NA	NA	NA	NA	NA	NA	NA	NA	2.00 (1.44-2.78)	NA	NA	NA	NA	NA	6 (S:2, C:2, 0:2)	NA
	Vahabnezhad et al[35]	2014	Retrospective	31	≤21	12.0	NA	NA	47.0	65	29	100	0	NA	0	0	0	0	0	3 (S:1, C:0, 0:2)	NA
	Hyams et al[37]	2017	Retrospective	1432	<17	9.9†††	12.3†††	NA	19.2†††	NA†††	67†††	67†††	3	2.43 (1.29-4.15)†††	0	2	0	1	1	7 (S: 4, C:1, 0:2)	NA
	Olén et al[39]	2017	Retrospective	4648	<18	14.0	30.0	-	NA	NA	13	2	299	NA	96	13	NA	NA	NA	8 (S:4, C:2, 0:2)	NA
	Fang et al[41]	2018	Retrospective	4	0-6	1.2¶	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	0	0	NA	5 (S:2, C:0, 0:3)	NA
	Malham et al[43]	2019	Retrospective	3741	<18	14.0	NA	NA	117.6	NA	NA	NA	39	2.50 (1.80-3.40)	12	6	3	2	NA	8 (S:4, C:2, 0:2)	NA
	Olén et al[61,‡‡‡]	2020	Retrospective	1918	<18	NA	NA	NA	NA	NA	NA	NA	NA	NA	16	NA	NA	NA	NA	8 (S:4, C:2, 0:2)	NA
IBD (no distinction made between CD or UC)	Markowitz et al[62]	1993	Retrospective	165	NA	11.4	15.0****	-	NA	NA	NA	NA	0††††	NA	0††††	0††††	0††††	0††††	0††††	1 (S:1, C:0, 0:0)	NA
	Lee et al[63]	2005	Retrospective	112	5-21§	NA	NA	-	35.0	NA	NA	100	0	NA	0	0	0	0	0	3 (S:1, C:0, 0:2)	NA
	Chouliaras et al[64]	2010	Retrospective	31	NA	8.7	NA	NA	NA	NA	NA	NA	1	NA	0	1	0	1	0	3 (S:1, C:0, 0:2)	NA

(*continued*)

Table III. Continued

Diseases	Author	Year (reference*)	Study design	Patient numbers (n)	Age at diagnosis (y)	Age at diagnosis or onset (y, mean)	Age at study (y, mean)	Age at diagnosis of cancers (y, median) †	Follow-up duration (mean, mo)	Concomitant medications (%)			Numbers of patients with overall cancers (n)	SIR of overall cancers (95% CI)	Numbers of patients with CRC	Numbers of patients with hematologic cancer (n)				Newcastle-Ottawa scale‡	Jadad score
										Steroids	AZA, 6 MP	Anti-TNFα				Overall	HL	NHL	Leukemia		
	Colletti et al[65]	2013	Retrospective	4343	≤18	NA	NA	NA	NA	NA	NA	NA	7	Anti-TNFα exposed: 4.77 (1.56-14.61); Non biologic therapies: 5.09 (1.35-19.15)	0	4	1	0	1	5 (S:2, C:2, O:1)	NA
	El-Matary et al[66]	2020	Retrospective	947	<18	14.0	NA	NA	NA	NA	NA	NA	17	NA	NA	NA	NA	NA	NA	6 (S:4, C:0, O:2)	NA

AZA, azathioprine; *C*, comparability; *HL*, Hodgkin's lymphoma; *NA*, not available; *NHL*, non-Hodgkin's lymphoma; *O*, outcome; *S*, selection.
*See supplementary reference list.
†NA indicates data regarding age of cancer diagnosis is not available and "-" indicates no reported case of cancer.
‡Newcastle-Ottawa scale, total score (S, selection (0-4); C, Comparability (0-2); O, Outcome (0-3)).
§Data as the definition of age at study.
¶Mean or median ages of patients with CD and UC (Gold 1993, Kelsen 2011, Peneau 2013, Fang 2018).
**Follow-up duration from the patients who completed the trial (Markowitz 2000).
††Mean ages at start of IFX (Hyams 2009, Sinitsky 2010, Kelsen 2011).
‡‡Two patients who were over 21 years old were included (Ashworth 2012).
§§Mean age was calculated from each medium data of step-wise age (Skyring 1965, Michener 1979).
¶¶Mean follow-up duration of 124 patients (Hyams 2012).
***Patients were defined as "children".
†††Data as IBDs (Hyams 2017).
‡‡‡Data were from cohort of Denmark. The cohort of Sweden in this study were duplicate with that of Olén 2017.
§§§Mean ages at admission (Holowach 1956).
¶¶¶Mean follow-up duration of 333 patients (Michener 1979).
****Mean ages at start of immunosuppressive (Markowitz 1993).
††††Data were quoted from the study by Kirschner et al (Markowitz 1993).

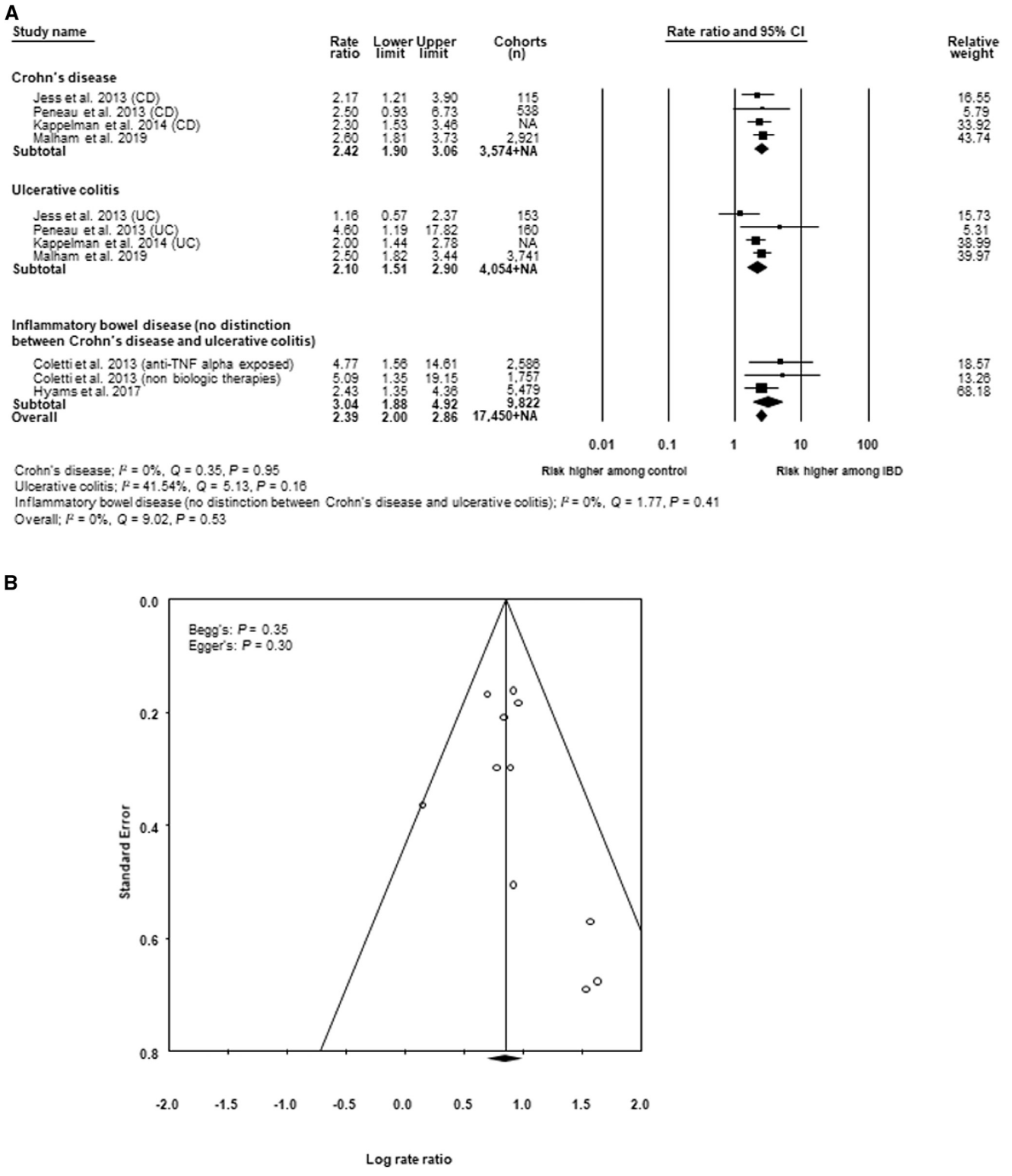


Figure 2. Meta-analysis of the risk of overall cancers reported as SIR among patients with pediatric IBD. **A,** Forest plot of the risk of overall cancers reported as SIR among patients with pediatric IBD. **B,** Funnel plot of the studies included in **Figure 2**, A.

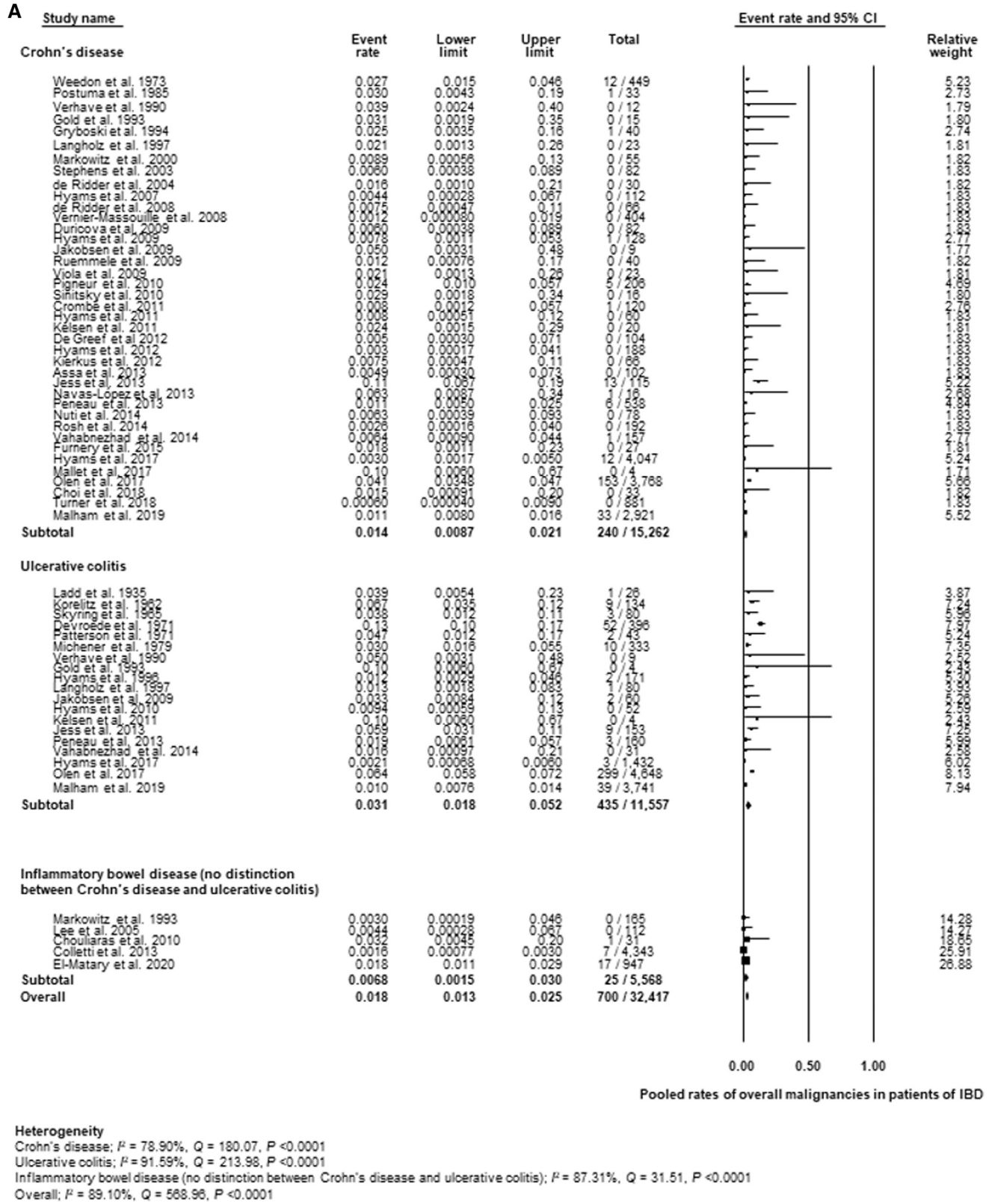


Figure 3. Meta-analysis of incidence rates of overall cancers among pediatric IBD. **A,** Forest plot of incidence rates of overall cancers among pediatric IBD. **B,** Meta-regression of the follow-up duration (*months*) and the risk of overall cancers. **C,** Funnel plot of the studies included in **Figure 3**, A.

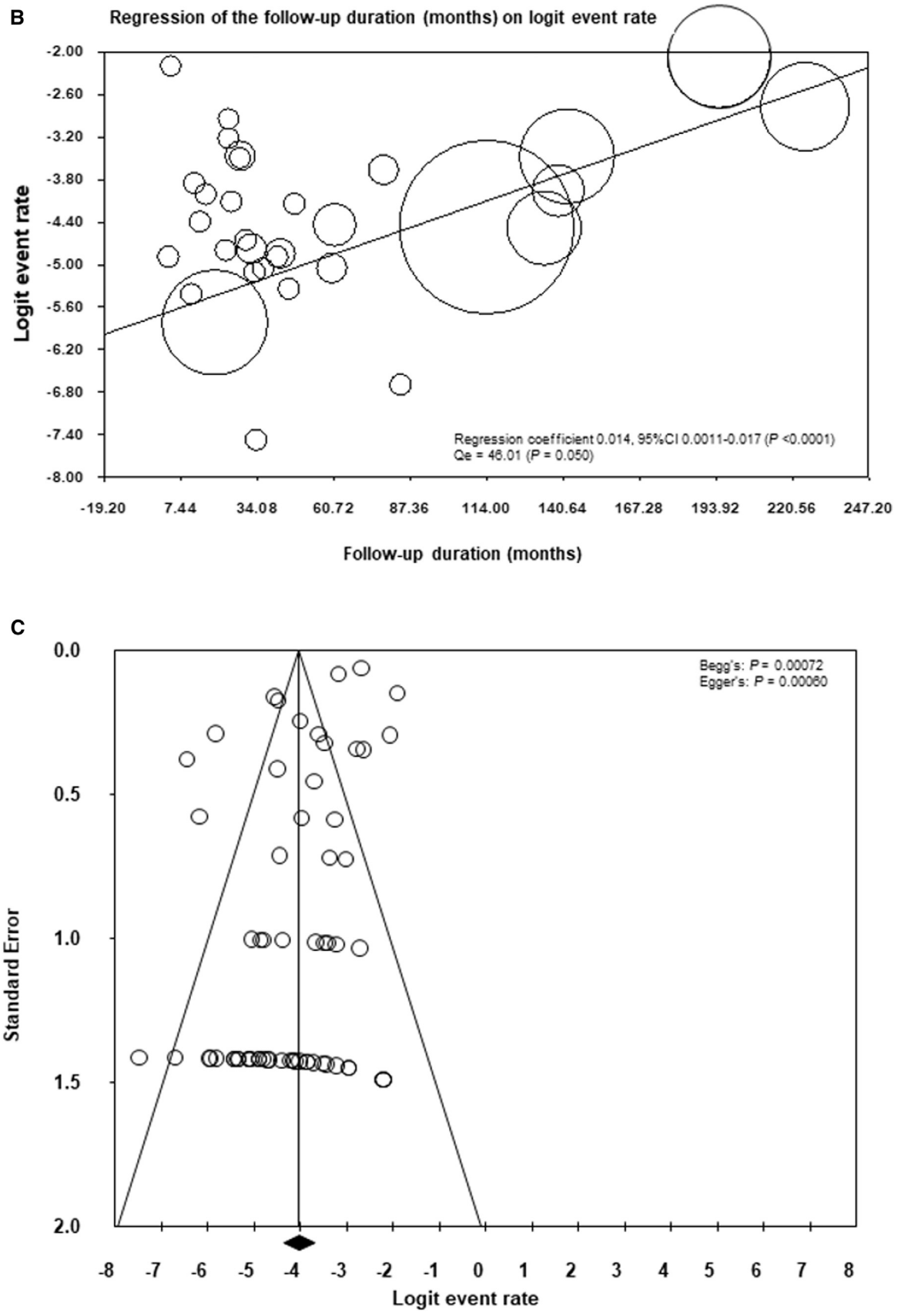


Figure 3. (continued)

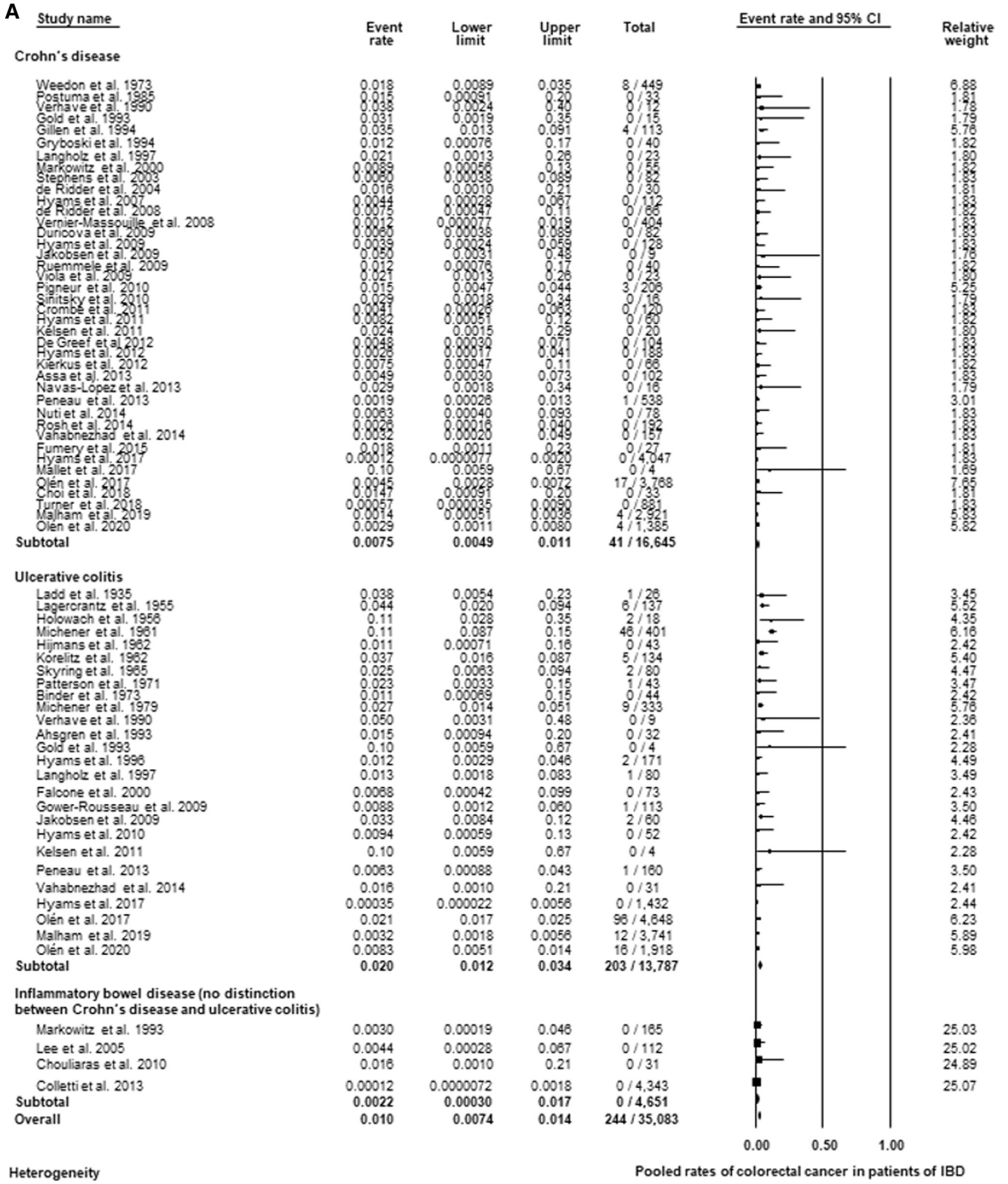
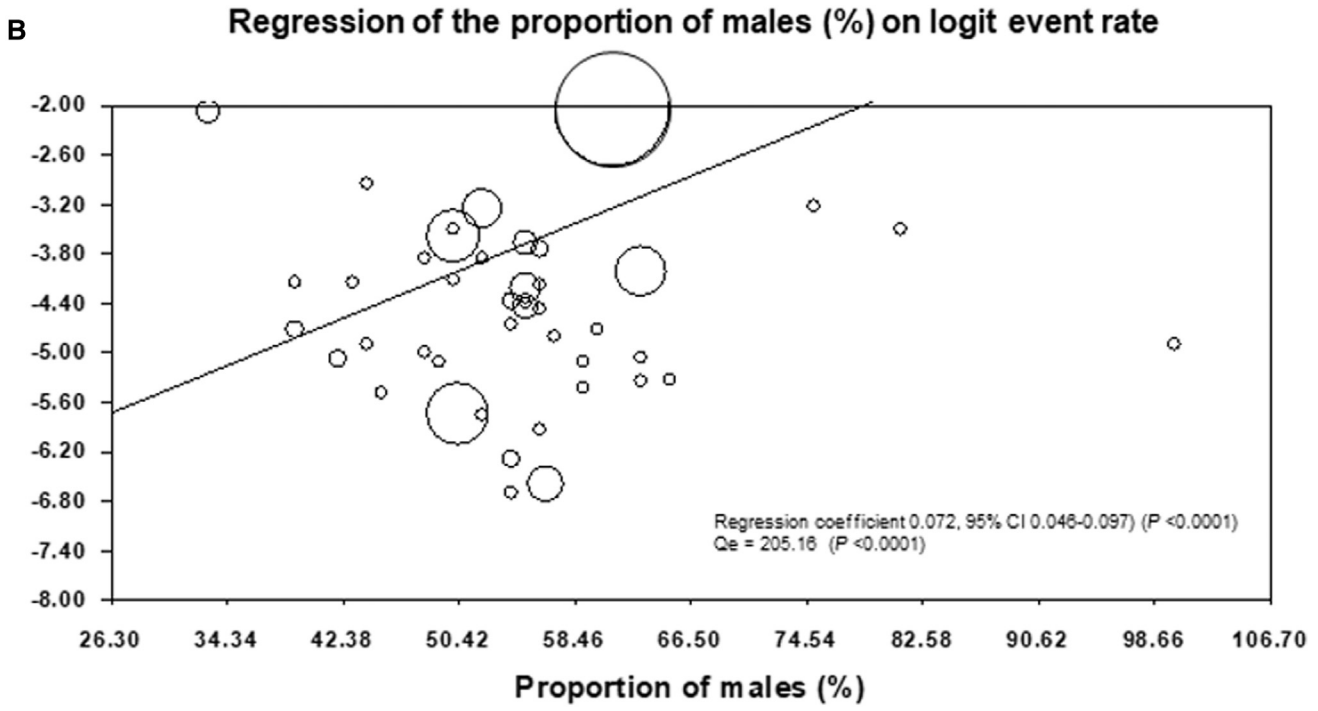


Figure 5. Meta-analysis of incidence rates of CRC among pediatric IBD. **A,** Forest plot of incidence rates of CRC among pediatric IBD. **B,** Meta-regression of the proportion of male (%) and the risk of CRC. **C,** Meta-regression of the age at diagnosis (*year*) and the risk of CRC. **D,** Funnel plot of the studies included in **Figure 5**, A.



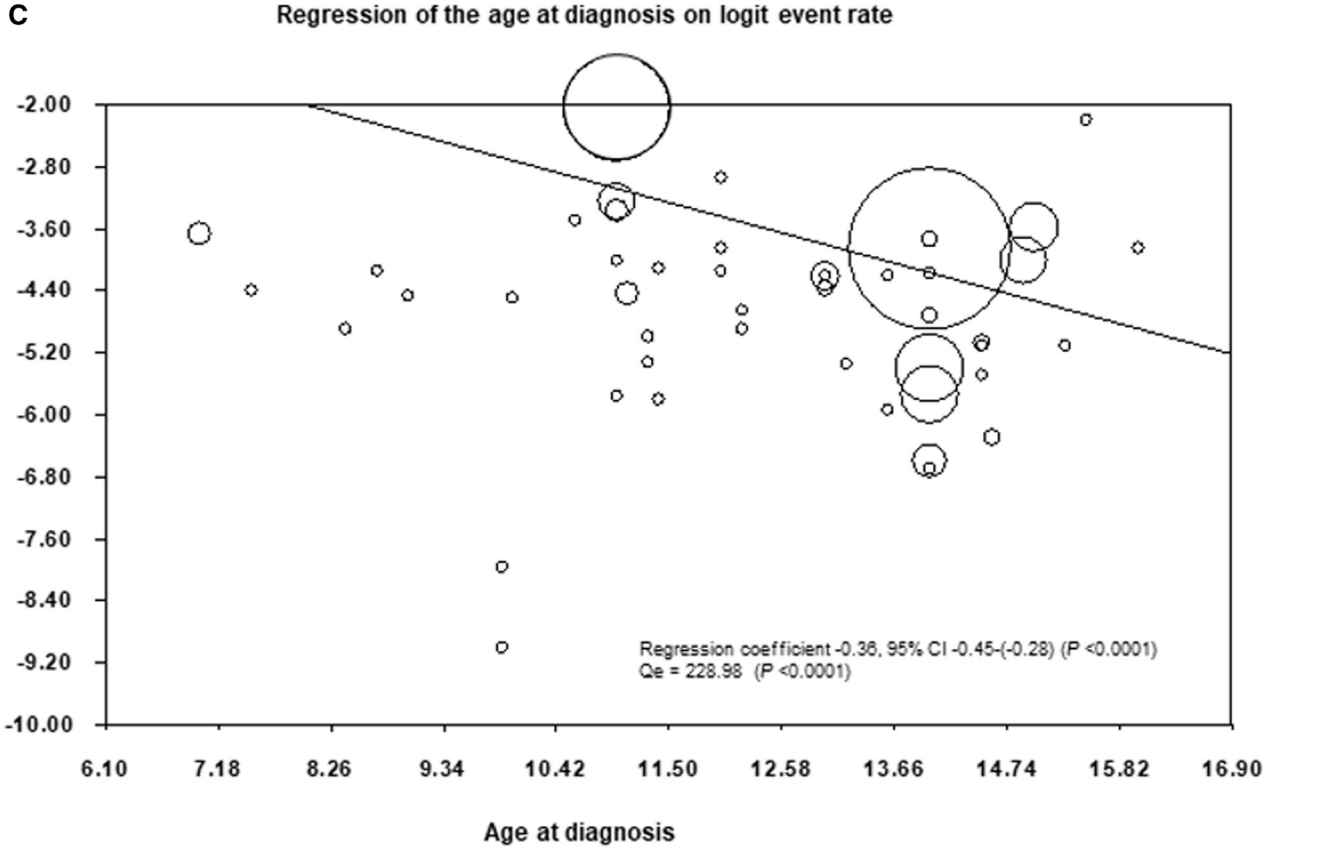


Figure 5. (continued)

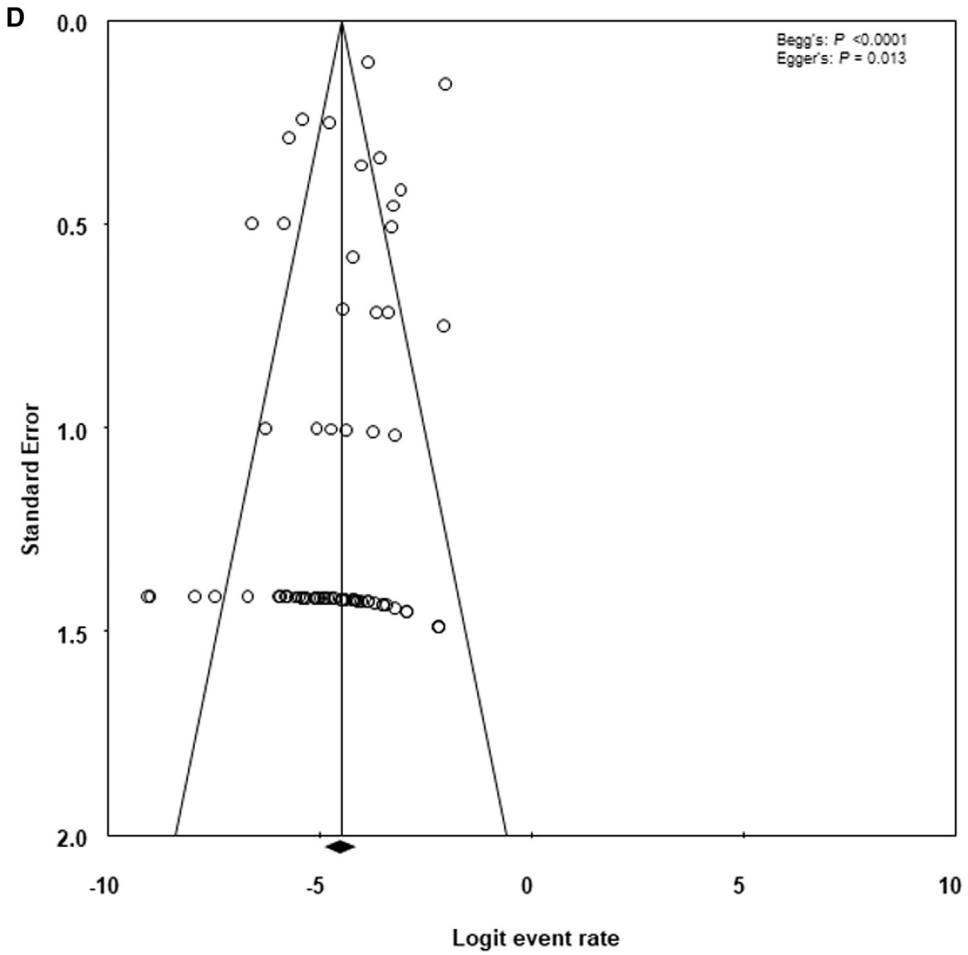


Figure 5. (continued)

Meta-Analysis of Incidence Rates of Colorectal Cancer in Pediatric IBD

There were only 2 pediatric IBD (no distinction between CD and UC) studies and 1 pediatric UC study reporting the SIR of CRC, therefore, meta-analysis by SIR was not possible. The pooled incidence rate of CRC was performed from 9 prospective and 52 retrospective studies (1 study included both study designs) with a total of 35 083 patients with pediatric IBD.

As shown in **Figure 5**, A, the pooled incidence rate of CRC in CD was 0.0075 (95% CI 0.0049-0.011) with moderate heterogeneity (I^2 = 41.30%). The pooled incidence rate of CRC in UC was 0.020 (95% CI 0.012-0.034) with high heterogeneity (I^2 = 87.95%). When including all patients with pediatric IBD, the pooled incidence rate was 0.010 (95% CI 0.0074-0.014) with high heterogeneity (I^2 = 81.30%) (**Figure 5**, A). Meta-regression showed that there was a positive correlation between the proportion of male patients and the risk of CRC (regression coefficient 0.072, 95% CI 0.046-0.097, P <.0001) (**Figure 5**, B), suggestive of higher risk in male patients, and a negative correlation between the age at diagnosis or onset and the risk of CRC (regression coefficient −0.36, 95% CI -0.45 to −0.28, P < .0001) (**Figure 5**, C), suggestive of higher risk in patients with early onset disease. Analyses of variance showed that both Qe were statistically significant (Qe = 205.16, 228.98, P < .0001, < .0001, respectively), indicating that heterogeneity could not be explained only by each factor. According to meta-regression analyses, the risk of CRC development was not particularly affected by the history of concomitant medications such as steroid, immunomodulator and anti-TNF agents (**Tables V-VII**). Visual inspection of the funnel plot did not show asymmetry, but there were small-study effects or publication biases as assessed by the Begg and Egger tests (P <.0001, = 0.013, respectively; **Figure 5**, D). Funnel plots of the studies reporting the risk of CRC among patients with CD and UC were also shown in **Figure 6**, A, D, respectively (available at www.jpeds.com).

Meta-Analysis of Incidence Rates of Hematologic Cancers in Pediatric IBD

There was only 1 study that reported the SIR of hematologic cancers in patients with pediatric IBD, therefore, meta-analysis by SIR was not possible. The pooled incidence rates

of hematologic cancers were assessed from 9 prospective and 40 retrospective studies (1 study included both study designs) with a total of 31 477 patients with pediatric IBD.

As shown in **Figure 7**, A (available at www.jpeds.com), the pooled incidence rate of hematologic cancers in patients with CD and patients with UC were 0.0061 (95% CI 0.0040-0.0090) and 0.0045 (95% CI 0.0026-0.0079), respectively with low heterogeneities (I^2 = 27.14%, 31.66%, respectively). When all patients with pediatric IBD were included, the pooled incidence rate was 0.0054 (95% CI 0.0039-0.0075) with moderate heterogeneity (I^2 = 34.25%). Visual inspection of the funnel plot did not show asymmetry, but there were small-study effects or publication biases as assessed by the Begg and Egger tests (P <.0001, <.0001, respectively; **Figure 7**, B).

When individual hematologic cancers were analyzed separately, the pooled incidence rates of Hodgkin's lymphoma in all patients with pediatric IBD was 0.0061 (95% CI 0.0040-0.0093) with low heterogeneity (I^2 = 36.77%) (**Figure 8**, A; available at www.jpeds.com). The pooled incidence rates of non-Hodgkin's lymphoma in all patients with IBD was 0.0065 (95% CI 0.0041-0.010) with moderate heterogeneity (I^2 = 41.90%) (**Figure 9**, A; available at www.jpeds.com). The pooled rates of leukemia in all patients with IBD was 0.0056 (95% CI 0.0028-0.011) with low heterogeneity (I^2 = 24.20%) (**Figure 10**, A; available at www.jpeds.com). According to meta-regression analyses, the risk of hematologic cancers development including Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia was not particularly affected by the history of concomitant medications such as steroid, immunomodulatory, and anti-TNF agents (**Tables V-VII**).

Temporal Trend of Cancer Incidence Assessed by Cumulative Meta-Analysis

Cumulative meta-analyses of each outcomes ranked by year were performed and shown in **Figure 9**, A-G. The number of studies included for overall risk of cancers reported as SIR were small and were all published after 2013, so no temporal trend could be assessed (**Figure 11**, A; available at www.jpeds.com). For the incidence of colorectal and hematologic cancers, we investigated the temporal change of the risk of each type of cancer by assessing the correlation coefficient of each cumulative meta-analysis. We found that as the reporting years became more recent, the incidence of cancer were significantly reduced in all cumulative meta-analyses (overall cancer, CRC, hematologic cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia) for CD and UC (**Figure 11**, B-G). Regression coefficients for cumulative meta-analyses among patients with IBD about overall cancer, CRC, and hematologic cancer were 0.019, 0.0049, and 0.0018, respectively (95% CI 0.018-0.021 [P < .0001], 0.0043-0.0054 [P <.0001], and 0.0017-0.0019 [P <.0001], respectively).

Sensitivity Analyses

We performed influence analyses by removing individual studies from the meta-analyses to assess the influence of any particular study on the results (**Figure 12**, A-G; available at www.jpeds.com). This demonstrated that the random effects estimate was not greatly influenced by any particular study.

We also undertook meta-analyses excluding studies with less than 30 patients when possible. Each analysis showed similar results compared with the aforementioned results (data not shown).

Discussion

We performed a systematic review and meta-analysis and demonstrated that patients with IBD diagnosed in childhood have a significantly increased risk of cancer when compared with the general population. In addition, we comprehensively analyzed incidence rates of CRC and hematologic cancers, and demonstrated that the incidence of these cancers appeared to be down-trending, which have not been referred in the previous systematic review.[7]

Nearly 10% of newly diagnosed patients with CD or UC are below 15 years of age[27,28]; therefore, understanding the risk of cancer development in the pediatric population is essential in the accurate evaluation and management of patients with pediatric IBD. Our meta-analysis demonstrated that patients with pediatric CD have a 2.42-fold increased risk of cancers and patients with UC have a 2.10-fold increased risk when compared with a general pediatric population. Interpreting the SIR, however, is strengthened when evaluated with a corresponding incidence rate. Thus, we also assessed the pooled incidence rates of the risk of overall cancer and cancer subtypes among patients with pediatric IBD. The incidence rate of overall cancer in CD and UC was 0.014 and 0.031, respectively. For comparative purposes, within the surveillance, epidemiology, and end result (SEER) database, the incidence rate of cancer among children and adolescents were 0.00014 (ages 10-14 years), 0.00022 (ages 15-19 years), and 0.00036 (ages 20-24 years), respectively.[29]

In a population-based study, Ekbom et al reported that children who develop UC before 14 years of age had a cumulative CRC incidence rate of 5% at 20 years and 40% at 35 years.[30] In our analysis, the incidence rate of CRC among pediatric patients with UC was 0.020. When compared with UC, pediatric patients with CD had a numerically lower incidence of CRC (0.0075). Meta-regression in UC demonstrated an increased risk of CRC development in male patients and with younger disease onset. The annual incidence of CRC within the SEER database (age-adjusted rate, 2007-2011) is 0.000010 for adolescents (ages 20-24 years) and 0.0022 for adults over age 65 years.[29]

Over the past decade, immunosuppressive agents as well as biologic agents, are increasingly used to treat pediatric IBD.[31,32] However, the risks of therapies need to be considered as evidence suggests that in particular, thiopurines,

when used alone or in combination with anti-TNFα therapies, increase the risk of lymphoma.[33] In our analysis, the incidence rates of Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia in pediatric CD and UC were greater than any age group of the general population within the SEER database (age-adjusted rate, 2007-2011).[29] The risk of cancers in patients exposed to thiopurines and anti-TNF agents remain controversial.[34,35] In our study, we did not find a correlation between thiopurine or anti-TNFα agent use and the risk of any cancers (**Tables V-VII**); this may have been due to the inclusion of several research articles with short follow-up periods. Indeed, there have been reports of lymphoma and non-melanoma skin cancer risk associated with thiopurine use which referred that patients using thiopurines seem to have an increased risk of lymphoma or non-melanoma skin cancer that is proportional to therapy duration.[34,36] Although not statistically significant, there was a trend of correlation between thiopurine use and the risk of lymphoma (**Table VI**). Recently, it has also been reported that hepatosplenic T-cell lymphoma is a rare but concerning issue in young adult male patients with IBD who have been exposed to thiopurines, however, there was not enough data to analyze this risk in our meta-analysis.

The results of cumulative analyses showed that the incidence of cancers appear to be down-trending in patients with pediatric IBD. This is in concordance with studies reporting a decreased risk of CRC incidence in adult IBD population.[37] The decrease in the risk of CRC over time may be owing to the changes in treatment of IBD.[38] However, our study found a down-trending risk of overall and hematologic cancers. This phenomenon may not be obvious in other autoimmune diseases treated with similar medications: the average lymphoma risk in recently diagnosed patients with rheumatoid arthritis is similar in magnitude to that reported in historical cohorts.[39] In addition, we could not investigate whether patients with very early onset IBD carry a higher risk of cancer because there was only one study which referred to this patient population.[40]

Our study has some limitations. At first, after we identified 969 127 records through database, 968 806 of records were excluded after initial screening of titles and abstracts. Papers not related to the outcome of our study, or duplicate papers in the databases were deleted at this stage. However, the number of duplicate papers cannot be accurately assessed: as mentioned in our study, only the first 1000 articles were technically available for review in each search for Google Scholar. Second, our analyses with patients with pediatric IBD mainly included retrospective observational studies. In addition, 16 studies (24.24%) included adolescent-onset patients with IBD with childhood-onset patients, though each average age of 12 years studies was below 15 years old. The remaining 4 studies did not mention the average age of onset of disease but have exclusively included patients with childhood-onset IBD. Moreover, the qualities of the observational studies were modest based on the Newcastle-Ottawa scale. Though overall quality of each assessment among this systematic review was low, it seems to be due to the fact that the quality of the observational studies included was modest, as we referred above. Most of the studies, which were included in our analyses, described the occurrence of cancers among patients with IBD diagnosed in childhood, but all cancers might not occur during the childhood period. Therefore, we were not able to simply compare the event rates of our analyses with the existing age-adjusted rates of SEER database. Besides, the incidence rate findings of our meta-analyses were compared with the SEER database, but a formal statistical analysis could not be undertaken. Skin cancer and other solid cancers could not be analyzed because there were no reports among patients with pediatric IBD. Our review could not assess the influence of various treatment on the risk of cancers. Aardoom et al reported cancer risk in patients with childhood-onset IBD separately as fatal and nonfatal, however, it was unclear whether treatments were significantly involved in the onset of cancer.[7] We conducted meta-regressions with factors such as concomitant steroids, anti-TNF agents, or immunomodulator use, and found that none of these drugs was significantly associated with the occurrence of cancer. These findings are in concordance with a previous study that reported that disease activity of rheumatologic diseases among adults are involved in the subsequent development of cancer.[41] In particular, there was no evidence of an association between anti-TNF agent use and cancer risk among patients with rheumatological diseases. It may be conceivable that improved disease control with newer, more effective therapeutic agents will help mitigate the increased risk of cancer associated with pediatric rheumatologic diseases. The duration of immunomodulators use may influence the incidence of malignancy, however, because of the lack of papers describing the duration of anti-TNF agents and immunomodulators use, we could not account for duration of treatment with these medications in our analyses. In addition, we could not investigate the correlation of the development of malignancy between races: in a recent report, it was referred that there may be differences in the risk of lymphoma due to immunomodulators use between races.[42] There was some baseline variability in patient population among the different studies: for instance, some of the papers included in our analyses were on treatment-biased patients with IBD. This variability may also contribute to the heterogeneity that was seen in a small number of our analyses. Indeed, we undertook meta-regression with factors such as age of diagnosis, duration of follow-up period, and proportion of males for each analysis and found that there were correlations with some of our results. Our study presented the decrease in incidence of malignancies over time with analyzing cumulative meta-analyses. However, without detailed individual patient data, it may be difficult to confirm that the incidence of newly developed cancers is actually decreasing. We found small study effects (publication biases) among some of our meta-analyses, though visual inspection of the funnel plots showed no asymmetry. Some smaller studies may be more likely to be published when they have significant results, which in turn biases the results of a meta-analysis.[43] We performed meta-

analyses including or excluding studies with less than 30 patients when possible, but results were similar. We were unable to perform sensitivity analyses limited to population-based studies to avoid referral biases. Only 11 out of 66 papers were population-based studies in our analyses, and the numbers were even smaller for individual cancers. Instead, we conducted influence analyses as one of the sensitivity analyses to identify the influential papers. We demonstrated that the random effects estimate was not greatly influenced by any particular study.

In conclusion, this systematic review and meta-analysis showed that patients with IBD diagnosed in childhood have an increased risk of cancers when compared with the general population. This risk appeared to be attributed mostly to the development of CRC and hematologic cancers with risk factors that included patient sex (male) as well as younger onset and longer duration of disease, but not thiopurine or anti-TNF agent use. We also observed that the risk of these cancers appeared to be down-trending over time. ■

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50 Years Ago in *The Journal of Pediatrics*

Diagnosis of Coagulation Defects in Reye Syndrome

Schwartz A. The coagulation defect in Reye's syndrome. J Pediatr 1971;78:326-8.

Fifty years ago in *The Journal,* Schwartz described a child with Reye syndrome, likely from a myxovirus, admitted to Yale-New Haven Hospital with sudden hemorrhagic diathesis. This child had prolonged prothrombin time and partial thromboplastin time and generally low levels of coagulation factors. Although the low levels of coagulation factors was suggestive of disseminated intravascular coagulation (DIC), the normal levels of factor VIII, normal platelet count, and absence of fibrin split products clinched the correct diagnosis of hepatic failure, allowing for appropriate therapy. Schwartz cautioned about the potentially deleterious effect of an incorrect diagnosis of DIC, which was heparin therapy in a bleeding child.

The world is currently in the midst of the COVID-19 pandemic. The multisystem inflammatory syndrome in children (MIS-C) is thought to be a manifestation of COVID-19, which is caused by a coronavirus. In contrast to Reye syndrome, thrombosis is a major concern in MIS-C. Bleeding is not common with MIS-C, but these children tend to have prolonged prothrombin time, low platelet count, and elevated levels of D-dimer, a fibrin split product.[1] A large proportion of these children receive heparin therapy to prevent thrombosis. At Yale-New Haven Children's Hospital and other children's hospital in the US, viscoelastic testing of coagulation with thromboelastography or thromboelastometry is now available. Reports in adults with COVID-19 suggest a prothrombotic profile using these tests. Studies to characterize the coagulation profile using viscoelastic testing in children with MIS-C are ongoing.

For the past 50 years, prothrombin time, partial thromboplastin time and platelet count have been the first-line workup for children with probable defects in hemostasis. Novel tests, such as viscoelastic testing, are now able to assess the combined effect of coagulation factors and platelets. Increasing experience with the use of these test may provide further insight into defects in hemostasis in other virus-related syndromes. Although heparin has been abandoned as a therapy for DIC, viscoelastic testing also may be used to titrate heparin to avoid its deleterious effect of bleeding.

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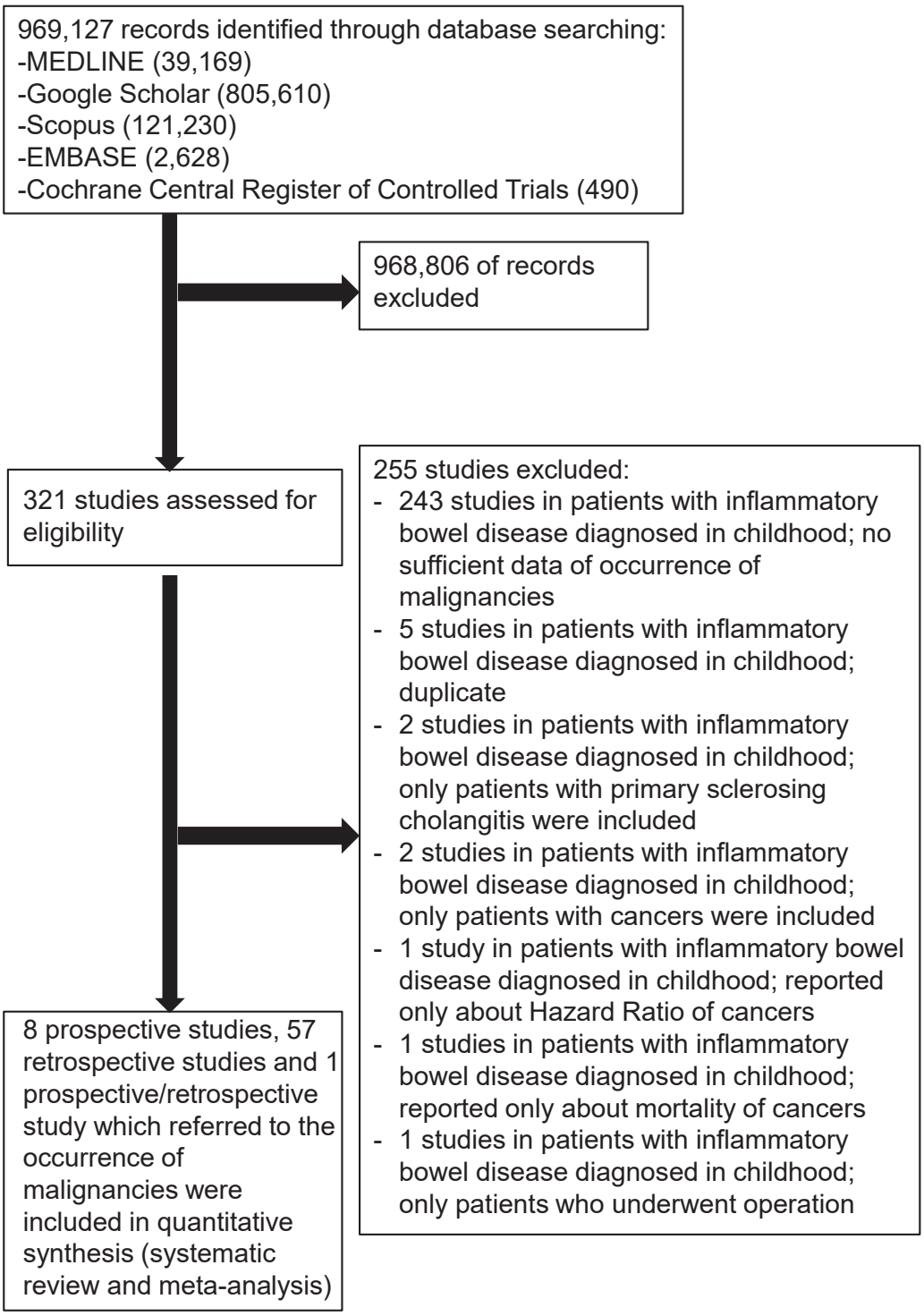


Figure 1. Flow chart of the assessment of the studies identified in the meta-analysis.

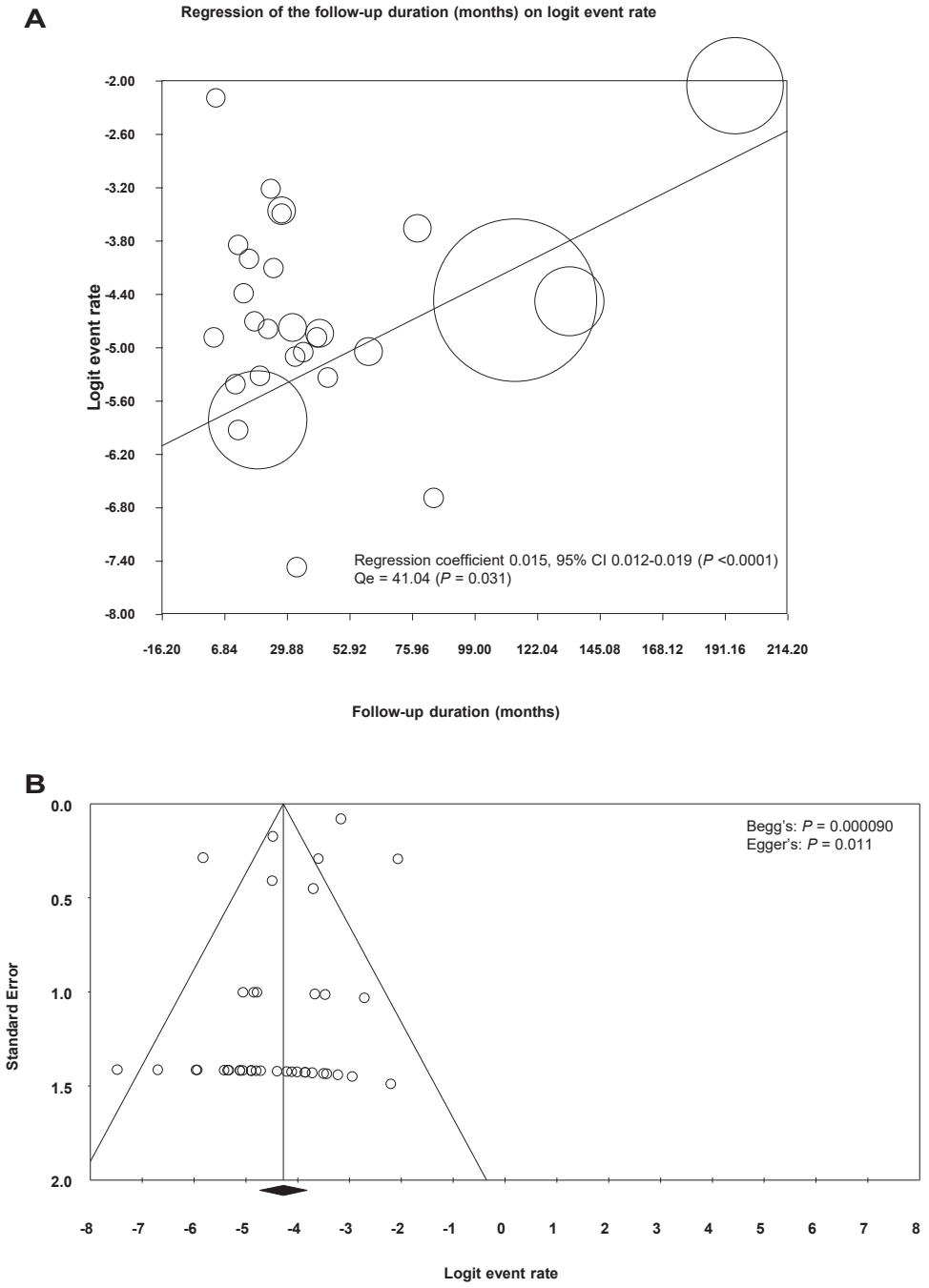
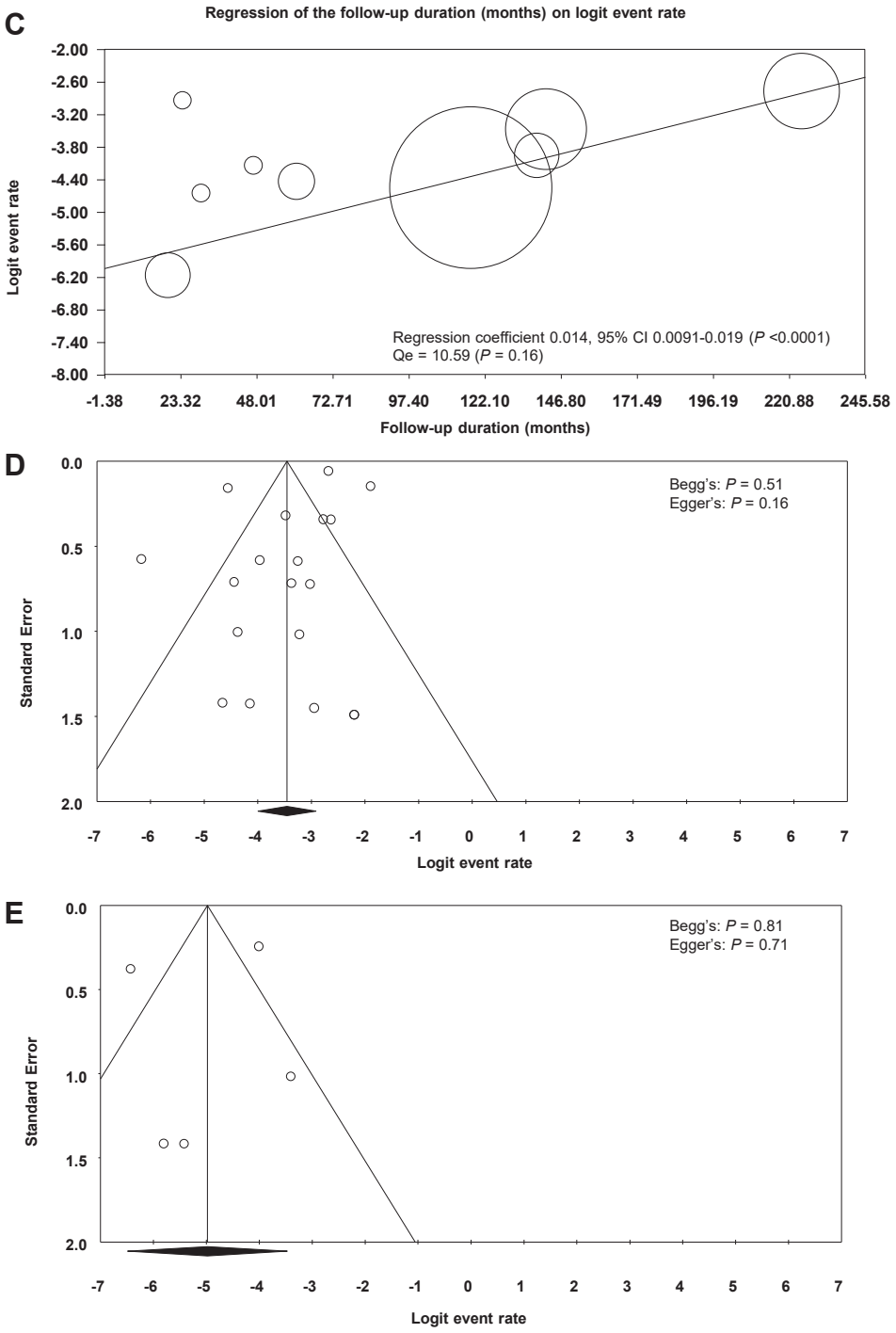


Figure 4. **A,** Meta-regression of the follow-up duration (*months*) and the risk of overall cancers among patients with CD. Meta-regression showed that there was a positive correlation between the follow-up duration of the studies and the risk of overall cancers (regression coefficient 0.015, 95% CI 0.012-0.019, $P < .0001$). ANOVA showed that *Qe* was statistically significant (*Qe* = 41.04, $P = .031$), indicating that heterogeneity could not be explained only by this factor. **B,** Funnel plot of the studies reporting the risk of overall cancers among patients with CD included in **Figure 3**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests ($P = .000090$, .011, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **C,** Meta-regression of the follow-up duration (months) and the risk of overall cancers among patients with UC. Meta-regression showed that there was a positive correlation between the follow-up duration of the studies and the risk of overall cancers (regression coefficient 0.014, 95% CI 0.0091-0.019, $P < .0001$). ANOVA showed that *Qe* was not statistically significant (*Qe* = 10.59, $P = .16$), indicating that heterogeneity was largely explained by this factor and that there remains no statistically significant heterogeneity once follow-up duration has been taken into consideration. **D,** Funnel plot of the studies reporting the risk of overall cancers among patients with UC included in **Figure 3**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger test ($P = .51$, .16, respectively). **E,** Funnel plot of the studies reporting the risk of overall cancers among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 3**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger tests ($P = .81$, .71, respectively).



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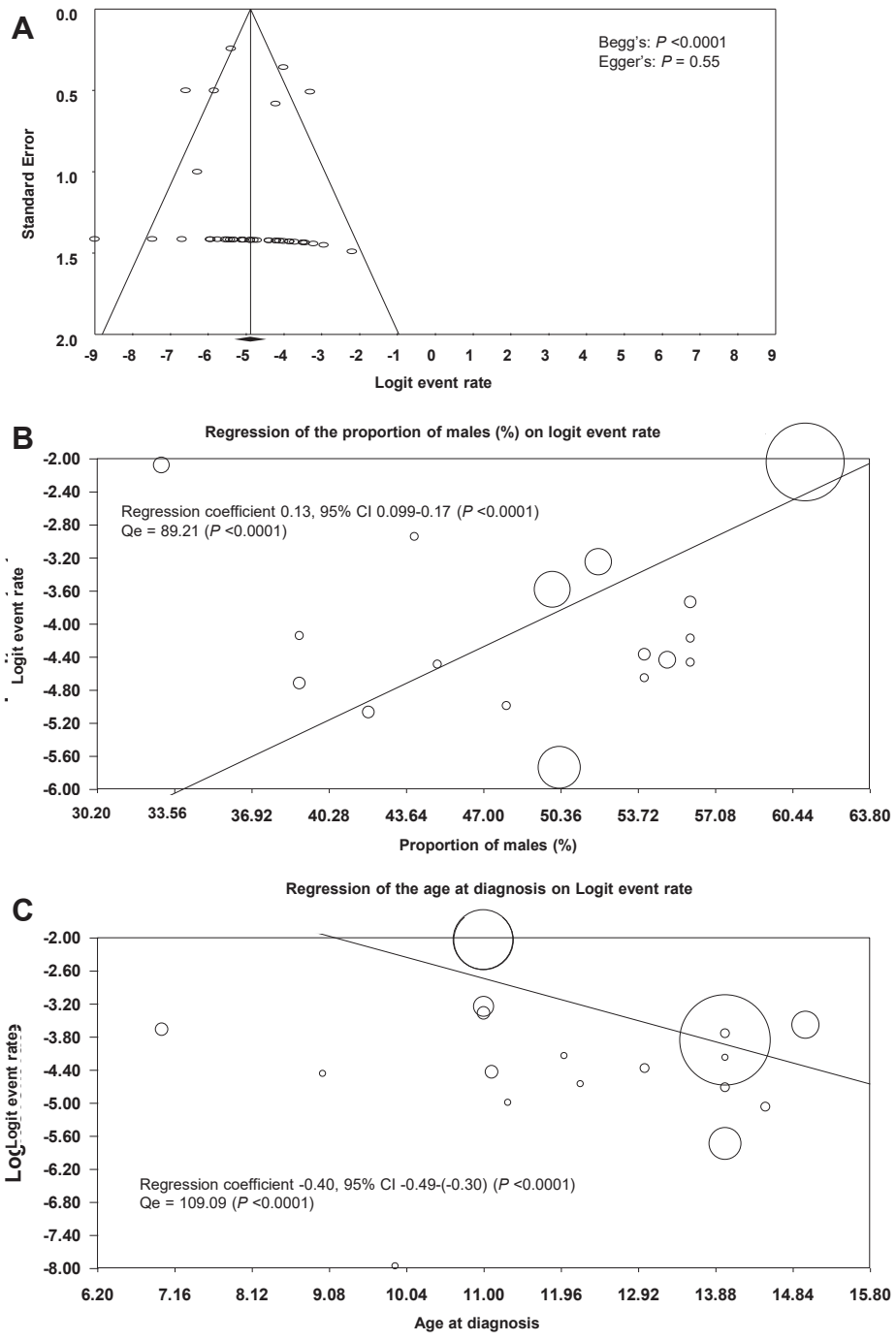
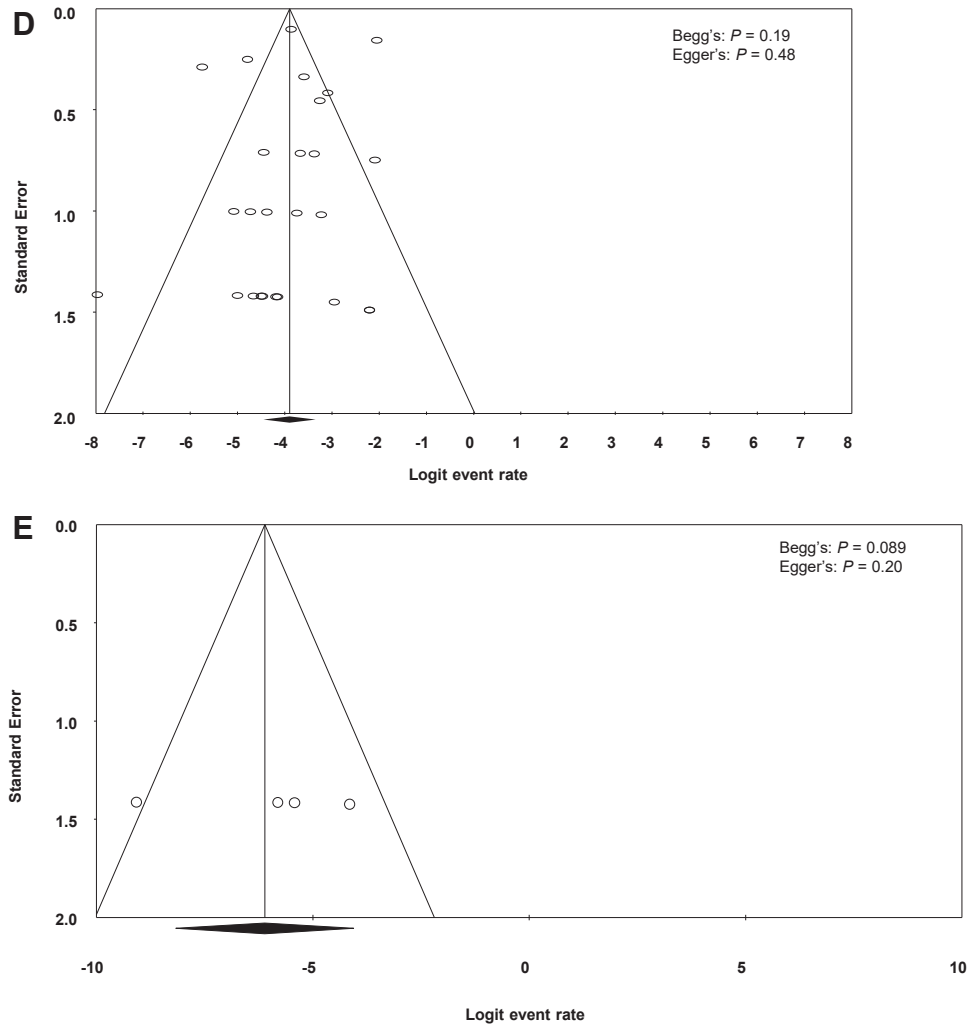


Figure 6. **A,** Funnel plot of the studies reporting the risk of CRC among patients with CD included in **Figure 5**, A. There were small-study effects or publication biases as assessed by the Begg test but not by the Egger tests ($P < .0001$, = .55, respectively). Visual inspection of the funnel plot appeared to show no asymmetry. **B,** Meta-regression of the proportion of male patients (%) and the risk of CRC among patients with UC. Meta-regression showed that there was a positive correlation between the proportion of male patients and the risk of CRC (regression coefficient 0.13, 95% CI 0.099-0.17, $P < .0001$). ANOVA showed that *Qe* was statistically significant (*Qe* = 89.21, $P < .0001$), indicating that heterogeneity could not be explained only by this factor. **C,** Meta-regression of age at diagnosis or onset (*year*), and the risk of CRC among patients with UC. Meta-regression showed that there was a negative correlation between age at diagnosis or onset, and the risk of CRC (regression coefficient −0.40, 95% CI -0.49 to −0.30, $P < .0001$). ANOVA showed that *Qe* was statistically significant (*Qe* = 109.09, $P < .0001$), indicating that heterogeneity could not be explained only by this factor. **D,** Funnel plot of the studies reporting the risk of CRC among patients with UC included in **Figure 5**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger tests ($P = .19$, .48, respectively). **E,** Funnel plot of the studies reporting the risk of CRC among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 5**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger tests ($P = .089$, .20, respectively).



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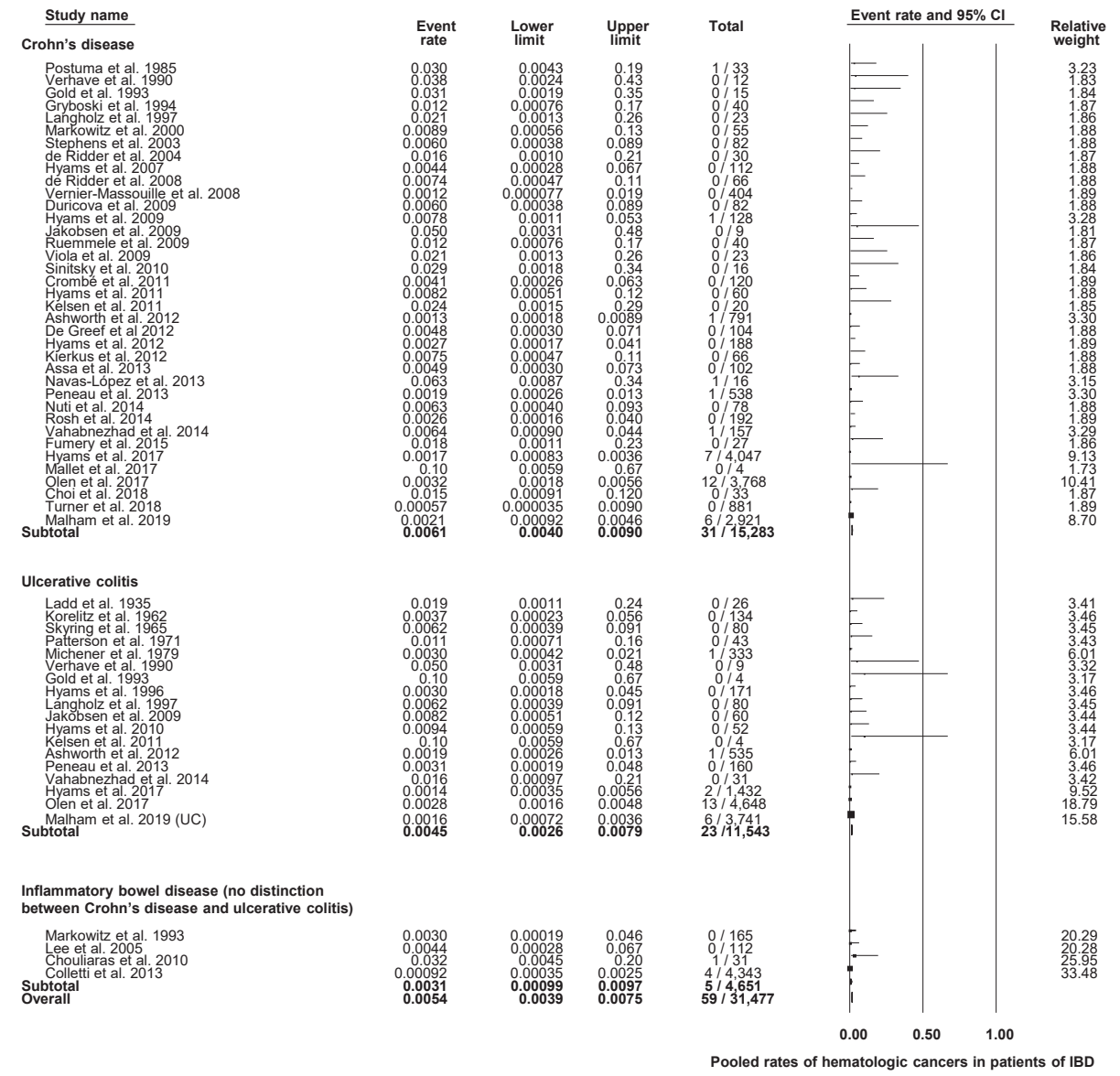
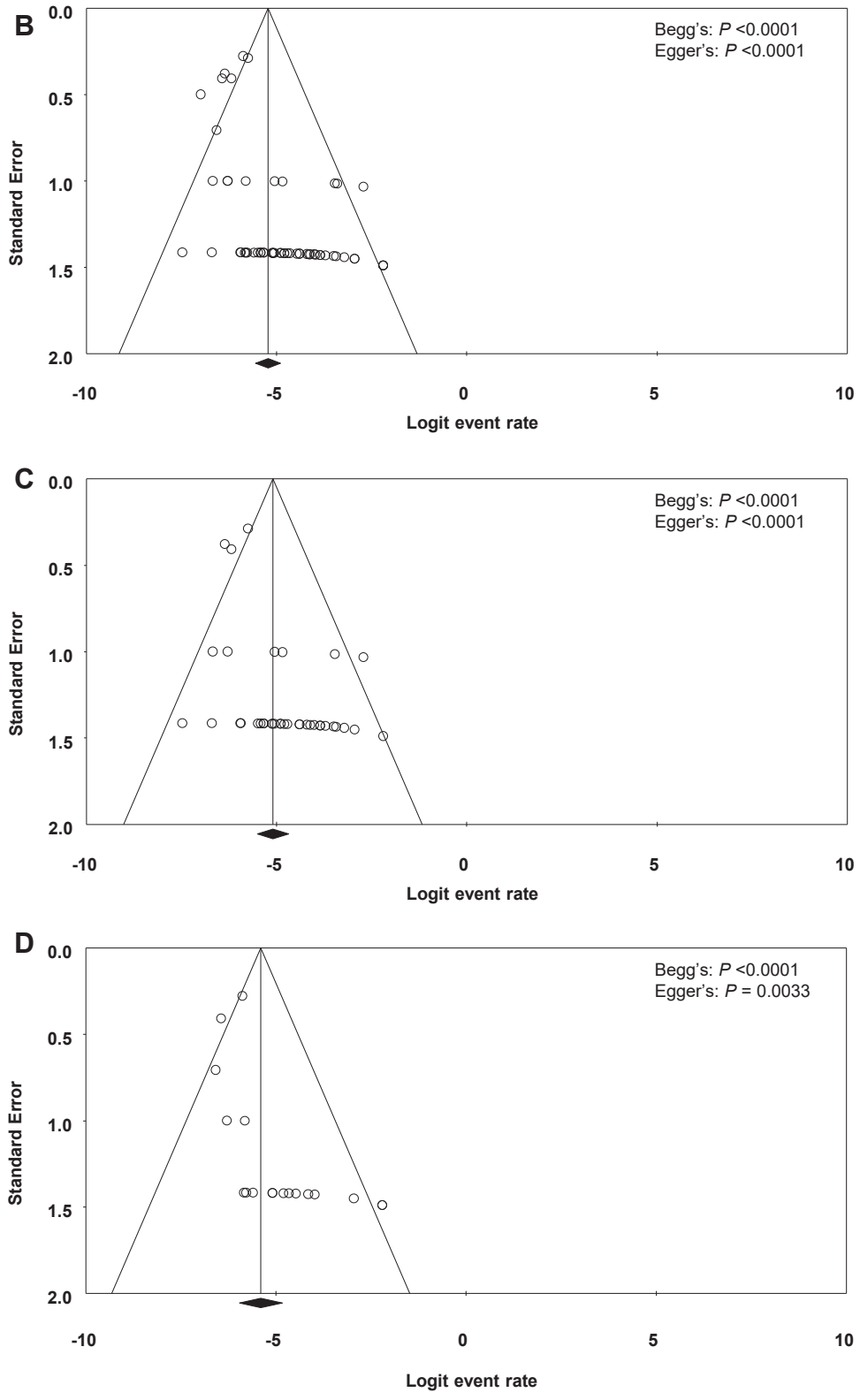


Heterogeneity
Crohn's disease; I^2 = 27.14%, Q = 49.41, P = 0.068
Ulcerative colitis; I^2 = 31.66%, Q = 24.88, P = 0.098
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); I^2 = 71.29%, Q = 10.45, P = 0.015
Overall; I^2 = 34.25%, Q = 88.21, P = 0.0064

Figure 7. Meta-analysis of incidence rates of hematologic cancers among pediatric IBD. **A,** Forest plot of incidence rates of hematologic cancers among pediatric IBD. **B,** Funnel plot of the studies included in **Figure 7**, A. **The** Begg and Egger tests; P < .0001, <.0001, respectively. **C,** Funnel plot of the studies reporting the risk of hematologic cancers among patients with CD included in **Figure 7**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **D,** Funnel plot of the studies reporting the risk of hematologic cancers among patients with UC included in **Figure 7**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .0033, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **E,** Funnel plot of the studies reporting of the risk of hematologic cancers among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 7**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger tests (P = .73, .32, respectively).



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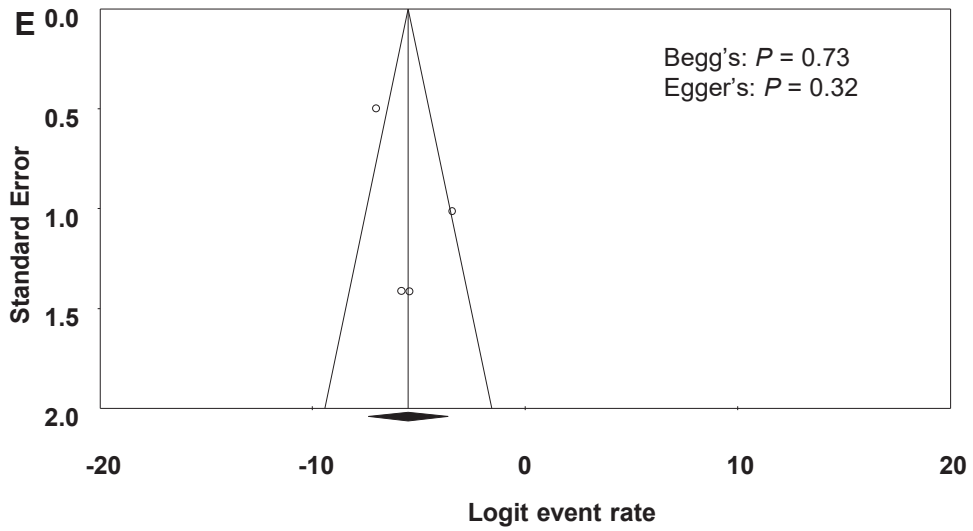

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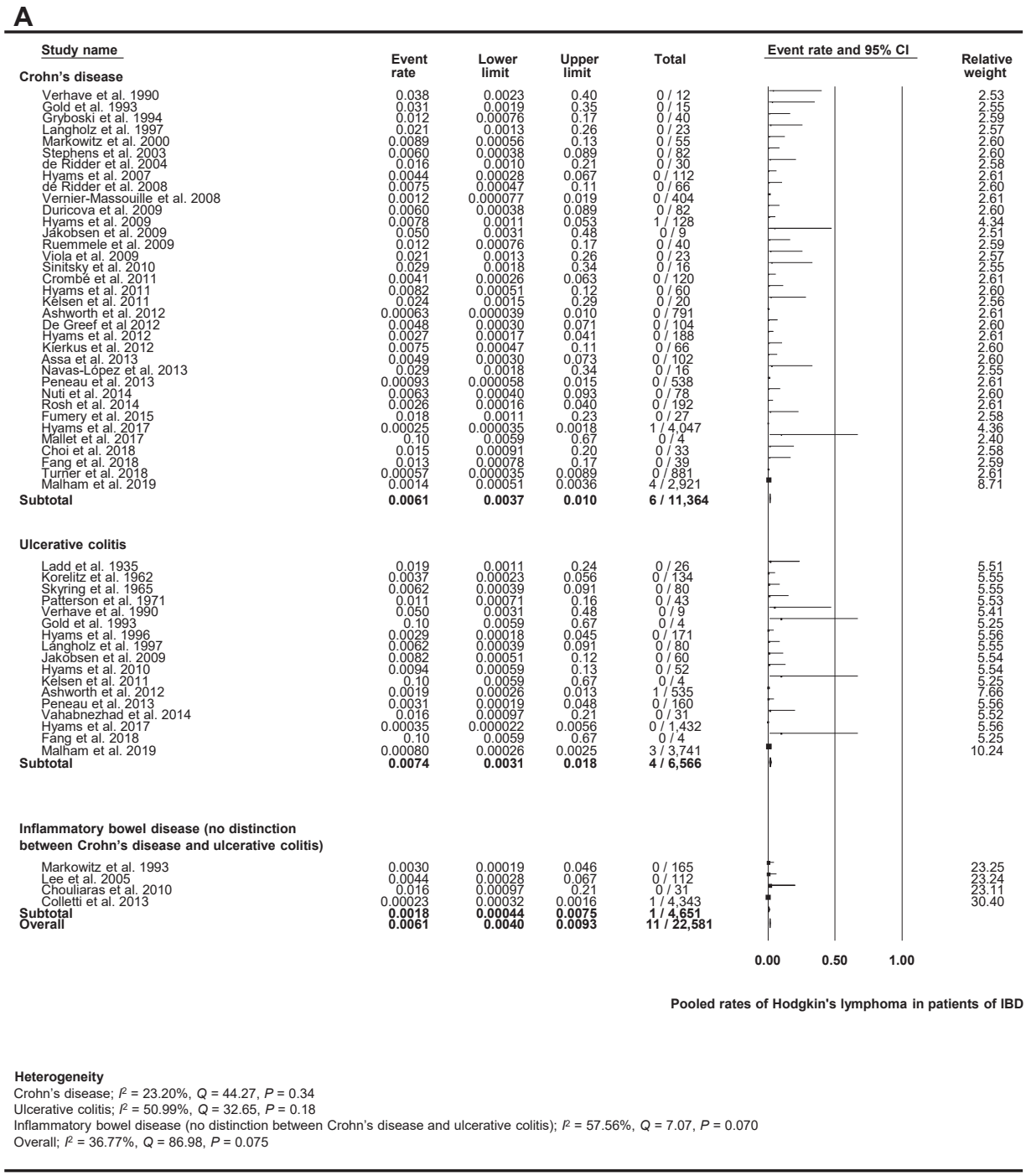
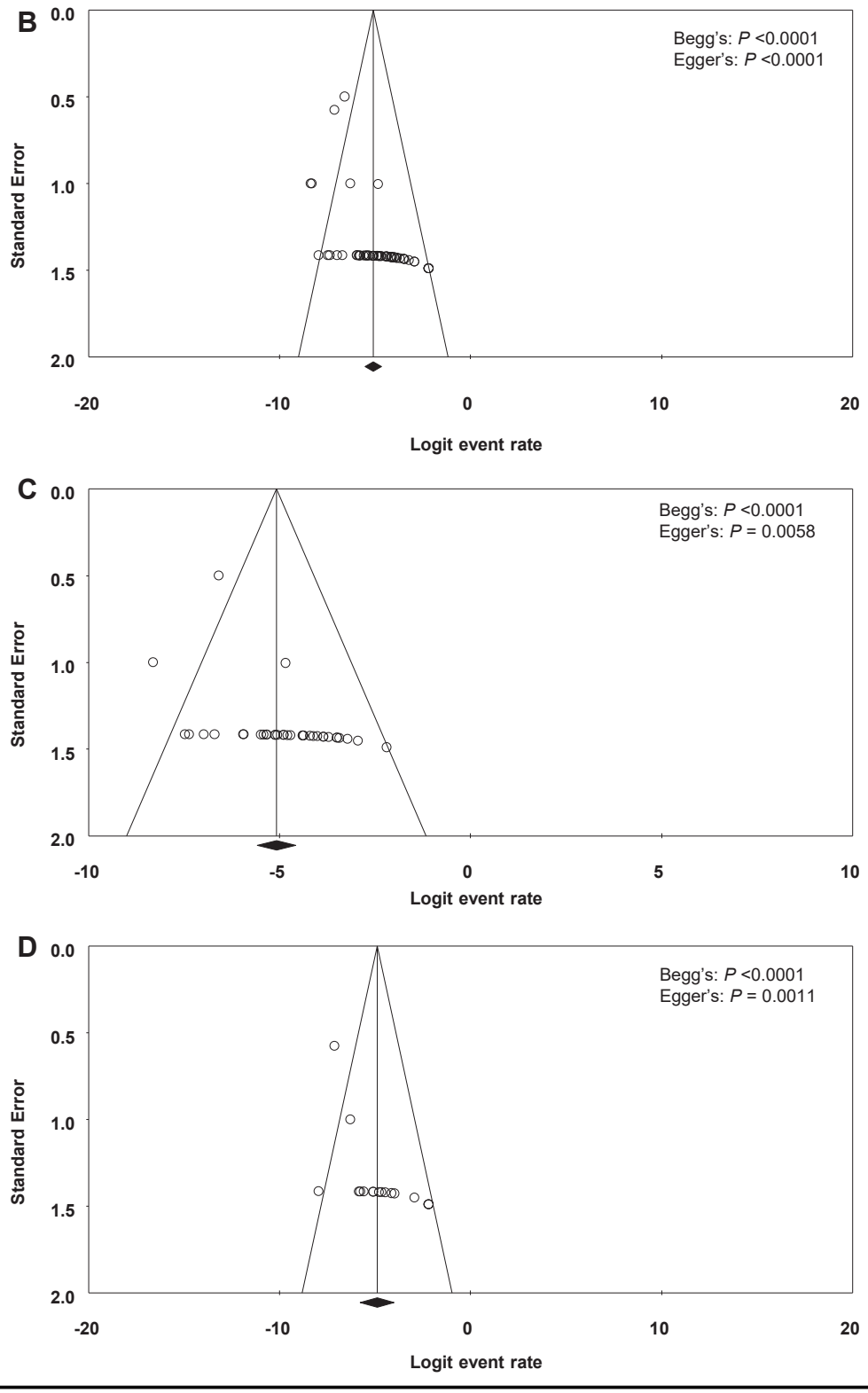


Figure 8. Meta-analysis of incidence rates of Hodgkin lymphoma among pediatric IBD. **A,** Forest plot of incidence rates of Hodgkin lymphoma among pediatric IBD. **B,** Funnel plot of the studies included in **Figure 8**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **C,** Funnel plot of the studies reporting the risk of Hodgkin lymphoma among patients with CD included in **Figure 8**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .0058, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **D,** Funnel plot of the studies reporting the risk of Hodgkin lymphoma among patients with UC included in **Figure 8**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .0011, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **E,** Funnel plot of the studies reporting the risk of Hodgkin lymphoma among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 8**, A. There were no small-study effects or publication biases as assessed by the Begg test (P = .089), but were present by the Egger tests (P = .049). Visual inspection of the funnel plot appeared to show no asymmetry.



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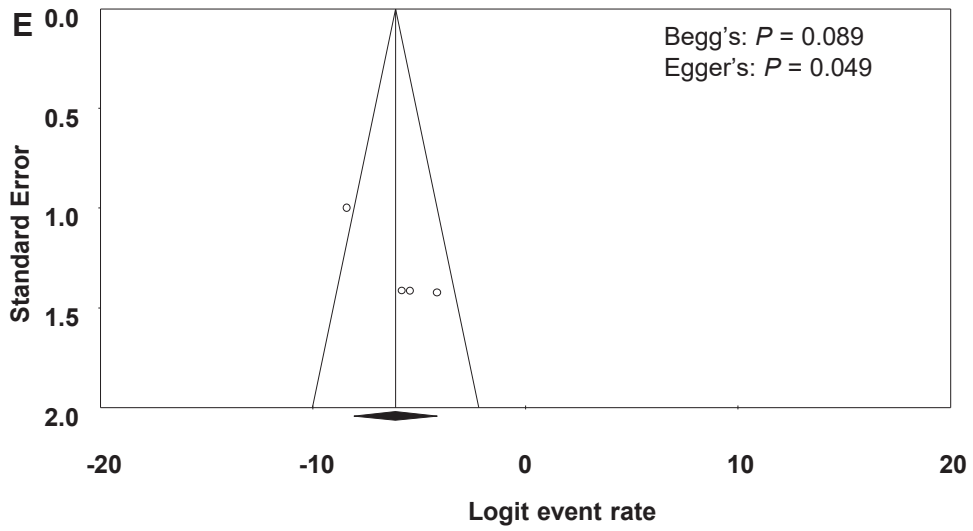

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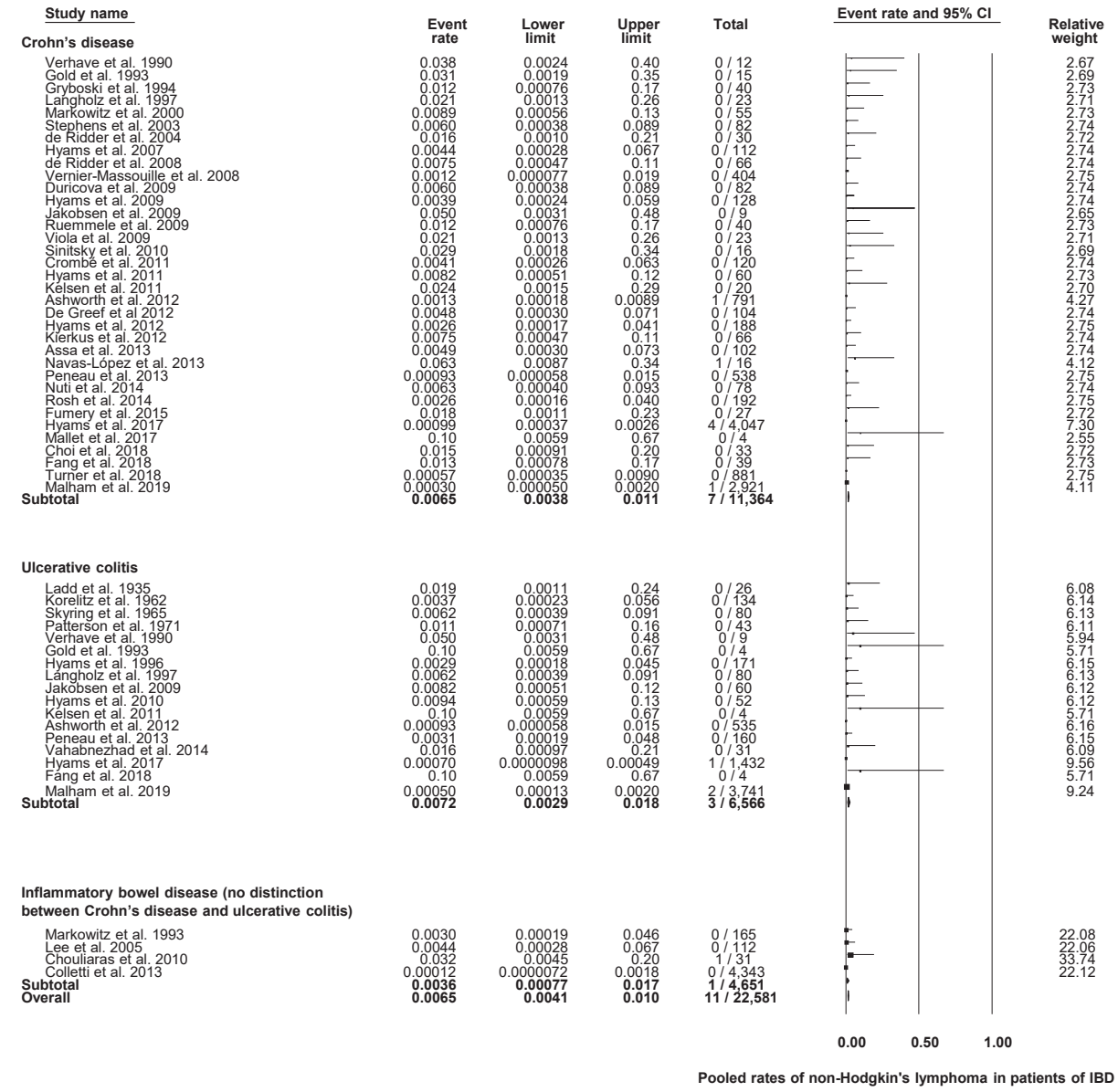


Heterogeneity

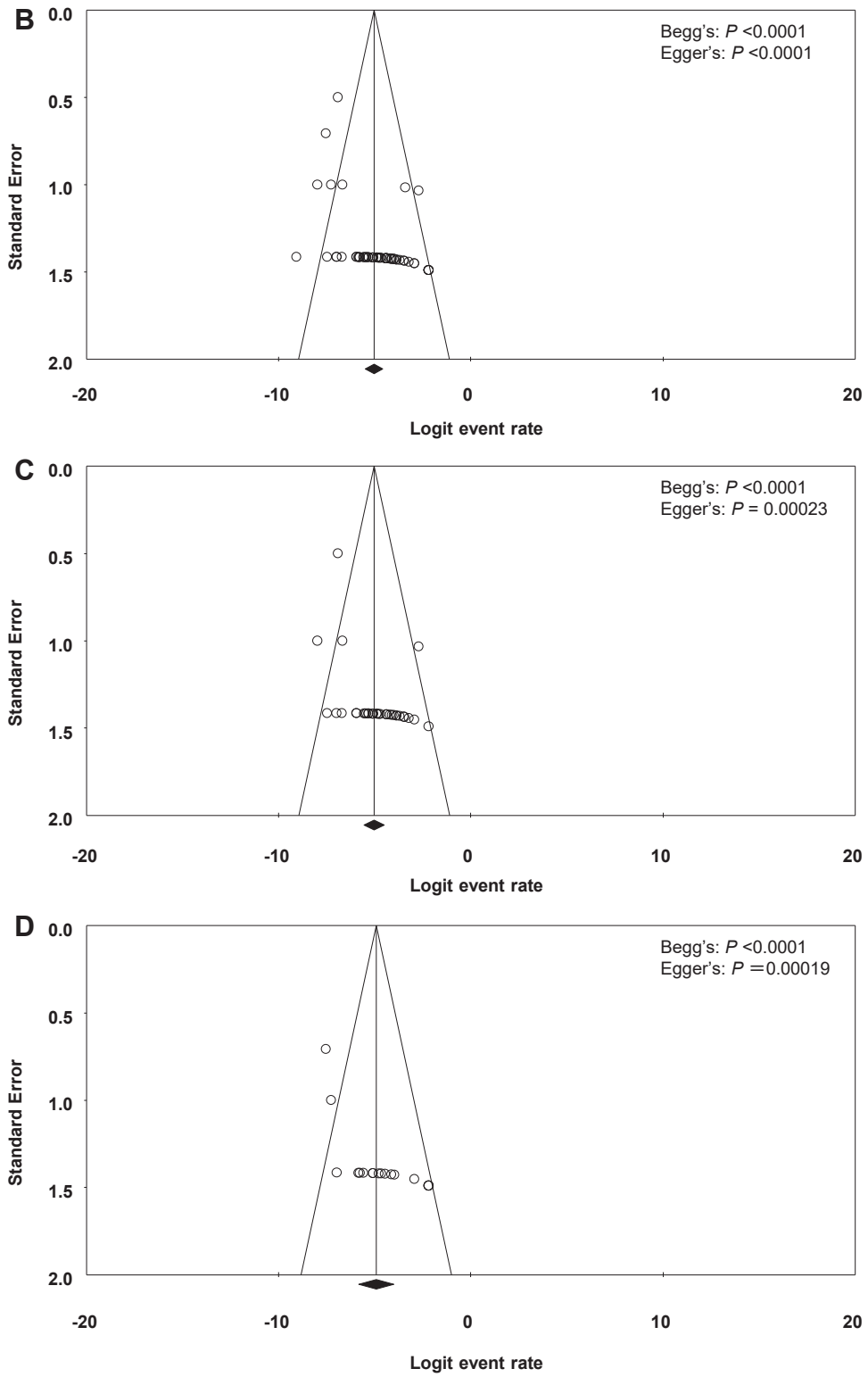
Crohn's disease; I^2 = 32.70%, Q = 50.52, P = 0.034

Ulcerative colitis; I^2 = 52.12%, Q = 33.42, P = 0.0065

Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); I^2 = 71.90%, Q = 10.67, P = 0.014

Overall; I^2 = 41.90%, Q = 94.66, P = 0.00071

Figure 9. Meta-analysis of incidence rates of non-Hodgkin lymphoma among pediatric IBD. **A,** Forest plot of incidence rates of non-Hodgkin lymphoma among pediatric IBD. **B,** Funnel plot of the studies included in **Figure 9**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, <.0001, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **C,** Funnel plot of the studies reporting the risk of non-Hodgkin lymphoma among patients with CD included in **Figure 9**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .00023, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **D,** Funnel plot of the studies reporting the risk of non-Hodgkin lymphoma among patients with UC included in **Figure 9**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .00019, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **E,** Funnel plot of the studies reporting the risk of non-Hodgkin lymphoma among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 9**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger tests (P = 1.00, .21, respectively).



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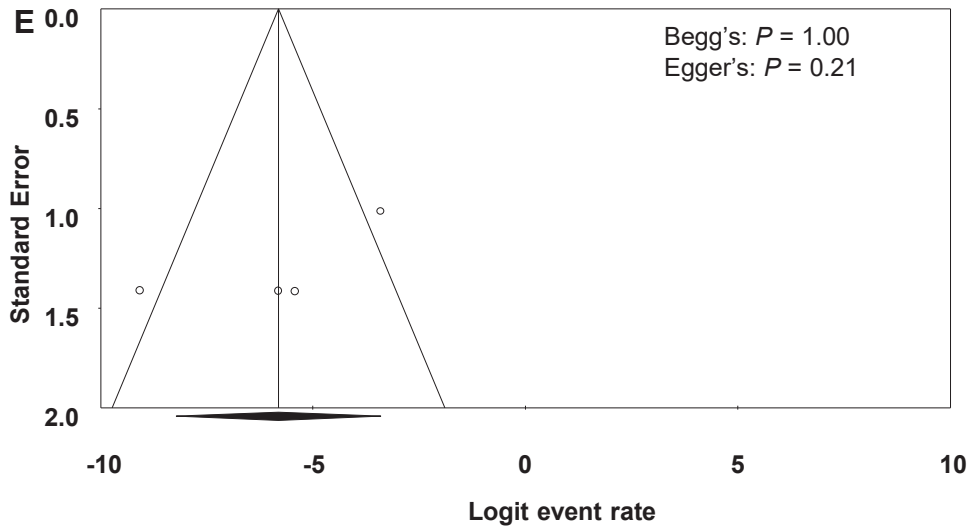

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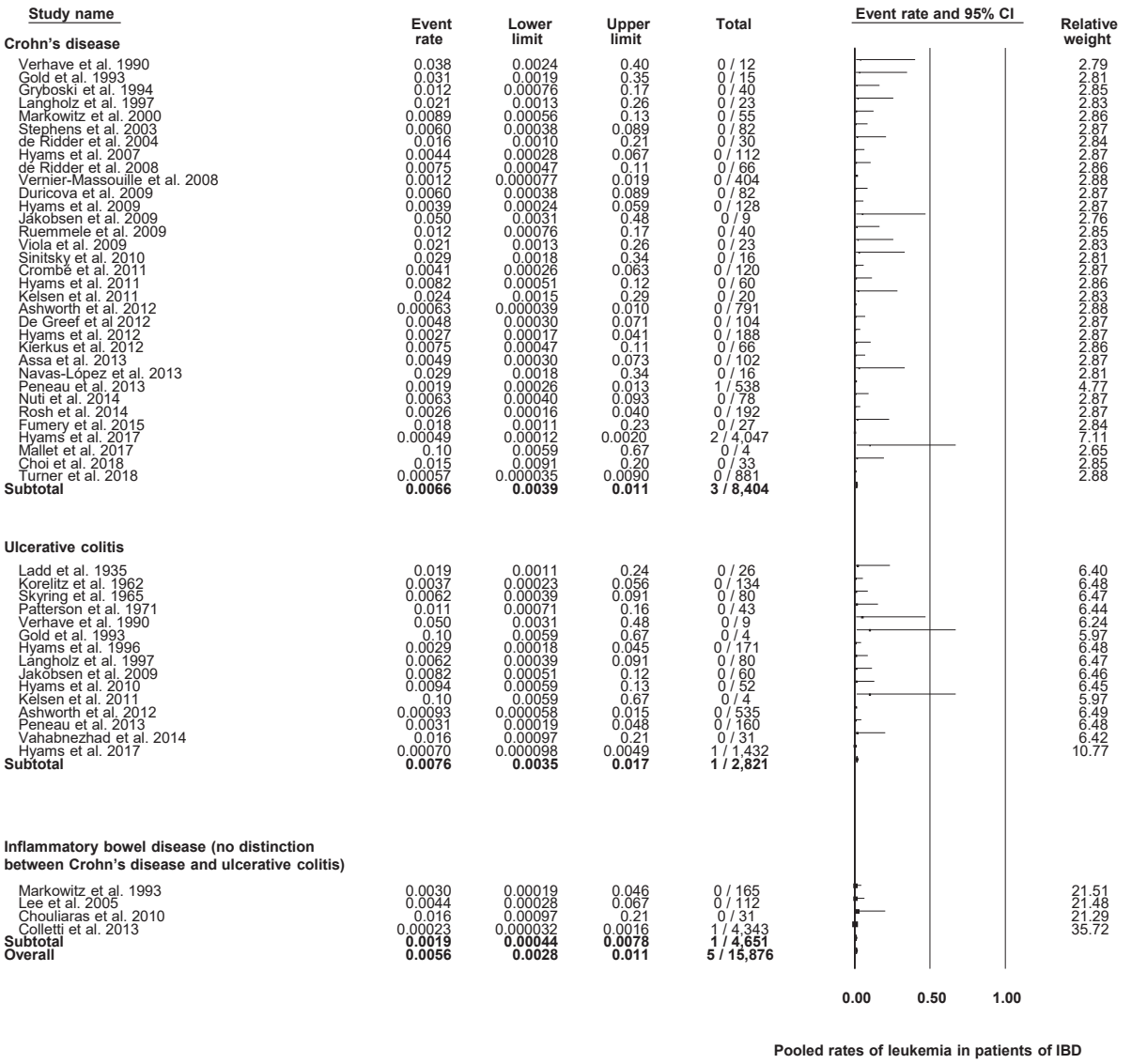
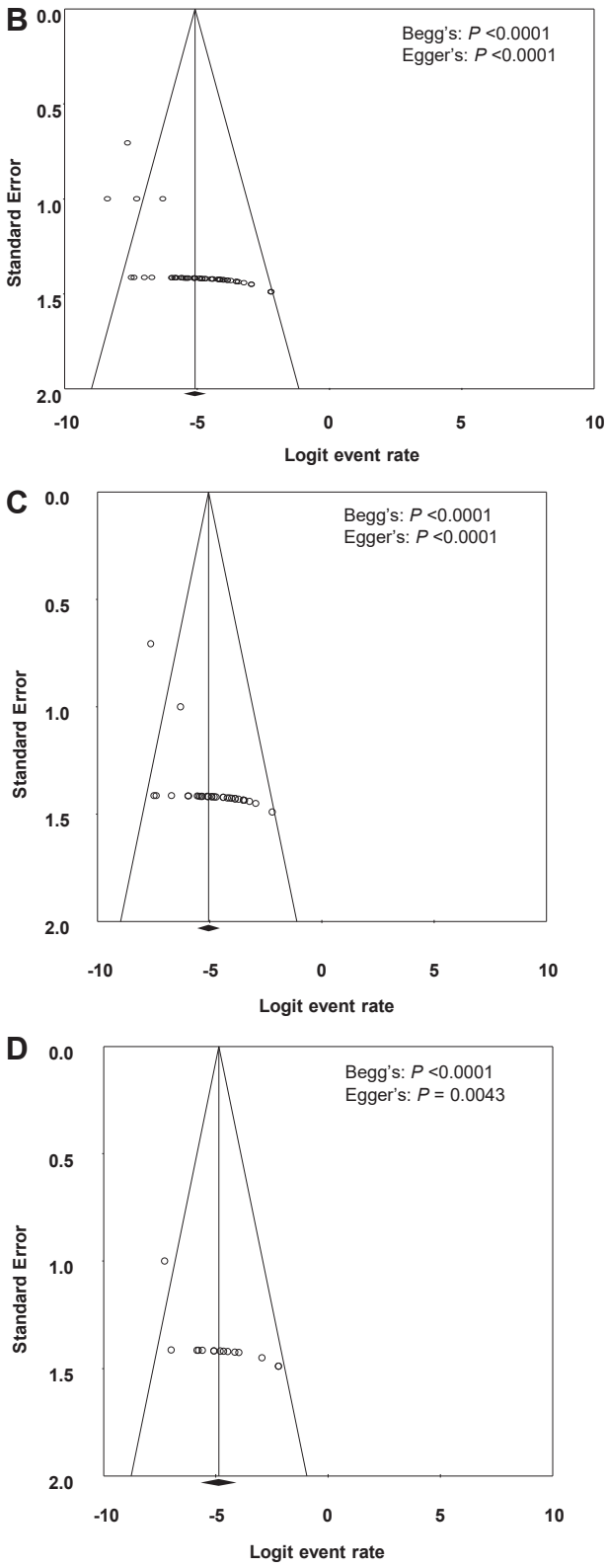


Heterogeneity

Crohn's disease; I^2 = 15.26%, Q = 37.76, P = 0.22
Ulcerative colitis; I^2 = 22.46%, Q = 18.06, P = 0.20
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); I^2 = 57.56%, Q = 7.07, P = 0.070
Overall; I^2 = 24.20%, Q = 67.28, P = 0.063

Figure 10. Meta-analysis of incidence rates of leukemia among pediatric IBD. **A,** Forest plot of incidence rates of leukemia among patients with pediatric IBD. **B,** Funnel plot of the studies included in **Figure 10**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **C,** Funnel plot of the studies reporting the risk of leukemia among patients with CD included in **Figure 10**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, respectively). Visual inspection of the funnel plot appeared to show no asymmetry. **D,** Funnel plot of the studies reporting the risk of leukemia among patients with UC included in **Figure 10**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .0043, respectively). Visual inspection of the funnel plot appeared to show no asymmetry. **E,** Funnel plot of the studies reporting the risk of leukemia among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 10**, A. There were no small-study effects or publication biases as assessed by the Begg test (P = .089), but were present by the Egger tests (P = .049). Visual inspection of the funnel plot appeared to show no asymmetry.



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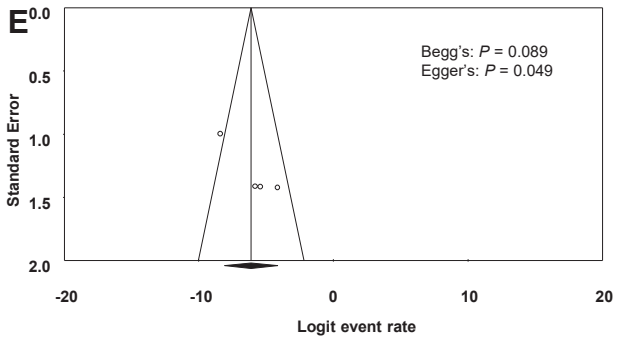

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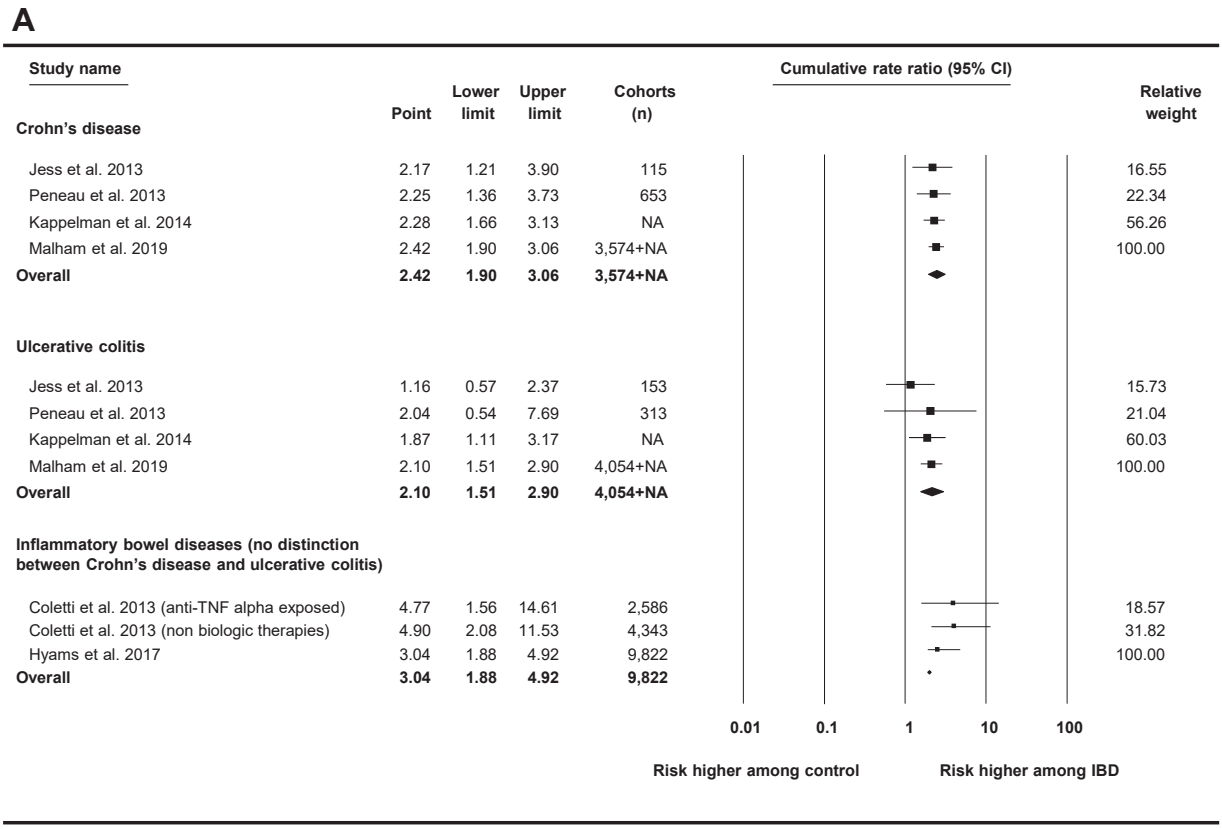
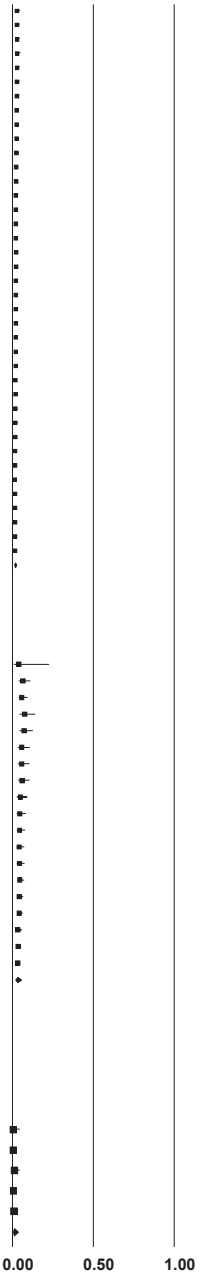


Figure 11. **A,** Cumulative meta-analysis of the overall risk of cancers reported as SIR among patients with pediatric IBD. **B,** Cumulative meta-analysis of incident rates of overall risk of cancers among patients with pediatric IBD. As the reporting years became more recent, the incidence of cancer was significantly reduced in the cumulative meta-analyses among CD, UC, and IBDs (regression coefficient 0.015, 0.039, 0.019, respectively. 95% CI 0.014-0.017 ($P < .0001$), 0.034-0.043 ($P < .0001$), 0.018-0.021 ($P < .0001$), respectively). **C,** Cumulative meta-analysis of the risk of CRC among patients with pediatric IBD. As the reporting years became more recent, the incidence of CRC was significantly reduced in the cumulative meta-analyses among CD, UC, and IBDs (regression coefficient 0.0018, 0.015, 0.0049, respectively. 95% CI 0.0016-0.0020 ($P < .0001$), 0.012-0.018 ($P < .0001$), 0.0043-0.0054 ($P < .0001$), respectively). **D,** Cumulative meta-analysis of the risk of hematologic cancers among patients with pediatric IBD. As the reporting years became more recent, the incidence of hematologic cancers was significantly reduced in the cumulative meta-analyses among CD, UC, and IBDs (regression coefficient 0.0020, 0.0021, 0.0018, respectively. 95% CI 0.0019-0.0021 ($P < .0001$), 0.0020-0.0022 ($P < .0001$), 0.0017-0.0019 ($P < .0001$), respectively). **E,** Cumulative analysis of the risk of Hodgkin lymphoma among patients with pediatric IBD. As the reporting years became more recent, the incidence of Hodgkin lymphoma was significantly reduced in the cumulative meta-analyses among CD, UC, and IBDs (regression coefficient 0.00033, 0.00060, 0.00034, respectively. 95% CI 0.00027-0.00040 ($P < .0001$), 0.00050-0.00069 ($P < .0001$), 0.00031-0.00038 ($P < .0001$), respectively). **F,** Cumulative meta-analysis of the risk of non-Hodgkin lymphoma among patients with pediatric IBD. As the reporting years became more recent, the incidence of non-Hodgkin lymphoma was significantly reduced in the cumulative meta-analyses among CD, UC, and IBDs (regression coefficient 0.00077, 0.00046, 0.00050, respectively. 95% CI 0.00072-0.00083 ($P < .0001$), 0.00040-0.00053 ($P < .0001$), 0.00047-0.00054 ($P < .0001$), respectively). **G,** Cumulative meta-analysis of the risk of leukemia among patients with pediatric IBD. As the reporting years became more recent, the incidence of leukemia was significantly reduced in the cumulative meta-analyses among CD, UC and IBDs (regression coefficient 0.00040, 0.00029, 0.00031, respectively. 95% CI 0.00035-0.00045 ($P < .0001$), 0.00016-0.00042 ($P < .0001$), 0.00028-0.00034 ($P < .0001$), respectively).

B

Study name	Point	Lower limit	Upper limit	Event / total (n)	Relative weight
Crohn's disease					
Weedon et al. 1973	0.027	0.015	0.046	12 / 449	5.23
Postuma et al. 1985	0.027	0.016	0.046	13 / 482	7.96
Verhave et al. 1990	0.027	0.016	0.046	13 / 494	9.75
Gold et al. 1993	0.028	0.016	0.046	13 / 509	11.54
Gryboski et al. 1994	0.027	0.017	0.045	14 / 549	14.28
Langholz et al. 1997	0.027	0.017	0.044	14 / 572	16.09
Markowitz et al. 2000	0.026	0.016	0.042	14 / 627	17.92
Stephens et al. 2003	0.025	0.015	0.040	14 / 709	19.74
de Ridder et al. 2004	0.025	0.015	0.039	14 / 739	21.56
Hyams et al. 2007	0.024	0.015	0.037	14 / 851	23.39
de Ridder et al. 2008	0.023	0.014	0.036	14 / 917	25.22
Vernier-Massouille et al. 2008	0.021	0.013	0.033	14 / 1,321	27.05
Duricova et al. 2009	0.020	0.013	0.032	14 / 1,403	28.88
Hyams et al. 2009	0.019	0.013	0.030	15 / 1,531	31.64
Jakobsen et al. 2009	0.020	0.013	0.030	15 / 1,540	33.42
Ruemmele et al. 2009	0.020	0.013	0.030	15 / 1,580	35.24
Viola et al. 2009	0.020	0.013	0.030	15 / 1,603	37.05
Pigneur et al. 2010	0.020	0.014	0.030	20 / 1,809	41.73
Sinitsky et al. 2010	0.021	0.014	0.030	20 / 1,825	43.53
Crombé et al. 2011	0.020	0.014	0.029	21 / 1,945	46.30
Hyams et al. 2011	0.020	0.014	0.028	21 / 2,005	48.12
Kelsen et al. 2011	0.020	0.014	0.028	21 / 2,025	49.93
De Greef et al 2012	0.019	0.013	0.027	21 / 2,129	51.76
Hyams et al. 2012	0.019	0.013	0.026	21 / 2,317	53.59
Kierkus et al. 2012	0.018	0.013	0.026	21 / 2,383	55.42
Assa et al. 2013	0.018	0.013	0.025	21 / 2,485	57.25
Jess et al. 2013	0.017	0.010	0.028	34 / 2,600	62.47
Navas-López et al. 2013	0.018	0.011	0.029	35 / 2,616	65.15
Peneau et al. 2013	0.017	0.010	0.027	41 / 3,154	69.99
Nuti et al. 2014	0.017	0.010	0.027	41 / 3,232	71.82
Rosh et al. 2014	0.016	0.010	0.025	41 / 3,424	73.65
Vahabnezhad et al. 2014	0.015	0.010	0.024	42 / 3,581	76.42
Fumery et al. 2015	0.015	0.010	0.024	42 / 3,608	78.23
Hyams et al. 2017	0.013	0.0076	0.022	54 / 7,655	83.47
Mallet et al. 2017	0.014	0.0080	0.023	54 / 7,659	85.17
Olen et al. 2017	0.015	0.0091	0.024	207 / 11,427	90.83
Choi et al. 2018	0.015	0.0092	0.024	207 / 11,460	92.65
Turner et al. 2018	0.014	0.0085	0.022	207 / 12,341	94.48
Malham et al. 2019	0.014	0.0087	0.021	240 / 15,262	100.00
Overall	**0.014**	**0.0087**	**0.021**	**240 / 15,262**	
Ulcerative colitis					
Ladd et al. 1935	0.039	0.0054	0.23	1 / 26	3.87
Korelitz et al. 1962	0.064	0.035	0.11	10 / 160	11.11
Skyring et al. 1965	0.056	0.033	0.094	13 / 240	17.08
Devroede et al. 1971	0.075	0.038	0.14	65 / 636	25.05
Patterson et al. 1971	0.070	0.038	0.13	67 / 679	30.28
Michener et al. 1979	0.056	0.028	0.11	77 / 1,012	37.64
Verhave et al. 1990	0.056	0.029	0.11	77 / 1,021	40.15
Gold et al. 1993	0.058	0.030	0.11	77 / 1,025	42.58
Hyams et al. 1996	0.048	0.025	0.092	79 / 1,196	47.88
Langholz et al. 1997	0.044	0.023	0.083	80 / 1,276	51.81
Jakobsen et al. 2009	0.043	0.023	0.079	82 / 1,336	57.07
Hyams et al. 2010	0.040	0.022	0.074	82 / 1,388	59.67
Kelsen et al. 2011	0.042	0.023	0.075	82 / 1,392	62.09
Jess et al. 2013	0.044	0.026	0.074	91 / 1,545	69.34
Peneau et al. 2013	0.041	0.024	0.068	94 / 1,705	75.33
Vahabnezhad et al. 2014	0.040	0.024	0.066	94 / 1,736	77.91
Hyams et al. 2017	0.031	0.017	0.057	97 / 3,168	83.93
Olen et al. 2017	0.036	0.023	0.055	396 / 7,816	92.06
Malham et al. 2019	0.031	0.018	0.052	435 / 11,557	100.00
Overall	**0.031**	**0.018**	**0.052**	**435 / 11,557**	
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)					
Markowitz et al. 1993	0.0030	0.00019	0.046	0 / 165	14.28
Lee et al. 2005	0.0037	0.00051	0.025	0 / 277	28.56
Chouliaras et al. 2010	0.010	0.0021	0.046	1 / 308	47.21
Colletti et al. 2013	0.0046	0.00097	0.022	8 / 4,651	73.12
El-Matary et al. 2020	0.0068	0.0015	0.030	25 / 5,598	100.00
Overall	**0.0068**	**0.0015**	**0.030**	**25 / 5,598**	



Univariate regression analyses for the slope of cumulative analyses

Crohn's disease; regression coefficient 0.015, 95% CI 0.014-0.017 (P <0.0001)
Ulcerative colitis; regression coefficient 0.039, 95% CI 0.034-0.043 (P <0.0001)
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient 0.0036, 95% CI 0.00019-0.0069 (P = 0.044)
Overall; regression coefficient 0.019, 95% CI 0.018-0.021 (P <0.0001)

Figure 11. (continued)

C

Study name	Point	Lower limit	Upper limit	Event / total (n)	Relative weight
Crohn's disease					
Weedon et al. 1973	0.018	0.0089	0.035	8 / 449	6.88
Postuma et al. 1985	0.018	0.0090	0.034	8 / 482	8.69
Verhave et al. 1990	0.018	0.0096	0.035	8 / 494	10.47
Gold et al. 1993	0.019	0.010	0.035	8 / 509	12.26
Gillen et al. 1994	0.023	0.013	0.038	12 / 622	18.03
Gryboski et al. 1994	0.022	0.013	0.037	12 / 662	19.84
Langholz et al. 1997	0.022	0.013	0.037	12 / 685	21.65
Markowitz et al. 2000	0.022	0.013	0.035	12 / 740	23.47
Stephens et al. 2003	0.021	0.013	0.034	12 / 822	25.29
de Ridder et al. 2004	0.020	0.013	0.033	12 / 852	27.11
Hyams et al. 2007	0.020	0.012	0.031	12 / 964	28.93
de Ridder et al. 2008	0.019	0.012	0.030	12 / 1,030	30.76
Vernier-Massouille et al. 2008	0.018	0.011	0.028	12 / 1,434	32.59
Duricova et al. 2009	0.017	0.011	0.027	12 / 1,516	34.42
Hyams et al. 2009	0.016	0.010	0.026	12 / 1,644	36.25
Jakobsen et al. 2009	0.017	0.011	0.026	12 / 1,653	38.01
Ruemmele et al. 2009	0.017	0.011	0.026	12 / 1,693	39.82
Viola et al. 2009	0.017	0.011	0.026	12 / 1,716	41.43
Pigneur et al. 2010	0.016	0.011	0.025	15 / 1,922	46.88
Sinitsky et al. 2010	0.017	0.011	0.025	15 / 1,938	48.67
Crombé et al. 2011	0.016	0.011	0.024	15 / 2,058	50.50
Hyams et al. 2011	0.016	0.011	0.024	15 / 2,118	52.33
Kelsen et al. 2011	0.016	0.011	0.024	15 / 2,138	54.13
De Greef et al 2012	0.016	0.011	0.023	15 / 2,242	55.95
Hyams et al. 2012	0.015	0.010	0.022	15 / 2,430	57.78
Kierkus et al. 2012	0.015	0.010	0.022	15 / 2,496	59.61
Assa et al. 2013	0.015	0.010	0.021	15 / 2,598	61.44
Navas-López et al. 2013	0.015	0.010	0.022	15 / 2,614	63.23
Peneau et al. 2013	0.014	0.0096	0.020	16 / 3,152	66.24
Nuti et al. 2014	0.014	0.0095	0.020	16 / 3,230	68.06
Rosh et al. 2014	0.013	0.0092	0.019	16 / 3,422	69.90
Vahabnezhad et al. 2014	0.013	0.0090	0.018	16 / 3,579	71.73
Fumery et al. 2015	0.013	0.0091	0.018	16 / 3,606	73.53
Hyams et al. 2017	0.012	0.0084	0.017	16 / 7,653	75.37
Mallet et al. 2017	0.012	0.0082	0.017	16 / 7,657	77.06
Olén et al. 2017	0.010	0.0063	0.014	33 / 11,425	84.70
Choi et al. 2018	0.010	0.0064	0.014	33 / 11,458	86.52
Turner et al. 2018	0.0091	0.0060	0.014	33 / 12,339	88.35
Malham et al. 2019	0.0080	0.0050	0.012	37 / 15,260	94.18
Olén et al. 2020	0.0075	0.0049	0.011	41 / 16,645	100.00
Overall	**0.0075**	**0.0049**	**0.011**	**41 / 16,645**	
Ulcerative colitis					
Ladd et al. 1935	0.038	0.0050	0.23	1 / 26	3.45
Lagercrantz et al. 1955	0.043	0.021	0.087	7 / 163	8.97
Holowach et al. 1956	0.053	0.028	0.098	9 / 181	13.32
Michener et al. 1961	0.078	0.041	0.14	55 / 582	19.48
Hijmans et al. 1962	0.069	0.034	0.13	55 / 625	21.90
Korelitz et al. 1962	0.060	0.031	0.11	60 / 759	27.30
Skyring et al. 1965	0.053	0.028	0.099	62 / 839	31.77
Patterson et al. 1971	0.050	0.027	0.092	63 / 882	35.24
Binder et al. 1973	0.047	0.025	0.085	63 / 926	37.66
Michener et al. 1979	0.042	0.023	0.076	72 / 1,259	43.42
Verhave et al. 1990	0.042	0.023	0.076	72 / 1,268	45.78
Ahsgren et al. 1993	0.041	0.023	0.072	72 / 1,300	48.20
Gold et al. 1993	0.042	0.024	0.073	72 / 1,304	50.48
Hyams et al. 1996	0.038	0.021	0.066	74 / 1,475	54.97
Langholz et al. 1997	0.036	0.020	0.062	75 / 1,555	58.46
Falcone et al. 2000	0.034	0.019	0.058	75 / 1,628	60.89
Gower-Rousseau et al. 2009	0.031	0.018	0.054	76 / 1,741	64.38
Jakobsen et al. 2009	0.032	0.019	0.053	78 / 1,801	68.84
Hyams et al. 2010	0.030	0.018	0.051	78 / 1,853	71.27
Kelsen et al. 2011	0.032	0.019	0.052	78 / 1,857	73.55
Peneau et al. 2013	0.029	0.017	0.049	79 / 2,017	77.05
Vahabnezhad et al. 2014	0.029	0.017	0.048	79 / 2,048	79.46
Hyams et al. 2017	0.025	0.014	0.043	79 / 3,480	81.90
Olén et al. 2017	0.025	0.015	0.041	175 / 8,128	88.13
Malham et al. 2019	0.021	0.012	0.037	187 / 11,869	94.02
Olén et al. 2020	0.020	0.012	0.034	203 / 13,787	100.00
Overall	**0.020**	**0.012**	**0.034**	**203 / 13,787**	
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)					
Markowitz et al. 1993	0.0030	0.00019	0.046	0 / 165	25.03
Lee et al. 2005	0.0037	0.00051	0.025	0 / 277	50.05
Chouliaras et al. 2010	0.0059	0.0012	0.029	0 / 308	74.93
Colletti et al. 2013	0.0022	0.00028	0.017	0 / 4,651	100.00
Overall	**0.0022**	**0.00028**	**0.017**	**0 / 4,651**	

Cumulative rate ratio (95% CI)

0.00 0.50 1.00

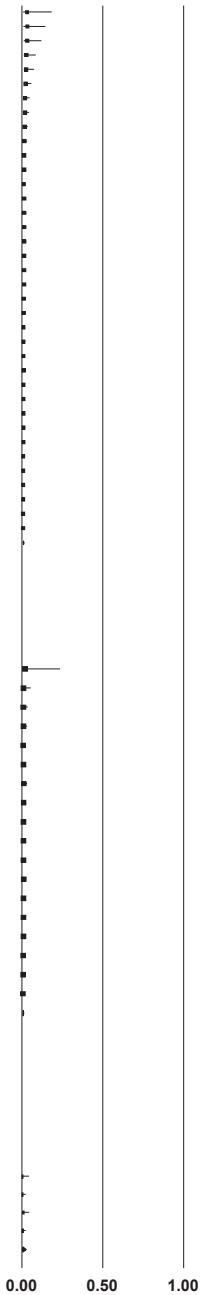
Univariate regression analyses for the slope of cumulative analyses

Crohn's disease; regression coefficient 0.0018, 95% CI 0.0016-0.0020 (P <0.0001)
Ulcerative colitis; regression coefficient 0.015, 95% CI 0.012-0.018 (P <0.0001)
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient NA, 95% CI NA
Overall; regression coefficient 0.0049, 95% CI 0.0043-0.0054 (P <0.0001)

Figure 11. (continued)

D

Study name	Point	Lower limit	Upper limit	Event / total (n)	Relative weight
Crohn's disease					
Postuma et al. 1985	0.030	0.0043	0.19	1 / 33	3.23
Verhave et al. 1990	0.033	0.0066	0.15	1 / 45	5.06
Gold et al. 1993	0.032	0.0081	0.12	1 / 60	6.90
Gryboski et al. 1994	0.027	0.0077	0.088	1 / 100	8.77
Langholz et al. 1997	0.026	0.0083	0.076	1 / 123	10.63
Markowitz et al. 2000	0.022	0.0077	0.061	1 / 178	12.50
Stephens et al. 2003	0.019	0.0070	0.049	1 / 260	14.39
de Ridder et al. 2004	0.018	0.0073	0.045	1 / 290	16.25
Hyams et al. 2007	0.016	0.0066	0.038	1 / 402	18.14
de Ridder et al. 2008	0.015	0.0064	0.034	1 / 468	20.02
Vernier-Massouille et al. 2008	0.012	0.0054	0.027	1 / 872	21.91
Duricova et al. 2009	0.011	0.0053	0.024	1 / 954	23.79
Hyams et al. 2009	0.011	0.0053	0.022	2 / 1,082	27.07
Jakobsen et al. 2009	0.012	0.0060	0.024	2 / 1,091	28.88
Ruemmele et al. 2009	0.012	0.0061	0.023	2 / 1,131	30.75
Viola et al. 2009	0.012	0.0064	0.024	2 / 1,154	32.61
Sinitsky et al. 2010	0.013	0.0068	0.024	2 / 1,170	34.45
Crombé et al. 2011	0.012	0.0065	0.023	2 / 1,290	36.34
Hyams et al. 2011	0.012	0.0065	0.022	2 / 1,350	38.22
Kelsen et al. 2011	0.012	0.0068	0.022	2 / 1,370	40.07
Ashworth et al. 2012	0.010	0.0058	0.018	3 / 2,161	43.37
De Greef et al 2012	0.0099	0.0057	0.017	3 / 2,265	45.25
Hyams et al. 2012	0.0094	0.0054	0.016	3 / 2,453	47.14
Kierkus et al. 2012	0.0093	0.0055	0.016	3 / 2,519	49.02
Assa et al. 2013	0.0091	0.0054	0.015	3 / 2,621	50.90
Navas-López et al. 2013	0.010	0.0062	0.017	4 / 2,637	54.05
Peneau et al. 2013	0.0092	0.0057	0.015	5 / 3,175	57.35
Nuti et al. 2014	0.0091	0.0056	0.015	5 / 3,253	59.23
Rosh et al. 2014	0.0088	0.0055	0.014	5 / 3,445	61.12
Vahabnezhad et al. 2014	0.0086	0.0054	0.014	6 / 3,602	64.40
Fumery et al. 2015	0.0088	0.0056	0.014	6 / 3,629	66.26
Hyams et al. 2017	0.0069	0.0044	0.011	13 / 7,676	75.40
Mallet et al. 2017	0.0077	0.0048	0.012	13 / 7,680	77.13
Olen et al. 2017	0.0069	0.0045	0.011	25 / 11,448	87.54
Choi et al. 2018	0.0069	0.0045	0.011	25 / 11,481	89.40
Turner et al. 2018	0.0067	0.0044	0.010	25 / 12,362	91.30
Malham et al. 2019	0.0061	0.0040	0.0091	31 / 15,283	100.00
Overall	**0.0061**	**0.0040**	**0.0091**	**31 / 15,283**	
Ulcerative colitis					
Ladd et al. 1935	0.019	0.0011	0.24	0 / 26	3.41
Korelitz et al. 1962	0.0083	0.0012	0.056	0 / 160	6.87
Skyring et al. 1965	0.0075	0.0015	0.036	0 / 240	10.32
Patterson et al. 1971	0.0083	0.0021	0.033	0 / 283	13.75
Michener et al. 1979	0.0059	0.0019	0.018	1 / 616	19.76
Verhave et al. 1990	0.0080	0.0028	0.023	1 / 625	23.08
Gold et al. 1993	0.011	0.0040	0.029	1 / 629	26.25
Hyams et al. 1996	0.0093	0.0037	0.023	1 / 800	29.71
Langholz et al. 1997	0.0089	0.0037	0.021	1 / 880	33.16
Jakobsen et al. 2009	0.0088	0.0038	0.020	1 / 940	36.60
Hyams et al. 2010	0.0089	0.0040	0.020	1 / 992	40.04
Kelsen et al. 2011	0.011	0.0049	0.023	1 / 996	43.21
Ashworth et al. 2012	0.0084	0.0041	0.017	2 / 1,531	49.23
Peneau et al. 2013	0.0079	0.0039	0.016	2 / 1,691	52.68
Vahabnezhad et al. 2014	0.0082	0.0042	0.016	2 / 1,722	56.11
Hyams et al. 2017	0.0065	0.0033	0.013	4 / 3,154	65.63
Olen et al. 2017	0.0054	0.0030	0.0098	17 / 7,802	84.42
Malham et al. 2019	0.0045	0.0026	0.0079	23 / 11,543	100.00
Overall	**0.0045**	**0.0026**	**0.0079**	**23 / 11,543**	
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)					
Markowitz et al. 1993	0.0030	0.00019	0.046	0 / 165	20.29
Lee et al. 2005	0.0037	0.00051	0.025	0 / 277	40.57
Chouliaras et al. 2010	0.010	0.0021	0.046	1 / 308	66.52
Colletti et al. 2013	0.0041	0.0063	0.026	5 / 4,651	100.00
Overall	**0.0041**	**0.0063**	**0.026**	**5 / 4,651**	



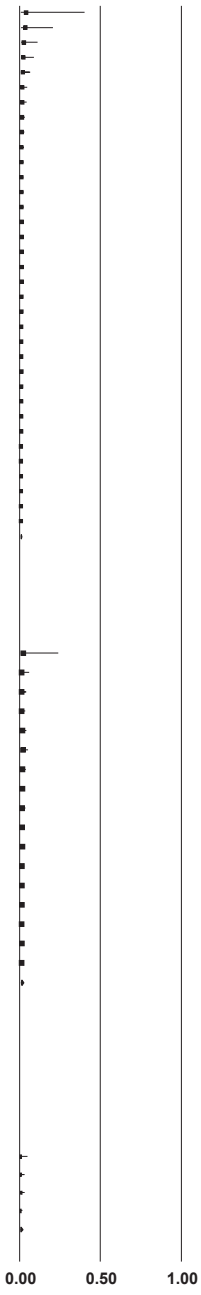
Univariate regression analyses for the slope of cumulative analyses

Crohn's disease; regression coefficient 0.0020, 95% CI 0.0019-0.0021 (P <0.0001)
Ulcerative colitis; regression coefficient 0.0021, 95% CI 0.0020-0.0022 (P <0.0001)
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient 0.0011, 95% CI 0.00047-0.0017 (P = 0.016)
Overall; regression coefficient 0.0018, 95% CI 0.0017-0.0019 (P <0.0001)

Figure 11. (continued)

E

Study name	Point	Lower limit	Upper limit	Event / total (n)	Relative weight
Crohn's disease					
Verhave et al. 1990	0.039	0.0024	0.40	0 / 12	2.53
Gold et al. 1993	0.035	0.0049	0.21	0 / 27	5.08
Gryboski et al. 1994	0.024	0.0049	0.11	0 / 67	7.67
Langholz et al. 1997	0.024	0.0059	0.089	0 / 90	10.24
Markowitz et al. 2000	0.019	0.0056	0.065	0 / 145	12.84
Stephens et al. 2003	0.016	0.0051	0.048	0 / 227	15.44
de Ridder et al. 2004	0.016	0.0056	0.045	0 / 257	18.02
Hyams et al. 2007	0.014	0.0051	0.036	0 / 369	20.63
de Ridder et al. 2008	0.013	0.0050	0.032	0 / 435	23.22
Vernier-Massouille et al. 2008	0.010	0.0042	0.024	0 / 839	25.84
Duricova et al. 2009	0.0096	0.0041	0.022	0 / 921	28.44
Hyams et al. 2009	0.0093	0.0043	0.020	1 / 1,049	32.77
Jakobsen et al. 2009	0.010	0.0050	0.022	1 / 1,058	35.28
Ruemmele et al. 2009	0.011	0.0052	0.021	1 / 1,098	37.87
Viola et al. 2009	0.011	0.0055	0.022	1 / 1,121	40.44
Sinitsky et al. 2010	0.012	0.0059	0.023	1 / 1,137	42.99
Crombé et al. 2011	0.011	0.0057	0.021	1 / 1,257	45.60
Hyams et al. 2011	0.011	0.0057	0.020	1 / 1,317	48.20
Kelsen et al. 2011	0.011	0.0061	0.021	1 / 1,337	50.76
Ashworth et al. 2012	0.0098	0.0054	0.018	1 / 2,128	53.37
De Greef et al 2012	0.0095	0.0053	0.017	1 / 2,232	55.98
Hyams et al. 2012	0.0090	0.0050	0.016	1 / 2,420	58.59
Kierkus et al. 2012	0.0089	0.0051	0.016	1 / 2,486	61.19
Assa et al. 2013	0.0087	0.0050	0.015	1 / 2,588	63.79
Navas-López et al. 2013	0.0091	0.0053	0.016	1 / 2,604	66.34
Peneau et al. 2013	0.0084	0.0049	0.014	1 / 3,142	68.96
Nuti et al. 2014	0.0083	0.0049	0.014	1 / 3,220	71.56
Rosh et al. 2014	0.0079	0.0047	0.013	1 / 3,412	74.17
Fumery et al. 2015	0.0082	0.0049	0.014	1 / 3,439	76.74
Hyams et al. 2017	0.0066	0.0040	0.011	2 / 7,486	81.10
Mallet et al. 2017	0.0072	0.0043	0.012	2 / 7,490	83.50
Choi et al. 2018	0.0073	0.0045	0.012	2 / 7,523	86.09
Fang et al. 2018	0.0074	0.0046	0.012	2 / 7,562	88.67
Turner et al. 2018	0.0069	0.0043	0.011	2 / 8,443	91.29
Malham et al. 2019	0.0061	0.0037	0.010	6 / 11,364	100.00
Overall	**0.0061**	**0.0037**	**0.010**	**6 / 11,364**	
Ulcerative colitis					
Ladd et al. 1935	0.019	0.0011	0.236	0 / 26	5.51
Korelitz et al. 1962	0.0083	0.0012	0.056	0 / 160	11.06
Skyring et al. 1965	0.0075	0.0015	0.036	0 / 240	16.61
Patterson et al. 1971	0.0083	0.0021	0.033	0 / 283	22.14
Verhave et al. 1990	0.012	0.0034	0.040	0 / 292	27.55
Gold et al. 1993	0.017	0.0053	0.051	0 / 296	32.79
Hyams et al. 1996	0.013	0.0045	0.036	0 / 467	38.35
Langholz et al. 1997	0.012	0.0044	0.031	0 / 547	43.90
Jakobsen et al. 2009	0.011	0.0045	0.028	0 / 607	49.44
Hyams et al. 2010	0.011	0.0046	0.026	0 / 659	54.97
Kelsen et al. 2011	0.013	0.0058	0.031	0 / 663	60.22
Ashworth et al. 2012	0.0099	0.0045	0.021	1 / 1,198	67.88
Peneau et al. 2013	0.0091	0.0043	0.019	1 / 1,358	73.44
Vahabnezhad et al. 2014	0.0094	0.0046	0.019	1 / 1,389	78.95
Hyams et al. 2017	0.0079	0.0037	0.017	1 / 2,821	84.52
Fang et al. 2018	0.0092	0.0042	0.020	1 / 2,825	89.76
Malham et al. 2019	0.0074	0.0031	0.018	4 / 6,566	100.00
Overall	**0.0074**	**0.0031**	**0.018**	**4 / 6,566**	
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)					
Markowitz et al. 1993	0.0030	0.00019	0.046	0 / 165	23.25
Lee et al. 2005	0.0037	0.00051	0.025	0 / 277	46.49
Chouliaras et al. 2010	0.0059	0.0012	0.029	0 / 308	69.60
Colletti et al. 2013	0.0022	0.00031	0.015	1 / 4,651	100.00
Overall	**0.0022**	**0.00031**	**0.015**	**1 / 4,651**	



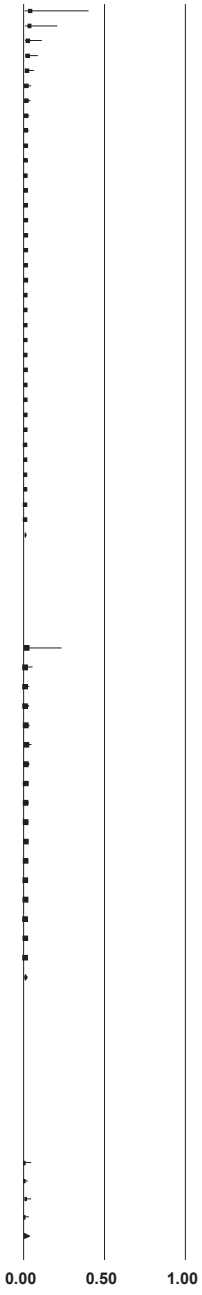
Univariate regression analysis for the slope of cumulative analysis

Crohn's disease; regression coefficient 0.00033, 95% CI 0.00027-0.00040 (P <0.0001)
Ulcerative colitis; regression coefficient 0.00060, 95% CI 0.00050-0.00069 (P <0.0001)
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient 0.00023, 95% CI 0.00021-0.00025 (P = 0.00039)
Overall; regression coefficient 0.00034, 95% CI 0.00031-0.00038 (P <0.0001)

Figure 11. (continued)

F

Study name	Point	Lower limit	Upper limit	Event / total (n)	Relative weight
Crohn's disease					
Verhave et al. 1990	0.039	0.0024	0.40	0 / 12	2.56
Gold et al. 1993	0.035	0.0049	0.21	0 / 27	5.14
Gryboski et al. 1994	0.024	0.0049	0.11	0 / 67	7.75
Langholz et al. 1997	0.024	0.0059	0.089	0 / 90	10.34
Markowitz et al. 2000	0.019	0.0056	0.065	0 / 145	12.96
Stephens et al. 2003	0.016	0.0051	0.048	0 / 227	15.58
de Ridder et al. 2004	0.016	0.0056	0.045	0 / 257	18.19
Hyams et al. 2007	0.014	0.0051	0.036	0 / 369	20.81
de Ridder et al. 2008	0.013	0.0050	0.032	0 / 435	23.43
Vernier-Massouille et al. 2008	0.010	0.0042	0.024	0 / 839	26.06
Duricova et al. 2009	0.0096	0.0041	0.022	0 / 921	28.69
Hyams et al. 2009	0.0089	0.0040	0.020	0 / 1,049	31.31
Jakobsen et al. 2009	0.010	0.0047	0.022	0 / 1,058	33.85
Ruemmele et al. 2009	0.010	0.0049	0.021	0 / 1,098	36.46
Viola et al. 2009	0.011	0.0052	0.022	0 / 1,121	39.06
Sinitsky et al. 2010	0.011	0.0057	0.023	0 / 1,137	41.64
Crombé et al. 2011	0.011	0.0055	0.021	0 / 1,257	44.26
Hyams et al. 2011	0.011	0.0055	0.020	0 / 1,317	46.88
Kelsen et al. 2011	0.011	0.0059	0.021	0 / 1,337	49.47
Ashworth et al. 2012	0.0090	0.0049	0.016	1 / 2,128	53.58
De Greef et al 2012	0.0087	0.0048	0.016	1 / 2,232	56.20
Hyams et al. 2012	0.0083	0.0046	0.015	1 / 2,420	58.83
Kierkus et al. 2012	0.0082	0.0047	0.014	1 / 2,486	61.45
Assa et al. 2013	0.0081	0.0046	0.014	1 / 2,588	64.08
Navas-López et al. 2013	0.0093	0.0055	0.016	2 / 2,604	68.04
Peneau et al. 2013	0.0086	0.0051	0.014	2 / 3,142	70.67
Nuti et al. 2014	0.0085	0.0051	0.014	2 / 3,220	73.29
Rosh et al. 2014	0.0082	0.0049	0.014	2 / 3,412	75.92
Fumery et al. 2015	0.0084	0.0051	0.014	2 / 3,439	78.52
Hyams et al. 2017	0.0066	0.0039	0.011	6 / 7,486	85.60
Mallet et al. 2017	0.0073	0.0043	0.012	6 / 7,490	88.04
Choi et al. 2018	0.0074	0.0044	0.012	6 / 7,523	90.65
Fang et al. 2018	0.0075	0.0045	0.012	6 / 7,562	93.26
Turner et al. 2018	0.0071	0.0043	0.012	6 / 8,443	95.89
Malham et al. 2019	0.0065	0.0038	0.011	7 / 11,364	100.00
Overall	**0.0065**	**0.0038**	**0.011**	**7 / 11,364**	
Ulcerative colitis					
Ladd et al. 1935	0.019	0.0011	0.24	0 / 26	5.58
Korelitz et al. 1962	0.0083	0.0012	0.056	0 / 160	11.20
Skyring et al. 1965	0.0075	0.0015	0.036	0 / 240	16.81
Patterson et al. 1971	0.0083	0.0021	0.033	0 / 283	22.41
Verhave et al. 1990	0.012	0.0034	0.040	0 / 292	27.89
Gold et al. 1993	0.017	0.0053	0.051	0 / 296	33.22
Hyams et al. 1996	0.013	0.0045	0.036	0 / 467	38.84
Langholz et al. 1997	0.012	0.0044	0.031	0 / 547	44.45
Jakobsen et al. 2009	0.011	0.0045	0.028	0 / 607	50.06
Hyams et al. 2010	0.011	0.0046	0.026	0 / 659	55.67
Kelsen et al. 2011	0.013	0.0058	0.031	0 / 663	60.99
Ashworth et al. 2012	0.011	0.0048	0.024	0 / 1,198	66.62
Peneau et al. 2013	0.0097	0.0045	0.021	0 / 1,358	72.24
Vahabnezhad et al. 2014	0.010	0.0048	0.021	0 / 1,389	77.83
Hyams et al. 2017	0.0076	0.0034	0.017	1 / 2,821	85.44
Fang et al. 2018	0.0090	0.0040	0.020	1 / 2,825	90.76
Malham et al. 2019	0.0072	0.0029	0.018	3 / 6,566	100.00
Overall	**0.0072**	**0.0029**	**0.018**	**3 / 6,566**	
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)					
Markowitz et al. 1993	0.0030	0.00019	0.046	0 / 165	23.91
Lee et al. 2005	0.0037	0.00051	0.025	0 / 277	47.81
Chouliaras et al. 2010	0.010	0.0021	0.046	1 / 308	76.07
Colletti et al. 2013	0.0030	0.00027	0.032	1 / 4,651	100.00
Overall	**0.0030**	**0.00027**	**0.032**	**1 / 4,651**	



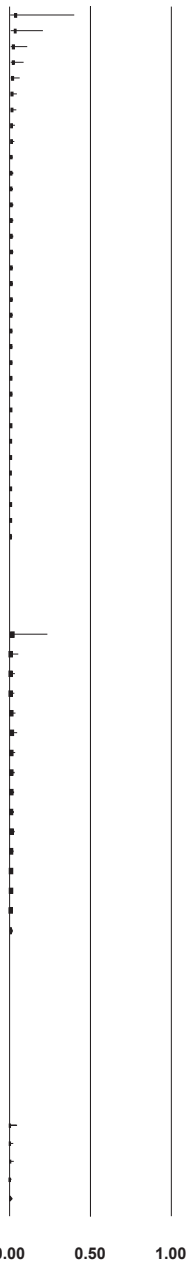
Univariate regression analysis for the slope of cumulative analysis

Crohn's disease; regression coefficient 0.00077, 95% CI 0.00072-0.00083 (P <0.0001)
Ulcerative colitis; regression coefficient 0.00046, 95% CI 0.00040-0.00053 (P <0.0001)
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient 0.00016, 95% CI -0.00049-0.00080 (P = 0.41)
Overall; regression coefficient 0.00050, 95% CI 0.00047-0.00054 (P <0.0001)

Figure 11. (continued)

G

Study name	Point	Lower limit	Upper limit	Event / total (n)	Relative weight
Crohn's disease					
Verhave et al. 1990	0.039	0.0024	0.40	0 / 12	2.75
Gold et al. 1993	0.035	0.0049	0.21	0 / 27	5.52
Gryboski et al. 1994	0.024	0.0049	0.11	0 / 67	8.34
Langholz et al. 1997	0.024	0.0059	0.089	0 / 90	11.13
Markowitz et al. 2000	0.020	0.0056	0.065	0 / 145	13.96
Stephens et al. 2003	0.016	0.0051	0.048	0 / 227	16.79
de Ridder et al. 2004	0.016	0.0056	0.045	0 / 257	19.60
Hyams et al. 2007	0.014	0.0051	0.036	0 / 369	22.43
de Ridder et al. 2008	0.013	0.0050	0.032	0 / 435	25.26
Vernier-Massouille et al. 2008	0.010	0.0042	0.024	0 / 839	28.10
Duricova et al. 2009	0.0096	0.0041	0.022	0 / 921	30.94
Hyams et al. 2009	0.0089	0.0040	0.020	0 / 1,049	33.77
Jakobsen et al. 2009	0.010	0.0047	0.022	0 / 1,058	36.50
Ruemmele et al. 2009	0.010	0.0049	0.021	0 / 1,098	39.31
Viola et al. 2009	0.011	0.0052	0.022	0 / 1,121	42.11
Sinitsky et al. 2010	0.011	0.0057	0.023	0 / 1,137	44.88
Crombé et al. 2011	0.011	0.0055	0.021	0 / 1,257	47.72
Hyams et al. 2011	0.011	0.0055	0.020	0 / 1,317	50.54
Kelsen et al. 2011	0.011	0.0059	0.021	0 / 1,337	53.33
Ashworth et al. 2012	0.0096	0.0051	0.018	0 / 2,128	56.18
De Greef et al 2012	0.0093	0.0051	0.017	0 / 2,232	59.01
Hyams et al. 2012	0.0087	0.0048	0.016	0 / 2,420	61.85
Kierkus et al. 2012	0.0087	0.0049	0.015	0 / 2,486	64.68
Assa et al. 2013	0.0085	0.0048	0.015	0 / 2,588	67.52
Navas-López et al. 2013	0.0089	0.0051	0.015	0 / 2,604	70.29
Peneau et al. 2013	0.0079	0.0046	0.013	1 / 3,142	75.27
Nuti et al. 2014	0.0079	0.0047	0.013	1 / 3,220	78.10
Rosh et al. 2014	0.0076	0.0045	0.013	1 / 3,412	80.94
Fumery et al. 2015	0.0078	0.0047	0.013	1 / 3,439	83.75
Hyams et al. 2017	0.0059	0.0036	0.010	3 / 7,486	91.75
Mallet et al. 2017	0.0066	0.0040	0.011	3 / 7,490	94.34
Choi et al. 2018	0.0067	0.0041	0.011	3 / 7,523	97.15
Turner et al. 2018	0.0064	0.0039	0.011	3 / 8,404	100.00
Overall	**0.0064**	**0.0039**	**0.011**	**3 / 8,404**	
Ulcerative colitis					
Ladd et al. 1935	0.019	0.0011	0.24	0 / 26	6.41
Korelitz et al. 1962	0.0083	0.0012	0.056	0 / 160	12.90
Skyring et al. 1965	0.0075	0.0015	0.036	0 / 240	19.37
Patterson et al. 1971	0.0083	0.0021	0.033	0 / 283	25.81
Verhave et al. 1990	0.012	0.0034	0.040	0 / 292	32.06
Gold et al. 1993	0.017	0.0053	0.051	0 / 296	38.05
Hyams et al. 1996	0.013	0.0045	0.036	0 / 467	44.54
Langholz et al. 1997	0.012	0.0044	0.031	0 / 547	51.01
Jakobsen et al. 2009	0.011	0.0045	0.028	0 / 607	57.47
Hyams et al. 2010	0.011	0.0046	0.026	0 / 659	63.93
Kelsen et al. 2011	0.013	0.0058	0.031	0 / 663	69.91
Ashworth et al. 2012	0.011	0.0048	0.024	0 / 1,198	76.41
Peneau et al. 2013	0.0097	0.0045	0.021	0 / 1,358	82.90
Vahabnezhad et al. 2014	0.010	0.0048	0.021	0 / 1,389	89.32
Hyams at al. 2017	0.0076	0.0034	0.017	1 / 2,821	100.00
Overall	**0.0076**	**0.0034**	**0.017**	**1 / 2,821**	
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)					
Markowitz et al. 1993	0.0030	0.00019	0.046	0 / 165	23.25
Lee et al. 2005	0.0037	0.00051	0.025	0 / 277	46.49
Chouliaras et al. 2010	0.0059	0.0012	0.029	0 / 308	69.60
Colletti et al. 2013	0.0022	0.00031	0.015	1 / 4,651	100.00
Overall	**0.0022**	**0.00031**	**0.015**	**1 / 4,651**	



Univariate regression analysis for the slope of cumulative analysis

Crohn's disease; regression coefficient 0.00040, 95% CI 0.00035-0.00045 (P <0.0001)
Ulcerative colitis; regression coefficient 0.00029, 95% CI 0.00016-0.00042 (P <0.0001)
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient 0.00023, 95% CI 0.00021-0.00025 (P = 0.00039)
Overall; regression coefficient 0.00031, 95% CI 0.00028-0.00034 (P <0.0001)

Figure 11. (Continued)

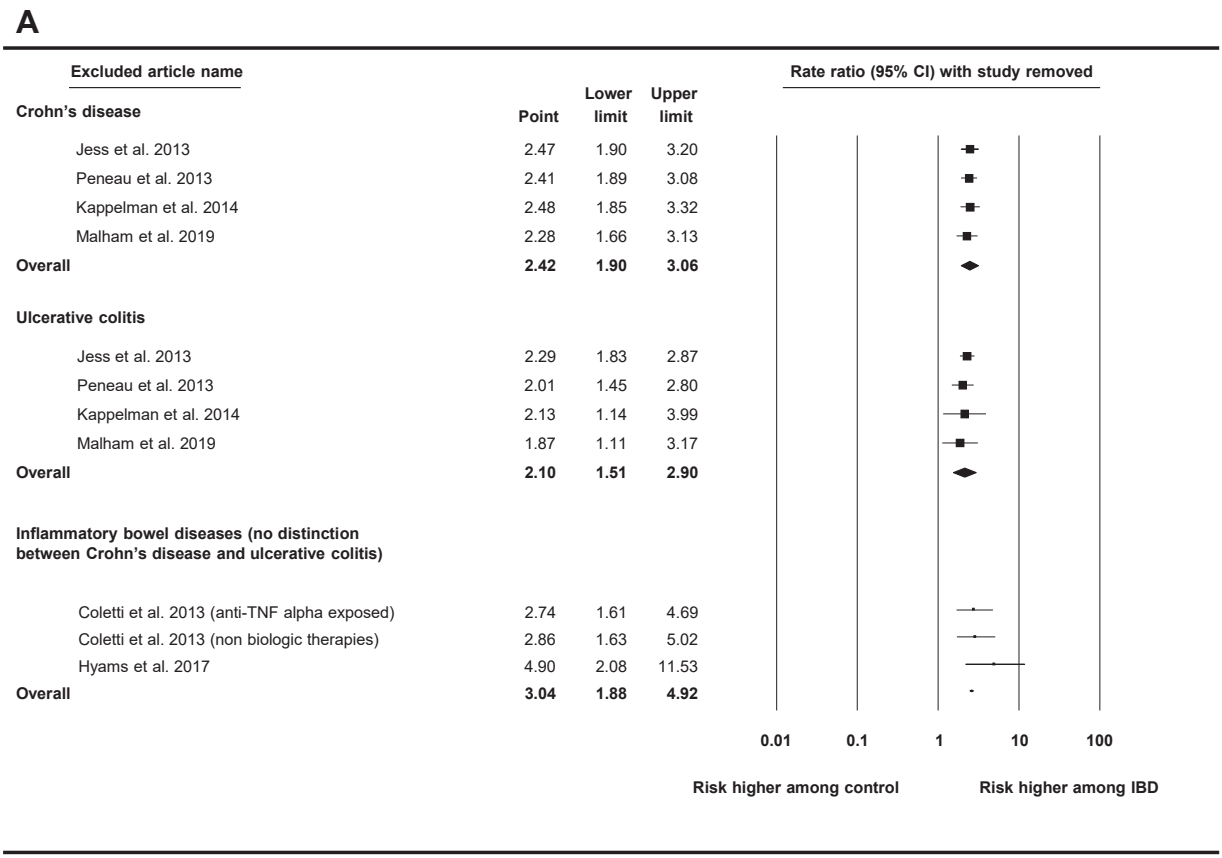


Figure 12. **A,** Influence analysis of the overall risk of cancers reported as SIR among patients with pediatric IBD. **B,** Influence analysis of incident rates of overall risk of cancers among patients with pediatric IBD. **C,** Influence analysis of the risk of CRC among patients with pediatric IBD. **D,** Influence analysis of the risk of hematologic cancers among patients with pediatric IBD. **E,** Influence analysis of the risk of Hodgkin lymphoma among patients with pediatric IBD. **F,** Influence analysis of the risk of non-Hodgkin lymphoma among patients with pediatric IBD. **G,** Influence analysis of the risk of leukemia among patients with pediatric IBD.

B

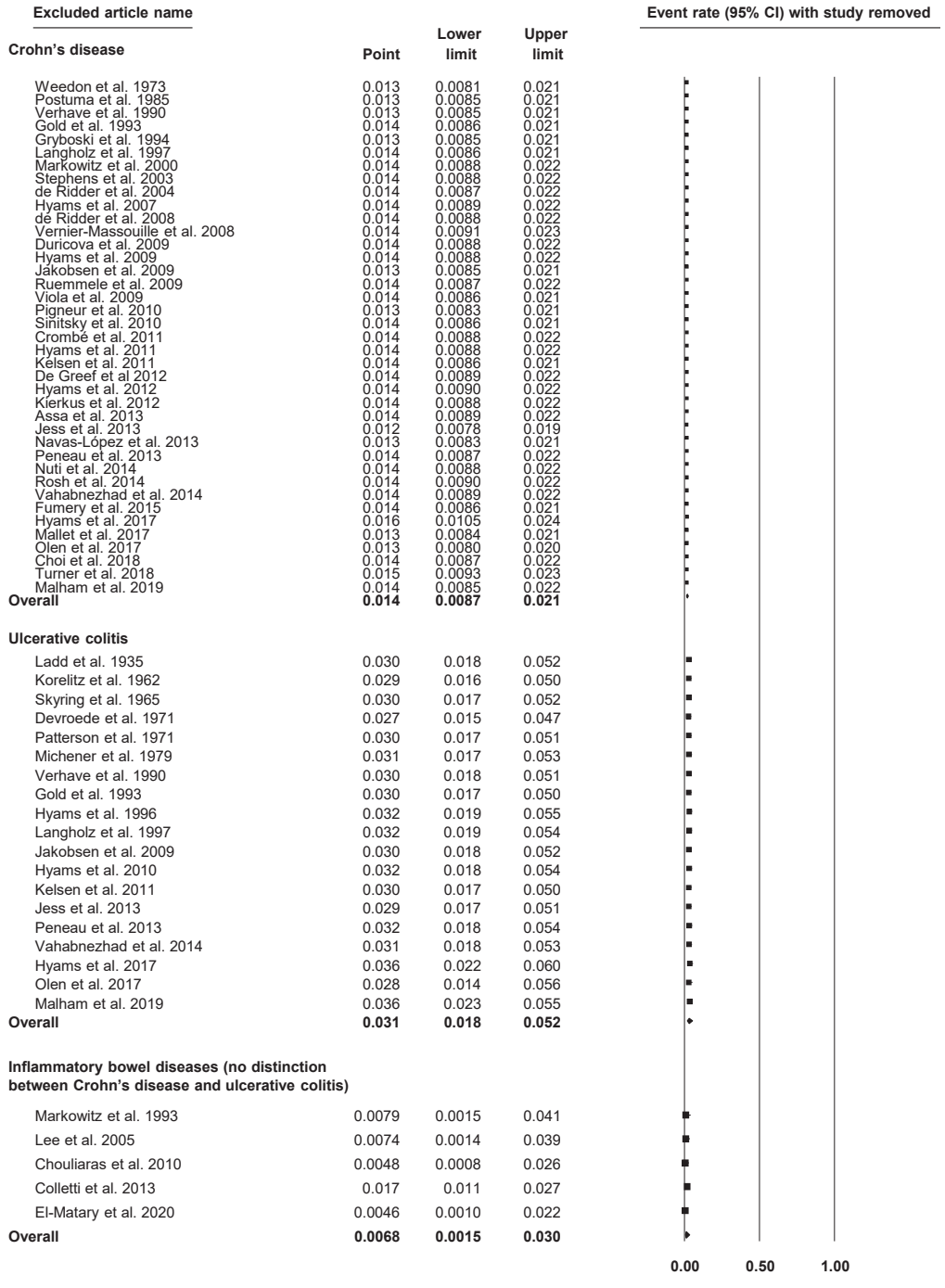


Figure 12. (continued)

C

Excluded article name	Point	Lower limit	Upper limit
Crohn's disease			
Weedon et al. 1973	0.0070	0.0046	0.011
Postuma et al. 1985	0.0074	0.0048	0.011
Verhave et al. 1990	0.0073	0.0048	0.011
Gold et al. 1993	0.0073	0.0048	0.011
Gillen et al. 1994	0.0067	0.0045	0.010
Gryboski et al. 1994	0.0074	0.0048	0.011
Langholz et al. 1997	0.0074	0.0048	0.011
Markowitz et al. 2000	0.0075	0.0049	0.011
Stephens et al. 2003	0.0075	0.0049	0.012
de Ridder et al. 2004	0.0074	0.0048	0.011
Hyams et al. 2007	0.0076	0.0049	0.012
de Ridder et al. 2008	0.0075	0.0049	0.012
Vernier-Massouille et al. 2008	0.0078	0.0051	0.012
Duricova et al. 2009	0.0075	0.0049	0.012
Hyams et al. 2009	0.0076	0.0049	0.012
Jakobsen et al. 2009	0.0072	0.0047	0.011
Ruemmele et al. 2009	0.0074	0.0048	0.011
Viola et al. 2009	0.0074	0.0048	0.011
Pigneur et al. 2010	0.0072	0.0047	0.011
Sinitsky et al. 2010	0.0073	0.0048	0.011
Crombé et al. 2011	0.0076	0.0049	0.012
Hyams et al. 2011	0.0075	0.0049	0.011
Kelsen et al. 2011	0.0073	0.0048	0.011
De Greef et al 2012	0.0076	0.0049	0.012
Hyams et al. 2012	0.0076	0.0050	0.012
Kierkus et al. 2012	0.0075	0.0049	0.012
Assa et al. 2013	0.0076	0.0049	0.012
Navas-López et al. 2013	0.0073	0.0048	0.011
Peneau et al. 2013	0.0078	0.0051	0.012
Nuti et al. 2014	0.0075	0.0049	0.012
Rosh et al. 2014	0.0076	0.0050	0.012
Vahabnezhad et al. 2014	0.0076	0.0050	0.012
Fumery et al. 2015	0.0074	0.0048	0.011
Hyams et al. 2017	0.0080	0.0054	0.012
Mallet et al. 2017	0.0072	0.0047	0.011
Olén et al. 2017	0.0078	0.0050	0.012
Choi et al. 2018	0.0074	0.0048	0.011
Turner et al. 2018	0.0079	0.0052	0.012
Malham et al. 2019	0.0084	0.0056	0.013
Olén et al. 2020	0.0079	0.0051	0.012
Overall	**0.0075**	**0.0049**	**0.011**
Ulcerative colitis			
Ladd et al. 1935	0.019	0.011	0.034
Lagercrantz et al. 1955	0.019	0.011	0.033
Holowach et al. 1956	0.018	0.011	0.032
Michener et al. 1961	0.018	0.011	0.027
Hijmans et al. 1962	0.020	0.012	0.035
Korelitz et al. 1962	0.019	0.012	0.034
Skyring et al. 1965	0.020	0.011	0.034
Patterson et al. 1971	0.020	0.011	0.034
Binder et al. 1973	0.020	0.012	0.035
Michener et al. 1979	0.020	0.011	0.034
Verhave et al. 1990	0.020	0.011	0.034
Ahsgren et al. 1993	0.020	0.012	0.035
Gold et al. 1993	0.019	0.011	0.033
Hyams et al. 1996	0.020	0.012	0.035
Langholz et al. 1997	0.020	0.012	0.035
Falcone et al. 2000	0.020	0.012	0.035
Gower-Rousseau et al. 2009	0.021	0.012	0.035
Jakobsen et al. 2009	0.019	0.011	0.034
Hyams et al. 2010	0.020	0.012	0.035
Kelsen et al. 2011	0.019	0.011	0.033
Peneau et al. 2013	0.021	0.012	0.036
Vahabnezhad et al. 2014	0.020	0.012	0.035
Hyams et al. 2017	0.022	0.013	0.038
Olén et al. 2017	0.020	0.010	0.038
Malham et al. 2019	0.023	0.014	0.038
Olén et al. 2020	0.021	0.012	0.037
Overall	**0.020**	**0.012**	**0.034**
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)			
Markowitz et al. 1993	0.0020	0.00011	0.035
Lee et al. 2005	0.0018	0.00010	0.029
Chouliaras et al. 2010	0.0012	0.00012	0.011
Colletti et al. 2013	0.0059	0.00119	0.029
Overall	**0.0022**	**0.00028**	**0.017**

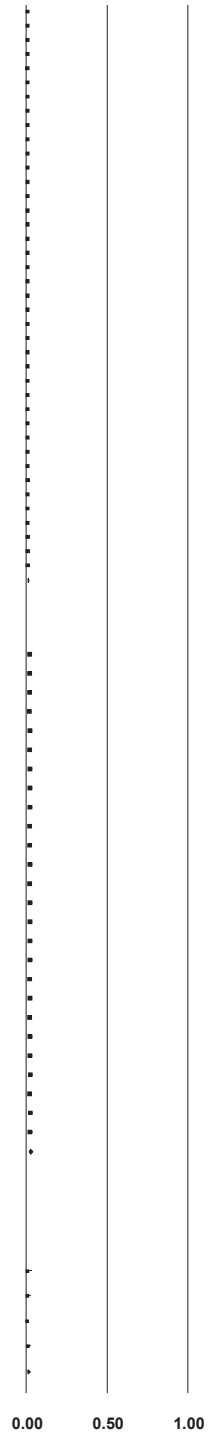


Figure 12. (continued)

D

Excluded article name	Point	Lower limit	Upper limit
Crohn's disease			
Postuma et al. 1985	0.0056	0.0037	0.0083
Verhave et al. 1990	0.0058	0.0038	0.0087
Gold et al. 1993	0.0058	0.0039	0.0088
Gryboski et al. 1994	0.0060	0.0040	0.0091
Langholz et al. 1997	0.0059	0.0039	0.0089
Markowitz et al. 2000	0.0061	0.0040	0.0092
Stephens et al. 2003	0.0061	0.0040	0.0093
de Ridder et al. 2004	0.0060	0.0039	0.0090
Hyams et al. 2007	0.0062	0.0041	0.0094
de Ridder et al. 2008	0.0061	0.0040	0.0093
Vernier-Massouille et al. 2008	0.0063	0.0041	0.0095
Duricova et al. 2009	0.0061	0.0040	0.0093
Hyams et al. 2009	0.0061	0.0040	0.0093
Jakobsen et al. 2009	0.0057	0.0038	0.0085
Ruemmele et al. 2009	0.0060	0.0040	0.0091
Viola et al. 2009	0.0059	0.0039	0.0089
Sinitsky et al. 2010	0.0058	0.0039	0.0088
Crombé et al. 2011	0.0062	0.0041	0.0094
Hyams et al. 2011	0.0061	0.0040	0.0093
Kelsen et al. 2011	0.0059	0.0039	0.0089
Ashworth et al. 2012	0.0064	0.0042	0.0097
De Greef et al 2012	0.0062	0.0041	0.0094
Hyams et al. 2012	0.0062	0.0041	0.0095
Kierkus et al. 2012	0.0061	0.0040	0.0093
Assa et al. 2013	0.0062	0.0041	0.0094
Navas-López et al. 2013	0.0051	0.0035	0.0075
Peneau et al. 2013	0.0064	0.0042	0.0097
Nuti et al. 2014	0.0061	0.0040	0.0093
Rosh et al. 2014	0.0062	0.0041	0.0095
Vahabnezhad et al. 2014	0.0061	0.0040	0.0094
Fumery et al. 2015	0.0060	0.0039	0.0090
Hyams et al. 2017	0.0066	0.0044	0.0099
Mallet et al. 2017	0.0055	0.0037	0.0081
Olen et al. 2017	0.0068	0.0043	0.011
Choi et al. 2018	0.0060	0.0040	0.0091
Turner et al. 2018	0.0063	0.0042	0.0094
Malham et al. 2019	0.0067	0.0044	0.0102
Overall	**0.0061**	**0.0040**	**0.0091**
Ulcerative colitis			
Ladd et al. 1935	0.0043	0.0024	0.0075
Korelitz et al. 1962	0.0047	0.0026	0.0084
Skyring et al. 1965	0.0046	0.0025	0.0082
Patterson et al. 1971	0.0044	0.0025	0.0078
Michener et al. 1979	0.0048	0.0026	0.0087
Verhave et al. 1990	0.0039	0.0023	0.0066
Gold et al. 1993	0.0036	0.0022	0.0058
Hyams et al. 1996	0.0047	0.0026	0.0085
Langholz et al. 1997	0.0046	0.0025	0.0082
Jakobsen et al. 2009	0.0045	0.0025	0.0080
Hyams et al. 2010	0.0045	0.0025	0.0079
Kelsen et al. 2011	0.0036	0.0022	0.0058
Ashworth et al. 2012	0.0049	0.0027	0.0089
Peneau et al. 2013	0.0047	0.0026	0.0084
Vahabnezhad et al. 2014	0.0043	0.0024	0.0076
Hyams et al. 2017	0.0051	0.0028	0.0093
Olen et al. 2017	0.0055	0.0028	0.011
Malham et al. 2019	0.0054	0.0030	0.0098
Overall	**0.0045**	**0.0026**	**0.0079**
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)			
Markowitz et al. 1993	0.0046	0.00041	0.050
Lee et al. 2005	0.0041	0.00038	0.044
Chouliaras et al. 2010	0.0012	0.00050	0.0029
Colletti et al. 2013	0.010	0.0021	0.046
Overall	**0.0041**	**0.00063**	**0.026**

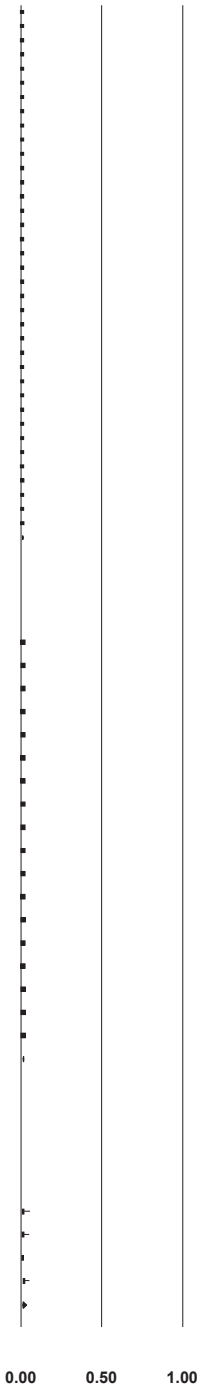


Figure 12. (continued)

E

Excluded article name	Point	Lower limit	Upper limit
Crohn's disease			
Verhave et al. 1990	0.0058	0.0035	0.010
Gold et al. 1993	0.0059	0.0035	0.010
Gryboski et al. 1994	0.0061	0.0036	0.010
Langholz et al. 1997	0.0060	0.0036	0.010
Markowitz et al. 2000	0.0061	0.0037	0.010
Stephens et al. 2003	0.0062	0.0037	0.010
de Ridder et al. 2004	0.0060	0.0036	0.010
Hyams et al. 2007	0.0063	0.0037	0.010
de Ridder et al. 2008	0.0062	0.0037	0.010
Vernier-Massouille et al. 2008	0.0064	0.0039	0.011
Duricova et al. 2009	0.0062	0.0037	0.010
Hyams et al. 2009	0.0061	0.0037	0.010
Jakobsen et al. 2009	0.0057	0.0035	0.0090
Ruemmele et al. 2009	0.0061	0.0036	0.010
Viola et al. 2009	0.0060	0.0036	0.010
Sinitsky et al. 2010	0.0059	0.0035	0.010
Crombé et al. 2011	0.0063	0.0037	0.010
Hyams et al. 2011	0.0061	0.0037	0.010
Kelsen et al. 2011	0.0059	0.0036	0.010
Ashworth et al. 2012	0.0065	0.0039	0.011
De Greef et al 2012	0.0062	0.0037	0.010
Hyams et al. 2012	0.0063	0.0038	0.011
Kierkus et al. 2012	0.0062	0.0037	0.010
Assa et al. 2013	0.0062	0.0037	0.010
Navas-López et al. 2013	0.0059	0.0035	0.010
Peneau et al. 2013	0.0064	0.0039	0.011
Nuti et al. 2014	0.0062	0.0037	0.010
Rosh et al. 2014	0.0063	0.0038	0.011
Fumery et al. 2015	0.0060	0.0036	0.010
Hyams et al. 2017	0.0063	0.0040	0.010
Mallet et al. 2017	0.0056	0.0034	0.0090
Choi et al. 2018	0.0060	0.0036	0.010
Fang et al. 2018	0.0061	0.0036	0.010
Turner et al. 2018	0.0065	0.0039	0.011
Malham et al. 2019	0.0069	0.0043	0.011
Overall	**0.0061**	**0.0037**	**0.010**
Ulcerative colitis			
Ladd et al. 1935	0.0071	0.0028	0.018
Korelitz et al. 1962	0.0078	0.0031	0.020
Skyring et al. 1965	0.0076	0.0030	0.019
Patterson et al. 1971	0.0073	0.0029	0.018
Verhave et al. 1990	0.0066	0.0027	0.016
Gold et al. 1993	0.0063	0.0026	0.015
Hyams et al. 1996	0.0079	0.0031	0.020
Langholz et al. 1997	0.0076	0.0030	0.019
Jakobsen et al. 2009	0.0075	0.0030	0.019
Hyams et al. 2010	0.0074	0.0029	0.019
Kelsen et al. 2011	0.0063	0.0026	0.015
Ashworth et al. 2012	0.0084	0.0033	0.021
Peneau et al. 2013	0.0079	0.0031	0.020
Vahabnezhad et al. 2014	0.0072	0.0029	0.018
Hyams et al. 2017	0.0087	0.0036	0.021
Fang et al. 2018	0.0063	0.0026	0.015
Malham et al. 2019	0.0092	0.0042	0.020
Overall	**0.0074**	**0.0031**	**0.018**
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)			
Markowitz et al. 1993	0.0022	0.00015	0.030
Lee et al. 2005	0.0019	0.00014	0.024
Chouliaras et al. 2010	0.0012	0.00016	0.008
Colletti et al. 2013	0.0059	0.0012	0.029
Overall	**0.0022**	**0.00031**	**0.015**

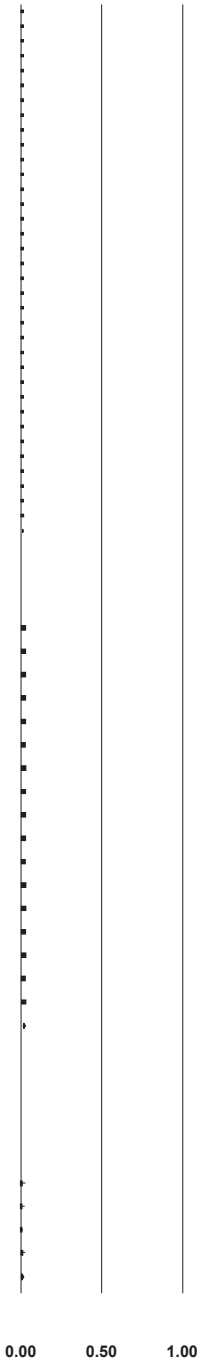


Figure 12. (continued)

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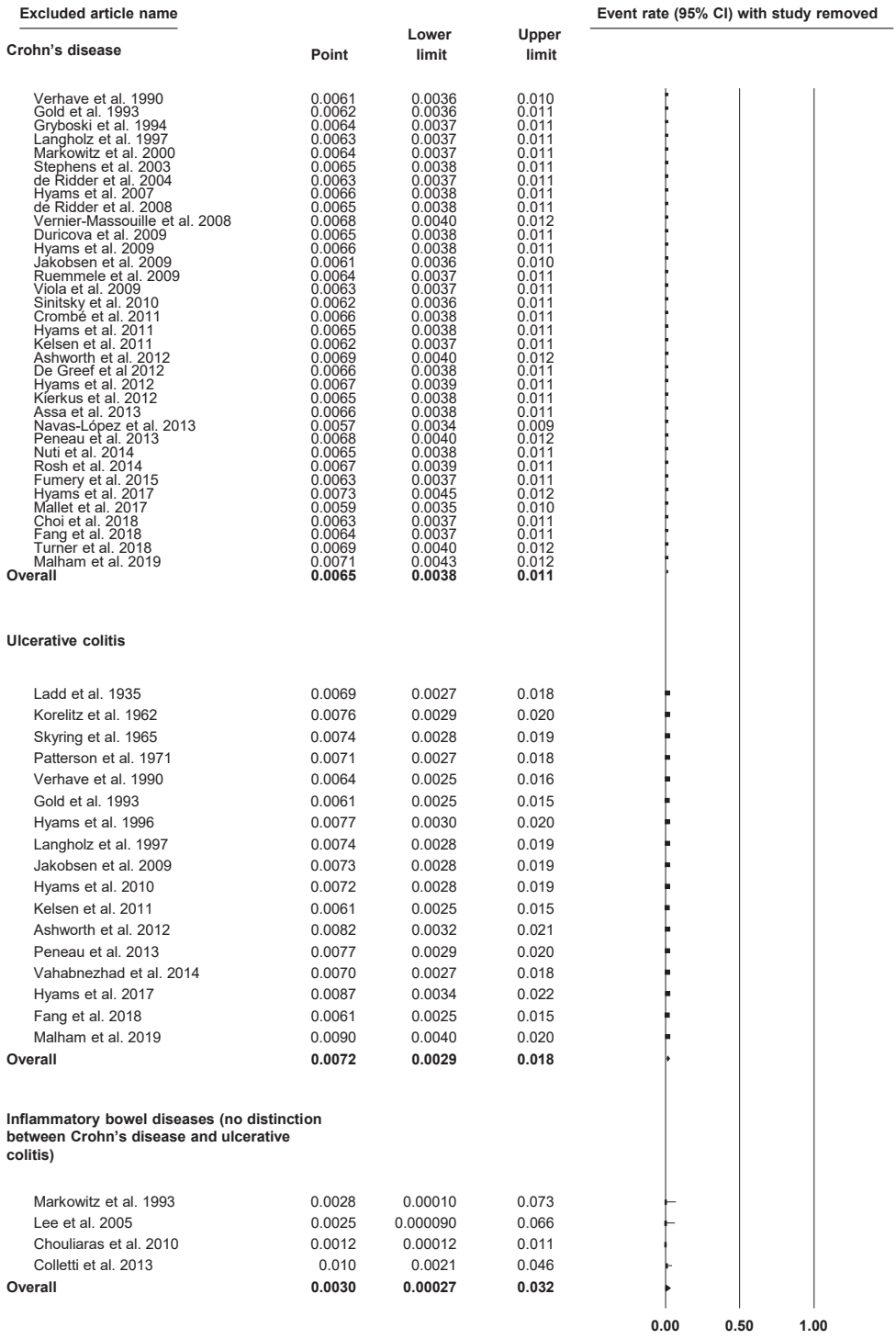

Figure 12. (continued)

G

Excluded article name	Point	Lower limit	Upper limit
Crohn's disease			
Verhave et al. 1990	0.0060	0.0036	0.010
Gold et al. 1993	0.0061	0.0037	0.010
Gryboski et al. 1994	0.0063	0.0038	0.011
Langholz et al. 1997	0.0062	0.0037	0.010
Markowitz et al. 2000	0.0064	0.0038	0.011
Stephens et al. 2003	0.0065	0.0039	0.011
de Ridder et al. 2004	0.0063	0.0037	0.010
Hyams et al. 2007	0.0065	0.0039	0.011
de Ridder et al. 2008	0.0064	0.0038	0.011
Vernier-Massouille et al. 2008	0.0067	0.0040	0.011
Duricova et al. 2009	0.0065	0.0039	0.011
Hyams et al. 2009	0.0066	0.0039	0.011
Jakobsen et al. 2009	0.0059	0.0036	0.010
Ruemmele et al. 2009	0.0063	0.0038	0.011
Viola et al. 2009	0.0062	0.0037	0.010
Sinitsky et al. 2010	0.0061	0.0037	0.010
Crombé et al. 2011	0.0066	0.0039	0.011
Hyams et al. 2011	0.0064	0.0038	0.011
Kelsen et al. 2011	0.0062	0.0037	0.010
Ashworth et al. 2012	0.0067	0.0041	0.011
De Greef et al 2012	0.0065	0.0039	0.011
Hyams et al. 2012	0.0066	0.0040	0.011
Kierkus et al. 2012	0.0064	0.0038	0.011
Assa et al. 2013	0.0065	0.0039	0.011
Navas-López et al. 2013	0.0061	0.0037	0.010
Peneau et al. 2013	0.0068	0.0041	0.011
Nuti et al. 2014	0.0065	0.0039	0.011
Rosh et al. 2014	0.0066	0.0040	0.011
Fumery et al. 2015	0.0062	0.0037	0.010
Hyams et al. 2017	0.0079	0.0049	0.013
Mallet et al. 2017	0.0057	0.0035	0.0093
Choi et al. 2018	0.0063	0.0038	0.011
Turner et al. 2018	0.0067	0.0041	0.011
Overall	**0.0064**	**0.0039**	**0.011**
Ulcerative colitis			
Ladd et al. 1935	0.0072	0.0031	0.017
Korelitz et al. 1962	0.0081	0.0035	0.019
Skyring et al. 1965	0.0078	0.0033	0.018
Patterson et al. 1971	0.0075	0.0032	0.017
Verhave et al. 1990	0.0067	0.0030	0.015
Gold et al. 1993	0.0062	0.0029	0.013
Hyams et al. 1996	0.0082	0.0035	0.019
Langholz et al. 1997	0.0078	0.0033	0.018
Jakobsen et al. 2009	0.0077	0.0033	0.018
Hyams et al. 2010	0.0076	0.0032	0.018
Kelsen et al. 2011	0.0062	0.0029	0.013
Ashworth et al. 2012	0.0087	0.0039	0.019
Peneau et al. 2013	0.0082	0.0035	0.019
Vahabnezhad et al. 2014	0.0073	0.0031	0.017
Hyams et al. 2017	0.010	0.0048	0.021
Overall	**0.0076**	**0.0034**	**0.017**
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)			
Markowitz et al. 1993	0.0022	0.00015	0.030
Lee et al. 2005	0.0019	0.00014	0.024
Chouliaras et al. 2010	0.0012	0.00016	0.0085
Colletti et al. 2013	0.0059	0.0012	0.029
Overall	**0.0022**	**0.00031**	**0.015**

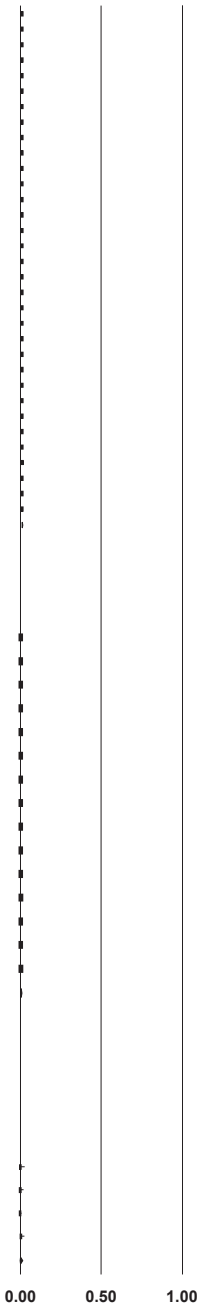

Figure 12. (Continued)

Table I. PubMed search strategy

PubMed search strategy		Number of studies
#1	pediatric* [MeSH Terms] OR childhood [Text Word]	332 986
#2	"inflammatory bowel diseases" [MeSH Terms] OR "Crohn's disease" [Text Word] OR "ulcerative colitis" [Text Word]	95 536
#3	cancer* [Text Word] OR malignancy* [Text Word] OR "colorectal cancer*" [Text Word] OR "hematologic cancer*" [Text Word] OR "Hodgkin's lymphoma" [Text Word] OR "non Hodgkin's lymphoma" [Text Word] OR lymphoma [Text Word] OR leukemia [Text Word]	2 260 522
#4	#1 OR #2 AND #3	39 169

Table II. Risk of bias in RCTs of pediatric IBDs reporting the risk of cancers

Authors	Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hyams et al[11]	2007	?	-	-	-	-	-	-
Hyams et al[26]	2012	+	-	-	-	-	-	-
Markowitz et al[8]	2000	+	?	?	?	+	-	-
Ruemmele et al[17]	2009	+	-	-	-	+	-	-

A plus sign indicate low risk of bias. A question mark indicates unclear risk of bias. A minus sign indicate high risk of bias. Other bias includes the risk of bias due to conflict of interest (for example, authors employed by, held stock in, or received funds from manufacturer).

Table IV. Summary of findings with quality of the evidence (GRADE)

Bibliographies

Outcomes	No of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)
The risk of overall cancers reported as SIR among patients with pediatric IBD rate ratio	17 450(6 studies)	⊕⊕⊕⊖Moderate* due to large effect	RR 2.39 (2-2.86)
Incidence rates of overall cancers among pediatric IBD.pooled event rate	32 417(52 studies†)	⊕⊖⊖⊖ Very low‡,§,¶ due to risk of bias, inconsistency, publication bias	pooled event rate 0.018 (0.013- 0.025)
Incidence rates of CRC among pediatric IBD.pooled event rate	35 083 (60 studies**)	⊕⊖⊖⊖ Very low††,‡‡,§§ due to risk of bias, inconsistency, publication bias	pooled event rate 0.010 (0.0074- 0.014)
Incidence rates of hematologic cancers among pediatric IBDpooled event rate	31 477 (48 studies¶¶)	⊕⊖⊖⊖ Very low††,***,††† due to risk of bias, inconsistency, publication bias	pooled event rate 0.0054 (0.0039-0.0075)
Incidence rates of Hodgkin lymphoma among pediatric IBDpooled event rate	22 581 (44 studies‡‡‡)	⊕⊖⊖⊖ Very low‡,††† due to risk of bias, publication bias	pooled event rate 0.0061 (0.004- 0.093)
Incidence rates of non-Hodgkin lymphoma among pediatric IBDpooled event rate	22581 (44 studies‡‡‡)	⊕⊖⊖⊖ Very low‡,§§§,¶¶¶ due to risk of bias, inconsistency, publication bias	pooled event rate 0.0065 (0.0041-0.01)
Incidence rates of leukemia among pediatric IBDpooled event rate	15876 (43 studies‡‡‡)	⊕⊖⊖⊖ Very low‡,††† due to risk of bias, publication bias	pooled event rate 0.0056 (0.0028-0.011)

RR, risk ratio.
*The pooled SIR is 2.39.
†Nine prospective and 44 retrospective studies (1 study included both study designs) were included. Four RCTs were counted as prospective studies.
‡There were only 8 high quality papers included in this analysis.
§The heterogeneity was high: I^2 = 89.10%.
¶There were small-study effects or publication biases as assessed by the Begg and Egger tests (P = .00072, .00060, respectively).
**Nine prospective and 52 retrospective studies (1 study included both study designs) were included. Four RCTs were counted as prospective studies.
††There were only 10 high quality papers included in this analysis.
‡‡The heterogeneity was high: I^2 = 81.30%.
§§There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .013, respectively).
¶¶Nine prospective and 40 retrospective studies (1 study included both study designs) were included. Four RCTs were counted as prospective studies.
***The heterogeneity was moderate: I^2 = 34.25%.
†††There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, <.0001, respectively).
‡‡‡Nine prospective and 36 retrospective studies (1 study included both study designs) were included. Four RCTs were counted as prospective studies.
§§§The heterogeneity was moderate: I^2 = 41.90%.
¶¶¶There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, respectively).

Table V. Results of meta-regression analyses of steroid as the concomitant medication and the risk of cancers among patients with IBDs

	Subgroups	Numbers of included studies	95% CI of the regression coefficient	*P* value (for regression coefficient)	Residual error sums of squares (*Qe*)	*P* value (for *Qe*)
Overall cancers	CD	21	−0.0095 to 0.019	.26	12.05	.80
	UC	6	−0.037 to 0.018	.24	8.47	.13
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	27	−0.018 to 0.0048	.13	30.98	.15
CRC	CD	21	−0.011 to 0.026	.79	8.90	.94
	UC	7	−0.040 to 0.014	.17	4.77	.69
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	28	−0.020 to 0.0078	.19	20.17	.78
Hematologic cancers	CD	20	−0.029 to 0.014	.24	12.01	.68
	UC	6	−0.024 to 0.067	.82	0.53	.99
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	26	−0.022 to 0.017	.41	14.17	.90
Hodgkin lymphoma	CD	18	−0.024 to 0.023	.48	7.66	.91
	UC	6	−0.024 to 0.067	.82	0.53	.99
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	24	−0.017 to 0.026	.66	8.93	1.00
Non-Hodgkin lymphoma	CD	18	−0.031 to 0.013	.22	10.73	.71
	UC	6	−0.024 to 0.067	.82	0.53	.99
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	24	−0.023 to 0.017	.39	12.81	.92
Leukemia	CD	19	−0.023 to 0.024	.52	7.54	.91
	UC	6	−0.024 to 0.067	.82	0.53	.99
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	25	−0.016 to 0.026	.69	8.71	.99

NA, not available.

Table VI. Results of meta-regression analyses of immunomodulator (thiopurine) as the concomitant medication and the risk of cancers among patients with IBDs

	Subgroups	Numbers of included studies	95% CI of the regression coefficient	*P* value (for regression coefficient)	Residual error sums of squares (*Qe*)	*P* value (for *Qe*)
Overall cancers	CD	27	−0.014 to 0.026	71	13.83	.84
	UC	8	−0.011 to 0.034	.84	2.13	.71
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	35	−0.011 to 0.013	.58	18.38	.86
CRC	CD	27	−0.018 to 0.027	.66	10.35	.96
	UC	10	−0.010 to 0.034	.15	3.27	.77
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	37	−0.013 to 0.011	.46	16.66	.96
Hematologic cancers	CD	27	−0.015 to 0.026	.70	15.80	.73
	UC	9	−0.0014 to 0.055	.31	4.10	.54
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	36	−0.0046 to 0.026	.083	21.74	.75
Hodgkin lymphoma	CD	25	−0.022 to 0.027	.57	12.54	.86
	UC	8	−0.0014 to 0.055	.31	4.10	.54
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	33	−0.0068 to 0.027	.12	18.81	.84
Non-Hodgkin lymphoma	CD	25	−0.024 to 0.027	.54	15.13	.65
	UC	8	−0.0092 to 0.061	.075	4.09	.39
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	33	−0.010 to 0.025	.79	20.66	.66
Leukemia	CD	25	−0.023 to 0.026	.54	12.84	.85
	UC	8	−0.0013 to 0.055	.31	4.11	.53
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	33	−0.0079 to 0.026	.15	19.52	.81

Table VII. Results of meta-regression analyses of antitumor necrosis factor agents as the concomitant medication and the risk of cancers among patients with IBDs

	Subgroups	Numbers of included studies	95% CI of the regression coefficient	*P* value (for regression coefficient)	Residual error sums of squares (*Qe*)	*P* value (for *Qe*)
Overall cancers	CD	28	−0.024 to 0.0022	.0052	12.46	.93
	UC	6	−0.025 to 0.018	.38	1.56	.46
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	35	−0.021 to 0.00026	.22	15.69	.94
CRC	CD	28	−0.022 to 0.0076	.17	9.31	.99
	UC	6	−0.019 to 0.021	.54	2.76	.43
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	35	−0.019 to 0.0026	.069	14.25	.98
Hematologic cancers	CD	28	−0.0093 to 0.029	.16	14.32	.86
	UC	7	−0.0033 to 0.046	.45	2.58	.46
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	36	−0.0027 to 0.025	.057	18.46	.89
Hodgkin lymphoma	CD	26	−0.014 to 0.028	.73	11.28	.94
	UC	6	−0.0033 to 0.046	.45	2.58	.46
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	33	−0.0049 to 0.024	.098	15.64	.94
Non-Hodgkin lymphoma	CD	26	−0.0095 to 0.029	.84	14.54	.80
	UC	6	−0.0053 to 0.049	.058	3.06	.38
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	33	−0.0035 to 0.026	.067	19.15	.83
Leukemia	CD	26	−0.015 to 0.027	.72	11.51	.93
	UC	6	−0.0053 to 0.049	.058	3.06	.38
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	33	−0.0064 to 0.025	.12	16.43	.93