

REVIEW ARTICLE

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Co-occurrence of Asthma and the Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis

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Abstract

Background: Inflammatory bowel diseases (IBD) and asthma share genetic and environmental risk factors. Consequently, several observational studies have explored an association between IBD and asthma. We systematically reviewed and summarized the literature on the co-occurrence of asthma and IBD.

Methods: MEDLINE and EMBASE (to April 2017) were searched to identify observational studies on the association between asthma and IBD. Relative risks (RR) were pooled using random effects models. Heterogeneity was assessed using the I^2 and Cochran Q statistics. Meta-regression based on study design, source of patients (population-based vs. tertiary-care center) and study location was conducted to explain between-study heterogeneity.

Results: Eighteen studies were identified (15 Crohn's disease, 15 ulcerative colitis (UC)). Asthma was associated with both Crohn's disease (pooled RR 1.30, 95% confidence interval (CI) 1.16–1.47, $I^2 = 88\%$) and UC (RR 1.34, 95% CI 1.24–1.44, $I^2 = 93\%$). The study design and source of patients and study location explained between-study heterogeneity in Crohn's disease, but not UC.

Conclusion: Asthma is associated with both Crohn's disease and UC. Additional research is needed to determine if one disease influences the risk of developing the other or if the frequent co-occurrence of these diseases result from shared genetic, environmental, and microbial risk factors.

Background

Inflammatory bowel disease (IBD) and asthma are both immune-mediated diseases that may be rooted in common pathology, as well as shared genetic and environmental risk factors. Aberrant epithelial barrier function in the lung and gastrointestinal tract, as well as abnormal immune responses to environmental factors and pathogens characterize asthma and IBD^{1–7}. The 'hygiene

hypothesis' has been proposed for both IBD and asthma, and postulates that children growing up in relatively sterile environments are more likely to develop chronic immune-mediated diseases later in life. Moreover, disruption of early life intestinal microbiota may exacerbate risk of disease development. For example, asthma and IBD are more common among individuals exposed to antibiotics early in life, while breastfeeding decreases the risk of both diseases^{8–10}. Lack of exposure to enteric pathogens early in life may increase the risk of developing immune-mediated diseases, including both asthma and IBD^{11,12}. IBD and asthma also share susceptibility genes, including SMAD3 and IL-23R^{13–15}. Both IBD and asthma have become increasingly common in the Western world

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during the 20th century and these trends are now being echoed in developing countries^{16–20}.

A previous systematic review and meta-analysis found that individuals with asthma were more likely to have a co-occurring gastrointestinal or urinary condition, but did not specifically evaluate the association between asthma and IBD²¹. There is growing epidemiologic evidence that asthma and IBD frequently co-occur^{22–29} and a family history of one disease may influence the risk of developing the other^{30,31}. However, studies evaluating the association between these two diseases have used heterogeneous study designs. Specifically, studies have differed in terms of (1) the relative timing of the two diagnoses and (2) the age of participants included in the study. These two factors have resulted in differing conclusions about the co-occurrence of asthma and IBD.

We conducted a systematic review and meta-analysis to summarize and quantify the association between IBD and asthma, as well as evaluating the impact of study and patient characteristics on the association between these two diseases.

Methods

This systematic review is based on a previously registered protocol³² and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines³³.

Study identification and selection

We searched MEDLINE, including articles available as online only ahead of print, (1946–1 April 2017) and EMBASE + EMBASE Classic (1947–1 April 2017) for observational epidemiologic studies evaluating the association between asthma and IBD (Crohn's disease, ulcerative colitis (UC), and IBD-type unclassified (IBD-U)). Search terms for IBD and asthma were grouped using the Boolean operator "AND." The complete search strategy is outlined in Supplementary Table 1. In addition, we hand-searched: (1) references of included studies and relevant review articles; (2) conference abstracts for major gastroenterology meetings (Digestive Diseases Week, American College of Gastroenterology, and United European Gastroenterology Week) and major thoracic meetings (American Thoracic Society Meeting, European Respiratory Society, and American Academy of Chest Physicians Conference) from 2013 to 2017. The review of abstracts and articles identified for full-text review was conducted via crowd sourcing using CrowdScreen SR³⁴. Crowdsourcing has previously been shown to increase the efficiency of the systematic review process, while maintaining high accuracy during the review process^{34,35}. Prior to screening, each member of the CrowdScreen SR Review team was asked to review a test set of 15 abstracts identified by the principal investigator (MEK). The test set

included a mix of abstracts that should be included in full-text review and abstracts that should be excluded from further review. Feedback was provided on the accuracy of their initial reviews to enhance performance. Members of the review team were medical students or undergraduate/graduate students in health sciences and all completed the initial test set with a high degree of accuracy. Each abstract and full-text was reviewed independently by at least two members of the review team. Discrepancies for both the abstract and full-text review stages were resolved by MEK.

Studies eligible for inclusion were observational epidemiologic studies (case-control, cohort, or cross-sectional studies) that either compared the rate of asthma in patients with and without IBD or the rate of IBD in patients with and without asthma. No restrictions were placed on date of publication, language, or region of study. Studies reporting on any subtype of IBD (Crohn's disease, UC, or IBD-U) were included. Case reports and case series were excluded, as were studies reporting on the association between pulmonary function tests or other respiratory illnesses with IBD. If multiple studies reported on the same cohort of patients, the study with the most complete cohort of patients was selected for inclusion in the study.

Data extraction and risk of bias

The following information was extracted from included studies independently by two investigators (MEK, KB) using a piloted data extraction form in REDCap electronic data capture tools hosted at the Children's Hospital of Eastern Ontario:³⁶ study characteristics, including the country and years in which the study was conducted; study design; method of identifying and recruiting individuals to participate in the study; the association between asthma and IBD (crude and adjusted, where possible, and the confounders adjusted for in the model); definitions used to identify and/or confirm cases of asthma and IBD; the age of study participants; the timing of exposure relative to the study outcome; and characteristics of individuals included in each study. Discrepancies were resolved by EIB. The risk of bias in individual studies was determined using the Newcastle-Ottawa Scale³⁷.

Study design and outcomes

The primary outcomes of our meta-analysis were the association between asthma and either Crohn's disease, UC, or IBD-U. All analyses were conducted separately for Crohn's disease, UC, and IBD-U. For the primary analysis, no restriction was placed on the timing of one diagnosis relative to the other.

Sensitivity analyses evaluating the temporal associations between asthma and IBD were conducted. Specifically, we conducted two sensitivity analyses in which included studies were limited to (1) those in which the diagnosis of

asthma preceded the diagnosis with IBD; and (2) those in which the diagnosis of IBD preceded the diagnosis with asthma. Subgroup analyses were conducted based on the age of diagnosis of IBD, defined according to the Montreal classification (pediatric-onset: ≤ 16 , young adult-onset: 17–40, and older adult-onset: >40)³⁸ and/or asthma.

Statistical analysis

Analyses were conducted separately for the association between asthma and (1) Crohn's disease; (2) UC; and (3) IBD-U. Relative risks (RR) and their 95% confidence intervals (CI) were pooled to estimate the association between asthma and IBD. Random effects models were used to account for expected heterogeneity across study designs. The most adjusted estimate was used. Odds ratios were assumed to approximate the RR due to the rare prevalence of IBD and asthma. We performed a sensitivity analysis separating case-control from cohort studies.

Between-study heterogeneity was assessed using the I^2 statistic and the Cochran Q statistic with $p < 0.1$ being considered statistically significant. Meta-regression was conducted to explore sources of study heterogeneity based on the source of patients involved in the study (population-based vs. recruited from tertiary-care center) and the country in which the study was conducted.

All statistical analyses were conducted using the meta and metafor packages in R Software version 3.4.2^{39–41}.

Results

Description of included studies

There were 3975 citations identified from the search of MEDLINE and EMBASE. After removing duplicates, 3022 references remained. Of the 97 studies identified for full-text review, 18 of these were included in the meta-analysis (Fig. 1). One additional study was identified after reviewing references of included studies. Fifteen studies reported the association between asthma and Crohn's disease^{22–24,26–29,42–49}. Sixteen studies reported the association between asthma and UC^{22–24,26–30,42–44,48–52}. One study reported on the association between asthma and IBD-U²⁷. Characteristics of included studies are described in Table 1.

Risk of bias of included studies

The risk of bias among included case-control and cohort studies is summarized in Supplementary Tables 3 and 4, respectively. The majority of studies were conducted using population-based health administrative data or tertiary-care studies enrolling consecutive patients. Bias may have been introduced to case-control studies based on the controls included in the studies: one study included hospital staff⁵⁰, one included partners of cases⁵¹, four included hospitalized patients or patients visiting a

clinic for reasons not related to IBD or asthma^{30,43,45,52}, and one included a mix of partners of cases and non-IBD patients⁴⁸. Nine case-control studies did not explicitly report that controls did not have IBD^{24,30,43,45–48,52,53}. Two of the four cohort studies included compared the frequency with which asthma and IBD co-occurred to previously published estimates of the rate of either asthma or IBD in the general population^{42,49}.

Association between asthma and IBD

Asthma and Crohn's disease were associated (pooled RR 1.31, 95% CI 1.16–1.47, 15 studies, 824,173 participants; heterogeneity: $I^2 = 88\%$, $p < 0.0001$; Fig. 2). There was a significant association between UC and asthma (pooled RR 1.30, 95% CI 1.21–1.40, 16 studies, 819,714 participants; heterogeneity: $I^2 = 93\%$, $p < 0.0001$; Fig. 3). Asthma and IBD-U were associated in a single study (OR 1.9, 95% CI 1.6–2.4, 51,459 participants)²⁷.

Explaining heterogeneity: study design

The association between asthma and IBD was consistently elevated in both case-control and cohort studies (Table 2). Although 22% of heterogeneity was accounted for by study design in studies evaluating the association between asthma and UC, significant heterogeneity persisted (residual heterogeneity: $I^2 = 91\%$, $p < 0.0001$). Separately analyzing case-control and cohort studies in Crohn's disease did not account for any heterogeneity (residual heterogeneity: $I^2 = 88\%$, $p < 0.0001$).

Explaining heterogeneity: data source

Among studies evaluating the association between asthma and Crohn's disease, there was a significantly elevated association in population-based studies (pooled RR 1.43, 95% CI 1.32–1.56, 10 studies, 822,775 participants; heterogeneity: $I^2 = 69\%$) but a protective association in studies recruiting patients from tertiary-care centers (pooled RR 0.89, 95% CI 0.83–0.97, 5 studies, 1398 participants; heterogeneity: $I^2 = 0\%$). Meta-regression based on source of patients (population-based or tertiary-care) accounted for 77% of heterogeneity among studies evaluating the association between asthma and Crohn's disease. However, significant heterogeneity between studies remained (residual heterogeneity: $I^2 = 59\%$, $p < 0.0001$). No heterogeneity could be accounted for in studies evaluating the association between asthma and ulcerative colitis (residual heterogeneity: $I^2 = 94\%$, $p < 0.0001$). Results of meta-regression and subgroup analyses based on source of patients are summarized in Table 3.

Explaining heterogeneity: location of study

Differences across countries were observed in the association between asthma and Crohn's disease ($p < 0.0001$). Between country differences accounted for 92%

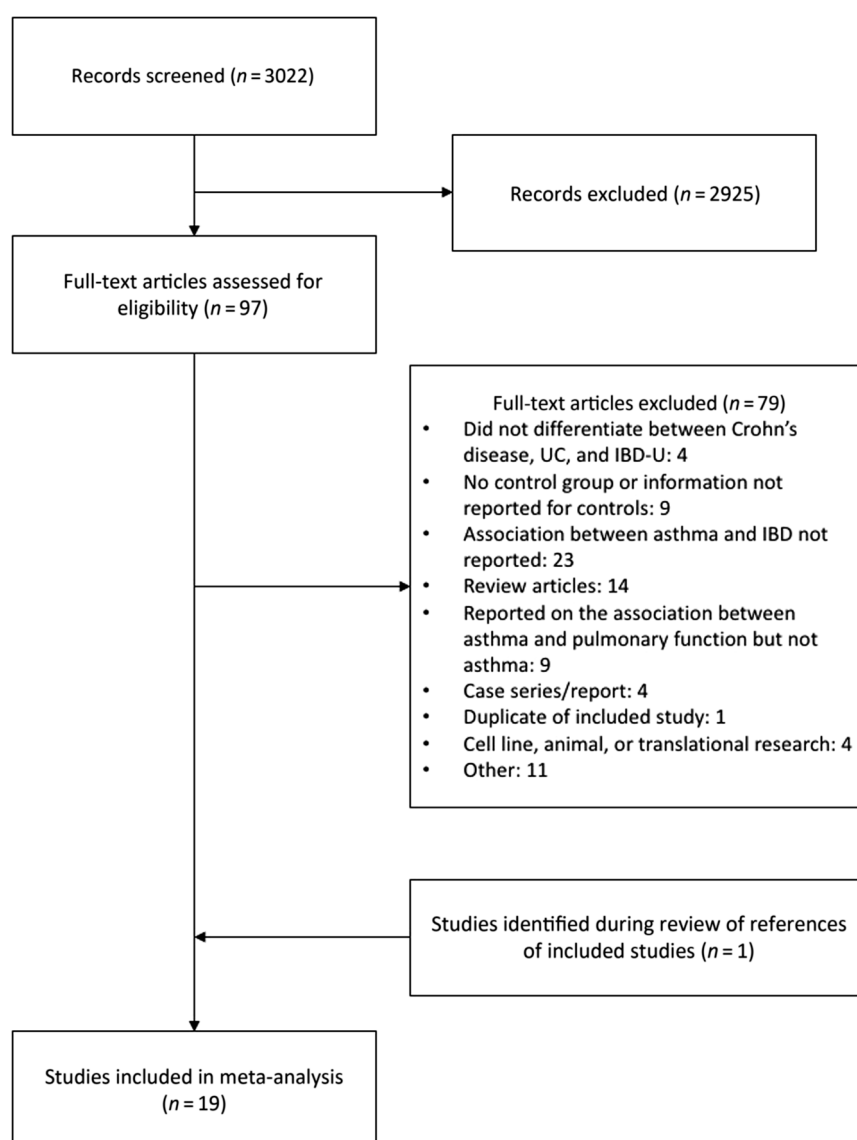


Fig. 1 PRISMA flow diagram

of the heterogeneity across case-control studies (residual heterogeneity: $I^2 = 33\%$, $p = 0.16$) evaluating the association between asthma and Crohn's disease (Table 4).

Similarly, differences between countries were noted for the association between asthma and UC ($p < 0.0001$; Table 4). However, no heterogeneity could be accounted for by country (residual heterogeneity: $I^2 = 96\%$; $p < 0.0001$).

Sensitivity analysis: relative timing of diagnoses

When restricting the analysis to studies in which the diagnosis of asthma preceded the diagnosis of Crohn's disease, there was a significant association (pooled RR 1.49, 95% CI 1.27–1.74, 4 studies, 691,525 participants;

heterogeneity: $I^2 = 86\%$, $p < 0.0001$; Supplementary Figure 1). In studies in which the diagnosis of asthma preceded the diagnosis of UC, the two diseases were not significantly associated (pooled RR 1.21, 95% CI 0.98–1.51, 5 studies, 692,228 participants; $I^2 = 97\%$, $p < 0.0001$; Supplementary Figure 2).

Patients previously diagnosed with both Crohn's disease and UC were at an increased risk of new-onset asthma in a single study (Crohn's disease: hazard ratio (HR) 1.50, 95% CI 1.31–1.72; UC: HR 1.46, 95% CI 1.03–2.07)²⁹.

Subgroup analysis: age at IBD diagnosis

The impact of age at IBD diagnosis on the association between asthma and IBD was evaluated in three studies:

Table 1 Characteristics of included studies

Study	Country	Study design	Data source (years of timing of study)	Definition of IBD	Definition of asthma	Relative timing of diagnoses	Type of IBD	Matched variables and covariates	Age of participants	Sample size
Bernstein ²³	Canada	Matched case-control	Provincial health administrative data (1984–2003)	Validated algorithm	≥5 health care contacts for asthma	Asthma diagnosed before or after IBD	CD, UC	Matched on age, sex, and rural/urban residence	Pediatric and adult	IBD: 8072 Controls: 80,489
Boneberger ⁵²	Chile	Case-control	Tertiary-care center (2009–2010)	Routine clinical practice	Not specified	Not specified	UC	Adjusted for age and sex	Range: 6 to 45 years at study entry	IBD: 52 Controls: 174
Brassard ⁴²	Canada	Retrospective cohort	Provincial health administrative data (2001–2006)	Externally validated algorithm	≥3 prescriptions for respiratory medication within 1 year, on at least two separate occasions; the third prescription must have occurred at ≤40 years of age	Asthma diagnosed before IBD	CD, UC	Incidence rates were standardized based on age and sex	≤40 years at asthma diagnosis	Asthma: 136,178 ^a
D'Arienzo ⁵⁰	Italy	Case-control	Tertiary-care center (1998)	Standard diagnostic criteria	Standard diagnostic criteria	Not specified	UC	None	Range: 16 to 69 years	IBD: 50 Controls: 50
D'Arienzo ⁵¹	Italy	Matched case-control	Tertiary-care center (2000)	Standard diagnostic criteria	Standard diagnostic criteria	Not specified	UC	Matched controls were partners of cases	Adult	IBD: 45 Controls: 37
Geary ²⁴	New Zealand	Frequency matched case-control	Canterbury IBD Study (2003–2005)	Standard diagnostic criteria	Not specified	Not specified	CD, UC	Frequency matched based on age (at recruitment) and sex. Adjusts for family history of IBD, smoking status, age, social class at birth, sex, and ethnicity	Adult	IBD: 1291 Controls: 600
Hammer ⁴³	United Kingdom	Matched case-control	Tertiary-care center (1952–1965)	Standard diagnostic criteria	Questionnaire or interview	Not specified	Colonic CD, UC	None	Not specified	IBD: 243 Controls: 319

Table 1 continued

Study	Country	Study design	Data source (years of study)	Definition of IBD	Definition of asthma	Relative timing of diagnoses	Type of IBD	Matched variables and covariates	Age of participants	Sample size
Hemminki ²⁸	Sweden	Prospective cohort	National health administrative data (1964–2007)	Hospitalization with an ICD code for IBD	Hospitalization with an ICD code for asthma	IBD diagnosed after asthma	CD, UC	Standardized incidence rates used expected number of cases based on age, sex, year, region, and socioeconomic status	Children and adults	Asthma: 148,295 ^c
Kappelman ⁴⁴	United States	Matched case-control	PharMetrics Patient-Centric Database (2003–2004)	Validated algorithm	ICD code for asthma	Not specified	CD, UC	Matched on age, sex, health plan type, and geographic region	Children only	IBD: 1242 Controls: 3353
Kuenzig ²²	Canada	Case-control	Population-based health administrative data (1994–2010)	Validated algorithm	Externally validated algorithm	1. Asthma before IBD 2. Asthma diagnosed before or after IBD	CD, UC	Age, sex, rural/urban residence, socioeconomic status	Children and adults	IBD: 5464 Controls: 402,800
Livnat ⁴⁵	Israel	Case-control	Tertiary-care center (2008–2009 ^b)	Standard diagnostic criteria	Self-report	Not specified	CD	None	Children and young adults	IBD: 23 Controls: 24
Myrelid ⁴⁶	Sweden	Matched case-control	Cases: Unclear controls: Southeastern Region Population Registry (2000)	Standard diagnostic criteria	Self-report	Not specified	CD	Age, gender, place of residence, and other atopic manifestations (allergic rhinitis, eczema)	Range: 18 to 50 years	IBD: 275 Controls: 777
Nakamura ³⁰	Japan	Matched case-control	Cases: Patients receiving financial aid from the Japanese government for the treatment of UC (1988–1990) Controls: Patients on the roster of a health check-up program	Diagnosis of UC by treating physician, and confirmation of diagnosis by independent group for approval of financial aid	Self-report questionnaire	Asthma before IBD	UC	Matched on age and sex	Children and adults	IBD: 384 Controls: 384

Table 1 continued

Study	Country	Study design	Data source (years of study)	Definition of IBD	Definition of asthma	Relative timing of diagnoses	Type of IBD	Matched variables and covariates	Age of participants	Sample size
Neilly ⁴⁷	Scotland	Matched case-control	Not specified	Not specified	Previous physician-diagnosed asthma and/or history of persistent or episodic wheeze with breathlessness, responsive to bronchodilator therapy	Not specified	CD	Matched on age, sex, and smoking history	Adults	IBD: 29 Controls: 29
Peng ²⁹	Taiwan	Frequency matched retrospective cohort	National health administrative data (2000–2011)	ICD codes for IBD	ICD code for asthma and treated with inhaled corticosteroids, systemic corticosteroids, or inhaled short-acting β_2 agonists	Asthma diagnosed after IBD	CD, UC	Frequency matched on age, sex, and index year. Adjusted for age, sex, and other comorbidities (rhinitis, chronic sinusitis, atopic dermatitis, and chronic obstructive pulmonary disease)	Adults	IBD: 319 Controls: 807
Pugh ⁴⁸	UK	Matched case-control	Tertiary care center; Ileostomy Association	Standard diagnostic criteria	Self-report	Not specified	CD, UC	Some controls were partners of cases. Others were matched to cases based on age and sex	Not specified	IBD: 500 Controls: 500
Raj ⁴⁹	UK	Cohort	Tertiary-care center (1995–2005)	Standard diagnostic criteria	Consistent clinical picture with objective evidence of variable outflow obstruction and/or airway hyper-responsiveness	IBD preceded the onset of respiratory disease in all cases but 1	CD, UC	None	Mean age: • UC: 61 • CD: 60	Asthma: 893 ^a
Virta ²⁶	Finland	Matched case-control	National health administrative data (1994–2010)	Received special reimbursement for IBD	Received special reimbursement for asthma	Asthma diagnosed before IBD	CD, UC	Matched on date of birth, sex, and place of residence	Pediatric	IBD: 595 Controls: 2380
Weng ²⁷	United States	Matched case-control			Asthma could be diagnosed	Asthma could be diagnosed	CD, UC, IBD-U	Matched on age, sex, and length of	Children and adults	

Table 1 continued

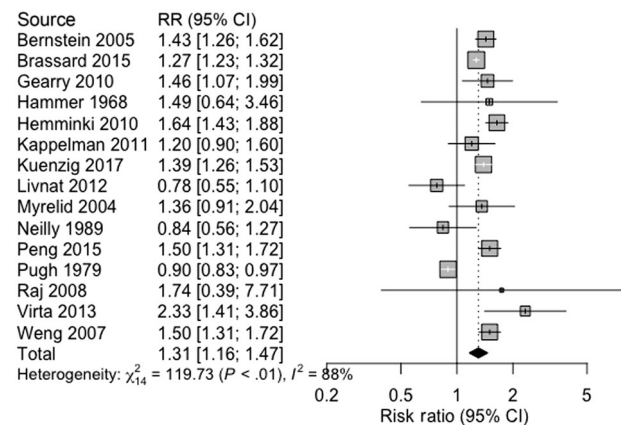
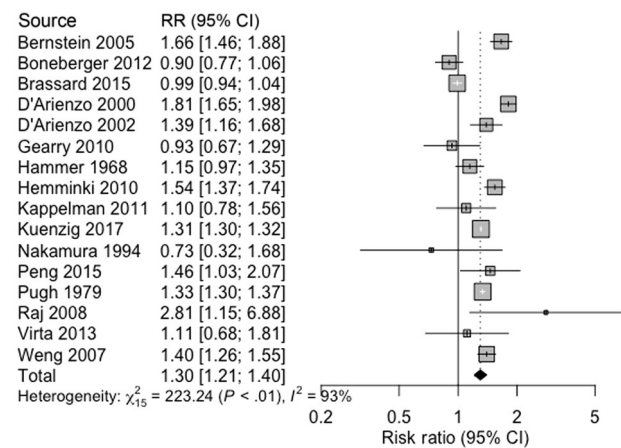
Study	Country	Study design	Data source (years of study)	Definition of IBD	Definition of asthma	Relative timing of IBD diagnoses	Type of IBD	Matched variables and covariates	Age of participants	Sample size
			Kaiser Permanente Medical Care Program (1996–2005)	≥2 inpatient or outpatient ICD codes for IBD	≥2 inpatient or outpatient ICD codes for asthma	either before or after the diagnosis with IBD		enrolment in health maintenance organization. Adjusted for smoking.		IBD: 12,601 Controls: 50,404

CD Crohn's disease, IBD inflammatory bowel disease, IBD-U inflammatory bowel disease type unclassified, ICD International Classification of Diseases, UC ulcerative colitis

^aThe risk of IBD in patients with asthma was compared to the previously reported risk of IBD in the general population

^bYears of study obtained from study protocol on clinicaltrials.gov

^cThe risk of IBD in patients with asthma was compared to the number of cases that would be expected if there was no association between asthma and IBD

**Fig. 2** Association between asthma and Crohn's disease**Fig. 3** Association between asthma and ulcerative colitis

one case-control study limited to the association between asthma and UC (408,264 participants)²², and one cohort study evaluating the association between asthma and both Crohn's disease and UC (136,178 participants)⁴², and one cohort study evaluating the association between asthma and IBD (26,300 participants)²⁹. An additional three studies were limited to pediatric patients and were included in subgroup analyses of pediatric-onset IBD (7554 participants)^{26,44,45}. There was no association between asthma and pediatric-onset Crohn's disease (pooled RR 1.35, 95% CI 0.94–1.93; heterogeneity: $I^2 = 92\%$, Supplementary Figure 3). Adult-onset Crohn's disease was associated with asthma (20–29 years at diagnosis: incident rate ratio (IRR) 1.18, 95% CI 1.10–1.26; 30–39 years: IRR 1.42, 95% CI 1.32–1.53; 40–49 years: IRR 1.31, 95% CI 1.23–1.41). Pooling across age groups in early adulthood (20–29 and 30–39 years), Crohn's disease and asthma were associated in adults diagnosed in young adulthood (pooled RR 1.29,

Table 2 Results of subgroup analyses and meta-regression based on study design

Type of IBD	Study design	RR (95% CI)	Heterogeneity	Number of studies	Number of participants	Subgroup differences	Residual heterogeneity
Crohn's disease	Case-control	1.25 (1.05–1.50)	$I^2 = 89\%$	11	513,008	$p = 0.24$ REF	$I^2 = 69\%$ $R^2 = 0\%$
	Cohort	1.45 (1.23–1.71)	$I^2 = 82\%$	4	311,165	β 1.6 (95% CI –0.14 to 0.46)	$p < 0.0001$
Ulcerative colitis	Case-control	1.33 (1.24–1.42)	$I^2 = 89\%$	12	512,807	$p = 0.78$ REF	$I^2 = 91\%$ $R^2 = 22\%$
	Cohort	1.40 (0.99–1.98)	$I^2 = 94\%$	4	306,907	β –0.046 (95% CI –0.21 to 0.12)	$p < 0.0001$

Table 3 Results of subgroup analyses and meta-regression based on source of study participants

Type of IBD	Data source	RR (95% CI)	Heterogeneity	Number of studies	Number of participants	Subgroup differences	Residual heterogeneity
Crohn's disease	Population-based or health maintenance organization	1.43 (1.32–1.56)	$I^2 = 69\%$	10	822,775	$p < 0.0001$ REF	$I^2 = 59\%$ $R^2 = 77\%$
	Tertiary-care center, not stated, or other	0.89 (0.83–0.97)	$I^2 = 0\%$	5	1398	β –0.48 (95% CI –0.65 to –0.30)	$p = 0.0024$
Ulcerative colitis	Population-based or health maintenance organization	1.29 (1.13–1.46)	$I^2 = 94\%$	9	816,528	$p = 0.94$ REF	$I^2 = 94\%$ $R^2 = 0\%$
	Tertiary-care center, not stated, or other	1.30 (1.08–1.56)	$I^2 = 92\%$	7	3186	β 0.012 (95% CI –0.20 to 0.22)	$p < 0.0001$

95% CI 1.08–1.55; heterogeneity: $I^2 = 92\%$). Meta-regression based on age group did not account for any heterogeneity (residual heterogeneity: $I^2 = 92\%$, $p < 0.0001$).

Asthma and UC were associated in patients diagnosed with UC as young adults (≤ 40 years: pooled RR 1.11, 95% CI 1.04–1.19; $I^2 = 0\%$; Supplementary Figure 4). There was no association between asthma and UC diagnosed during childhood (pooled RR 1.11, 95% CI 0.97–1.28; $I^2 = 0\%$) or after 40 years of age (pooled RR 1.07, 95% CI 0.57–2.00; $I^2 = 98\%$). Among studies analyzing the association between asthma and UC in those diagnosed as older adults, one study suggested there was an increased association while the other identified a protective association. Significant heterogeneity persisted following meta-regression based on age groups (residual heterogeneity: $I^2 = 87\%$, $p < 0.0001$).

Discussion

This systematic review and meta-analysis suggests the frequent co-occurrence of asthma with both Crohn's disease and UC. IBD has also been associated with other

respiratory disorders (e.g., chronic obstructive pulmonary disease)^{42,54}. Further, both asthma and IBD have been associated with other immune-mediated and atopic conditions, including multiple sclerosis, rheumatoid arthritis, diabetes, eczema, and rhinitis^{28,44,46,48,55–59}. However, there was a high degree of heterogeneity between studies, suggesting that the association between asthma and IBD may vary across populations and be impacted by differences in study methodology.

The association between Crohn's disease and asthma was consistent regardless of the relative timing of the diagnoses of the two diseases (i.e., asthma preceding Crohn's disease or Crohn's disease preceding asthma). However, the risk of asthma was elevated among patients with existing UC but patients with existing asthma did not appear to be at an increased risk of UC. Based on these findings, it is not clear if one disease results in a predisposition to the other or the co-occurrence of these diseases simply occurs due to the commonalities in the physiology of the gut and the lung, as well as shared genetic and environmental risk factors.

Table 4 Results of subgroup analyses and meta-regression based on study location

Type of IBD	Country	RR (95% CI)	Heterogeneity	Number of studies	Number of participants	Subgroup differences	Residual heterogeneity
Crohn's Disease	Canada	1.34 (1.24–1.45)	$I^2 = 64\%$	3	588,067	$p < 0.0001$ REF	$I^2 = 33\%$
	Finland	2.33 (1.41–3.86)	–	1	1165	β 0.55 (0.036 to 1.07)	$R^2 = 92\%$
	Israel	0.78 (0.55–1.10)	–	1	47	β –0.54 (–0.91 to –0.17)	$p = 0.16$
	New Zealand	1.46 (1.07–1.99)	–	1	1238	β 0.087 (–0.25 to 0.42)	
	Sweden	1.61 (1.41–1.83)	$I^2 = 0\%$	2	148,347	β 0.18 (0.0014 to 0.35)	
	Taiwan	1.50 (1.31–1.72)	–	1	25,799	β 0.11 (–0.071 to 0.30)	
	United Kingdom	0.90 (0.83–0.97)	$I^2 = 0\%$	4	1351	β –0.39 (–0.54 to –0.25)	
	United States	1.39 (1.13–1.71)	$I^2 = 47\%$	2	57,159	β 0.062 (–0.10 to 0.23)	
	Canada	1.28 (1.03–1.60)	$I^2 = 98\%$	3	583,902	$p < 0.0001$ REF	$I^2 = 96\%$
	Chile	0.90 (0.77–1.06)	–	1	226	β –0.35 (–0.80 to 0.099)	$R^2 = 0\%$
Ulcerative colitis	Finland	1.11 (0.68–1.81)	–	1	1810	β –0.14 (–0.79 to 0.50)	$p < 0.0001$
	Italy	1.61 (1.25–2.07)	$I^2 = 84\%$	2	182	β 0.22 (–0.13 to 0.57)	
	Japan	0.73 (0.32–1.68)	–	1	768	β –0.56 (–1.50 to 0.37)	
	New Zealand	0.93 (0.67–1.29)	–	1	1253	β –0.32 (–0.85 to 0.21)	
	Sweden	1.54 (1.37–1.74)	–	1	148,295	β 0.18 (–0.26 to 0.62)	
	Taiwan	1.46 (1.03–2.07)	–	1	21,541	β 0.13 (–0.42 to 0.68)	
	United Kingdom	1.29 (1.09–1.54)	$I^2 = 66\%$	3	2010	β 0.031 (–0.31 to 0.37)	
	United States	1.32 (1.07–1.62)	$I^2 = 41\%$	2	59,727	β 0.0018 (–0.37 to 0.37)	

Analyses stratified by age at diagnosis of IBD were inconsistent, with some studies suggesting a consistently elevated association between the two diseases across all ages, while others found contradictory age-specific associations. For example, one study found that the association between asthma and UC was decreased among people who were diagnosed with UC between 40 and 49 years of age⁴², while another study found an increased risk among patients diagnosed with UC > 40 years of age²². As both studies used health administrative data, and neither used an internally validated algorithm to identify cases of asthma, misclassification of asthma may have resulted in bias.

Additionally, failure to account for smoking status may have influenced the findings of these studies. Smoking is associated with an increased risk of Crohn's disease but a decreased risk of UC⁶⁰. Of the three included studies that adjusted for smoking status, two reported elevated associations between asthma and Crohn's disease while one suggested that there may be a protective effect of the two diseases but was underpowered to detect a difference^{24,27,47}. Asthma and UC were associated in one study that adjusted for smoking but not the other^{24,27}. Differential rates of smoking across ages at IBD diagnosis may also contribute to differences observed in the association between asthma and IBD. For example, smoking is significantly more common among patients who are older at the time of Crohn's disease diagnosis⁶¹. As a result, smokers with Crohn's disease may be at an elevated risk of respiratory disease due to smoking but not their IBD. The decreased rate of smoking among patients with UC may explain the protective association seen in one study⁴². Similarly, other environmental risk factors (e.g., air pollution) demonstrate age-specific associations with both asthma and IBD and may contribute to the differences in the age-specific associations between asthma and IBD^{62,63}.

A limitation of studies evaluating the associations between two conditions is that patients diagnosed with one condition have higher health services utilization than healthy individuals and may subsequently be more likely to be diagnosed with another condition⁶⁴. No study included in our systematic review accounted for increased health care use. As a result, our findings of an increased association between asthma and IBD may have resulted from detection bias.

The association between asthma and Crohn's disease varied across geographic regions. In Canada, New Zealand, Finland, Sweden, Taiwan, and the United States, the association between asthma and Crohn's disease was elevated. However, there was a negative association in the United Kingdom and Israel. Regional differences in the association between asthma and UC were less pronounced. Although the reasons for these regional differences are not known, it is possible that differing

penetrance of genetic or environmental risk factors may contribute. For example, the high prevalence of early-life exposure to peanuts has been associated with a decreased risk of peanut allergy in Israel⁶⁵. This decreased risk of atopy may also result in a decreased risk of asthma among these children but not impact their elevated risk of developing IBD, due to genetic predisposition of IBD amongst Ashkenazi Jews.

As this is a systematic review, our ability to make conclusions about the co-occurrence of asthma and IBD is limited by the availability and quality of previous studies evaluating the association between these two diseases. Although we included 19 studies in our review, there was high degree of heterogeneity across studies. Heterogeneity was reduced when accounting for study methodology (i.e., study design and source of study participants) in studies analyzing the association between asthma and Crohn's disease but not in the association between asthma and UC. In fact, there was an elevated association between asthma and Crohn's disease in population-based studies, but a protective association between the two diseases in studies conducted using patients recruited from tertiary-care centers. All samples recruiting patients from tertiary-care centers were conducted either in Israel or the United Kingdom. This suggests that there are other underlying differences between studies and populations when it comes to understanding the association between asthma and IBD and we are unable to ascertain if the differences we observed result from differing study design or differences across populations. Specifically, the majority of studies recruiting patients from tertiary-care centers may have introduced selection bias by their choice of controls (e.g., partners of cases). However, similar control groups were selected in studies evaluating the association between UC and asthma included control groups that could similarly have introduced selection bias, yet the association remained similar regardless of the source of patients. In addition, there may be other differences in study design that were not accounted for (e.g., differences in the case definitions for IBD and asthma and variables adjusted for), underlying differences in the study population, or the phenotypes of asthma and IBD identified in the study (i.e., disease severity, behavior, management approach).

Conclusions

Asthma is associated with both Crohn's disease and ulcerative colitis. Geographic differences, as well as differences in study design, contribute to this heterogeneity. We were unable to determine whether one disease increases the risk of the other or if both arise due to commonalities in pathology and shared risk factors. Future well-designed observational research should attempt to address these issues in their study design.

Study Highlights

What is current knowledge

- Asthma and the inflammatory bowel diseases share environmental, genetic, and microbial risk factors

What is new here

- Asthma is associated with both Crohn's disease and ulcerative colitis
- The relationship between these two diseases appears to vary by region

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Competing interests

Guarantor of the article: M. Ellen Kuenzig.

Specific author contributions: Study concept and design: M.E.K., G.G.K., E.I.B., Data acquisition: M.E.K., K.B., CrowdScreen SR Review Team, Statistical analysis: M.E.K., Interpretation of the data: M.E.K., G.G.K., E.I.B., Drafting of the manuscript: M.E.K., Critical revision of the manuscript for intellectual content: M.E.K., K.B., R.L., G.G.K., E.I.B., Final approval of the manuscript: M.E.K., K.B., R.L., G.G.K., E.I.B.

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Supplementary Table 1. Search strategy used to identify studies evaluating the association between asthma and the inflammatory bowel diseases.

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
1. exp asthma/ 2. asthma\$.mp. 3. (antiasthma\$ or anti-asthma\$).mp. 4. Respiratory sounds/ 5. wheez\$.mp. 6. Bronchial Spasm/ 7. bronchospas\$.mp. 8. (bronch\$ adj3 spasm\$).mp. 9. bronchoconstrict\$.mp. 10. Bronchoconstriction/ 11. (bronch\$ adj3 constrict\$).mp. 12. Bronchial Hyperreactivity/ 13. Respiratory Hypersensitivity/ 14. ((bronchial\$ or respiratory or airway\$ or lung\$) adj3 (hypersensitiv\$ or hyperreactiv\$ or allerg\$ or insufficien\$)).mp. 15. ((dust or mite\$) adj3 (allerg\$ or hypersensitiv\$)).mp. 16. or/1-15 17. exp inflammatory bowel diseases/ 18. exp crohn disease/ 19. exp colitis, ulcerative/ 20. exp enterocolitis/ 21. exp proctitis/ 22. exp ileitis/ 23. crohn*.mp. 24. ulcerative colitis.mp. 25. "inflammatory bowel disease*".mp. 26. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 27. 16 and 26
EMBASE

1. exp asthma/
2. asthma\$.mp.
3. (antiasthma\$ or anti-asthma\$).mp.
4. Abnormal Respiratory Sound/
5. Wheezing/
6. wheez\$.mp.
7. bronchospasm/
8. bronchospas\$.mp.
9. (bronch\$ adj3 spasm\$).mp.
10. exp Bronchoconstriction/
11. bronchoconstrict\$.mp.
12. Respiratory Tract Allergy/
13. (bronch\$ adj3 constrict\$).mp.
14. Bronchus Hyperreactivity/
15. House Dust Allergy/
16. ((bronchial\$ or respiratory or airway\$ or lung\$) adj3 (hypersensitiv\$ or hyperreactiv\$ or allerg\$ or insufficien\$)).mp.
17. ((dust or mite\$) adj3 (allerg\$ or hypersensitiv\$)).mp.
18. or/1-17
19. exp inflammatory bowel disease/
20. exp crohn disease/
21. exp ulcerative colitis/
22. exp enterocolitis/
23. exp proctitis/
24. exp ileitis/
25. crohn*.mp.
26. ulcerative colitis.mp.
27. "inflammatory bowel disease*".mp.
28. or/19-27
29. 18 and 28
30. limit 29 to conference abstract
31. 29 not 30

Supplementary Table 2. Reasons for exclusion

Study	Reason for Exclusion
Andreoletti 2015(1)	No control group
Anonymous 1985(2)	Did not report the association between asthma and IBD
Balzola 2010(3)	Review article
Balzola 2011(4)	Review article
Balzola 2011(5)	Review article
Balzola 2013(6)	Review article
Bernstein 2008(7)	Meeting summary
Bhat 2007(8)	Case report
Ceyhan 2015(9)	Rate of asthma in the control group not reported
Chandra 2011(10)	Did not report the association between asthma and IBD
Chen 2017(11)	Did not report the association between asthma and IBD
Colldahl 1965(12)	Case report
Conway 2017(13)	No control group
D'Amato 2007(14)	Did not report the association between asthma and IBD
D'Andrea 2010(15)	Review article
Desai 2011(16)	Assessed the impact of IBD on pulmonary function, not asthma
Edwards 2004(17)	Did not report the association between IBD and asthma
Eliakim 1996(18)	Review article
Fenta 2010(19)	Did not separate Crohn's disease and ulcerative colitis
Gibbs 1971(20)	Cell line, animal or translational research
Grover 2014(21)	Did not report the association between asthma and IBD
Grünberger 1984(22)	Did not report the association between asthma and IBD
Grünberger 1985(23)	Did not report the association between asthma and IBD
Gut 2011(24)	Case report
Haapamäki 2011(25)	Combined asthma with COPD
Heinzmann 2003(26)	Did not report the association between asthma and IBD
Hemminki 2010(27)	Evaluated familial asthma as a risk factor for IBD
Herrlinger 2002(28)	Assessed the impact of IBD on pulmonary function, not asthma
Hirota 2015(29)	Letter to the editor
Huang 2014(30)	Cell line, animal, or translational research
Hubbard 2004(31)	Review article
Hutchings 2008(32)	Did not report the association between IBD and asthma
Hyams 1988(33)	Did not report the association between IBD and asthma
Iannello 2003(34)	Did not report the association between IBD and asthma
Ikonomi 2016(35)	Did not report the association between IBD and asthma
Ilonidis 2004(36)	Assessed the impact of IBD on pulmonary function, not asthma
Kabesch 2003(37)	Did not report the association between IBD and asthma
Kanazawa 2005(38)	Cell line, animal or translational research
Kaplan 2011(39)	Review article
Kauppi 2015(40)	Did not separate Crohn's disease and ulcerative colitis
Koek 2002(41)	Assessed the impact of IBD on pulmonary function, not asthma
Koning 2013(42)	Did not evaluate the association between asthma and IBD
Li 2012(43)	Did not evaluate the association between asthma and IBD

Li 2014(44)	No control group
Louis 1995(45)	Assessed the impact of IBD on pulmonary function, not asthma
Louis 1999(46)	Assessed the impact of IBD on pulmonary function, not asthma
Majewski 2015(47)	Review article
Manguso 2002(48)	Duplicate of included study
Mansi 2000(49)	Assessed the impact of IBD on pulmonary function, not asthma
Mikhailova 2011(50)	Assessed the impact of IBD on pulmonary function, not asthma
Moes-Wójtowicz 2012(51)	No control group
Olén 2014(52)	Excluded patients with IBD
Parambil 2009(53)	Did not report the association between IBD and asthma
Park 2005(54)	Did not report the association between IBD and asthma
Pearson 1983(55)	Case report
Peradzynska 2012(56)	Rate of asthma in the control group not reported
Persson 1996(57)	Reports on asthma-specific mortality rates in patients with IBD
Poon 2004(58)	Cell line, animal or translational research
Ramagopalan 2013(59)	Did not report the association between IBD and asthma
Rodriguez-Roisin 2016(60)	Review article
Romano 2016(61)	Review article
Sarioglu 2006(62)	Letter to the editor
Sclano 2002(63)	Review article
Sharifpour 2012(64)	Excluded patients with pre-existing respiratory disease
Sibtain 2011(65)	Evaluated familial asthma as a risk factor for IBD
Sivagnanam 2007(66)	No control group
Sivagnanasundaram 2004(67)	Did not report the association between IBD and asthma
Skyring 1965(68)	No control group
Swynghedauw 2007(69)	Review article
Taherzadeh 2012(70)	Assessed the impact of IBD on pulmonary function, not asthma
Tanday 2015(71)	Review article
Tirosh 2006(72)	Did not separate Crohn's disease and ulcerative colitis
Upton 2015(73)	Did not report the association between IBD and asthma
Van Limbergen 2009(74)	No control group
Vutcovici 2016(75)	Reported on mortality in co-occurring asthma and COPD
Wang 2013(76)	Review article
Weidinger 2005(77)	Evaluated the association between genetic factors and asthma
Yang 2000(78)	Did not report the association between IBD and asthma
Yun 2012(79)	Duplicate cohort of Fenta 2010(19)

Supplementary Table 3. Risk of bias of included case-control and cross-sectional studies

Study	Adequate Case Definition	Representativeness of the Cases	Selection of Controls	Controls Did Not Have Disease	Comparability of Cases and Controls	Ascertainment of Exposure	Same method of ascertainment for cases and controls	Non-response rate
Bernstein 2005(80)	Yes, with independent validation	Consecutive or obviously representative series of cases (population-based)	Community controls	Yes	Study controls (adjusts) for important confounding variables	Secure record	Yes	Not relevant (administrative data)
Boneberg er 2012(81)	No description	Consecutive or obviously representative series of cases (tertiary-care centre)	Hospital controls	Not reported	Study controls (adjusts) for important confounding variables	No description	Not reported	Response rates not reported
D'Arienzo 2000(82)	Yes, with independent validation	Consecutive or obviously representative series of cases (tertiary-care centre)	Other – Hospital staff	Yes	No control (adjustment) for potential confounding variables	Structured interview where blinded to case/control status	Yes	Response rates not reported
D'Arienzo 2002(83)	Yes, with independent validation	Consecutive or obviously representative series of cases (tertiary-care centre)	Other – Partners of cases	Yes	No control (adjustment) for potential confounding variables	Structured interview where blinded to case/control status	Yes	Response rates not reported

Study	Adequate Case Definition	Representativeness of the Cases	Selection of Controls	Controls Did Not Have Disease	Comparability of Cases and Controls	Ascertainment of Exposure	Same method of ascertainment for cases and controls	Non-response rate
Gearry 2010(84)	Yes, with independent validation	Consecutive or obviously representative series of cases (population-based)	Community controls	Not reported	Study controls (adjusts) for important confounding variables	Written self-report or medical record only	Yes	Non respondents described
Hammer 1968(85)	Yes, with independent validation	Potential for selection biases or not stated (tertiary-care centre)	Hospital/clinic controls	Not reported	No control (adjustment) for potential confounding variables	Interview; unclear if blinded to case/control status	Yes	Not reported
Kappelman 2011(86)	Yes, with independent validation	Potential for selection biases or not stated (health maintenance organization)	Other – patients in same health maintenance organization without IBD	Yes	Study controls (adjusts) for important confounding variables	Secure record	Yes	Not relevant (administrative data)
Kuenzig 2017(87)	Yes, with independent validation	Consecutive or obviously representative series of cases (population-based)	Community Controls	Yes	Study controls (adjusts) for important confounding variables	Secure record	Yes	Not relevant (administrative data)

Study	Adequate Case Definition	Representativeness of the Cases	Selection of Controls	Controls Did Not Have Disease	Comparability of Cases and Controls	Ascertainment of Exposure	Same method of ascertainment for cases and controls	Non-response rate
Livnat 2012(88)	Yes, with independent validation	Consecutive or obviously representative series of cases (tertiary-care centre)	Hospital/clinic controls	Not reported	No control (adjustment) for potential confounding variables	Written self report or medical record only	Yes	Cases: Non respondents described Controls: Response rates not reported
Myrelid 2004(89)	Yes, with independent validation	Potential for selection biases or not stated	Community controls	Not reported	Study controls (adjusts) for important confounding variables	Written self-report or medical record only	Yes	Same rate for both groups
Nakamura 1994(90)	Yes, with independent validation	Consecutive or obviously representative series of cases (population-based)	Hospital/clinic controls	Not reported	Study controls (adjusts) for important confounding variables	Written self report or medical record only	Yes	Response rates not reported
Neilly 1989(91)	No description	Potential for selection biases or not stated	No description	Not reported	Study controls (adjusts) for important confounding variables	Interview; unclear if blinded to case/control status	Yes	Same rate for both groups

Study	Adequate Case Definition	Representativeness of the Cases	Selection of Controls	Controls Did Not Have Disease	Comparability of Cases and Controls	Ascertainment of Exposure	Same method of ascertainment for cases and controls	Non-response rate
Pugh 1979(92)	Yes, with independent validation	Potential for selection biases or not stated (tertiary-care centre; Ileostomy Association)	Other – Partners of cases (51%); hospital/clinic controls (49%)	Not reported	No control (adjustment) for potential confounding variables	Written self report or medical record only	Yes	Response rates not reported
Virta 2013(93)	Yes, with independent validation	Consecutive or obviously representative series of cases (population-based)	Community controls	Not reported	Study controls (adjusts) for potential confounding variables	Secure record	Yes	Response rates not relevant (e.g., administrative data)
Weng 2007(94)	Yes, with independent validation	Potential for selection biases or not stated (health maintenance organization)	Other – patients in same health maintenance organization without IBD	Yes	Study controls (adjusts) for important confounding variables	Secure records	Yes	Response rates not relevant (eg administrative data)

Supplementary Table 4. Risk of bias in cohort studies

Study	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of Outcome	Sufficient follow-up	Adequacy of follow-up cohorts
Brassard 2015(95)	Somewhat representative of the average rate of disease in the community ^a	Drawn from the same community as the exposed cohort ^b	Secure record	Yes	Study controls (adjusts) for important confounding variables	Record linkage	Yes	Not relevant (administrative data)
Hemminki 2010(96)	Somewhat representative of the average rate of disease (IBD or asthma) in the community	Drawn from the same community as the exposed cohort	Secure record	Yes	Study controls (adjusts) for important confounding variables	Record linkage	Yes	Not relevant (administrative data)
Peng 2015(97)	Truly representative of the average rate of disease (IBD or asthma) in the community	Drawn from the same community as the exposed cohort	Secure record	Yes	Study controls (adjusts) for important confounding variables	Record linkage	Yes	Not relevant (administrative data)
Raj 2008(98)	Selected group of users ^c	Drawn from the same	Secure record	No	No control (adjustment) for potential	Record linkage	Yes	No statement

community as the exposed cohort^b

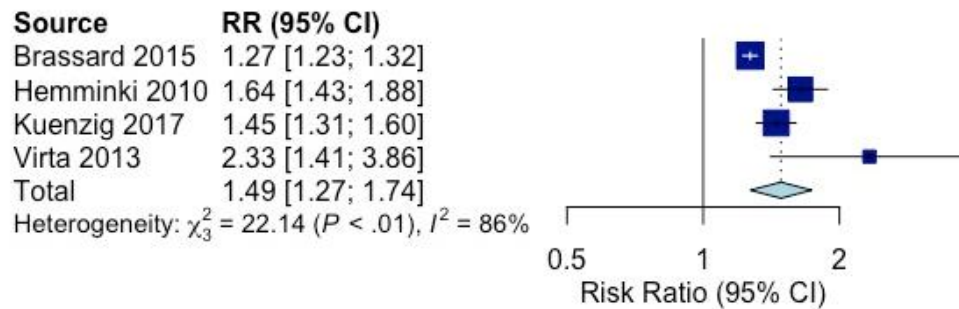
confounding variables

^aStudy was conducted using provincial health administrative data, but only included patients with provincial pharmacare (age ≥ 65 , on social assistance, or with no employee benefits)

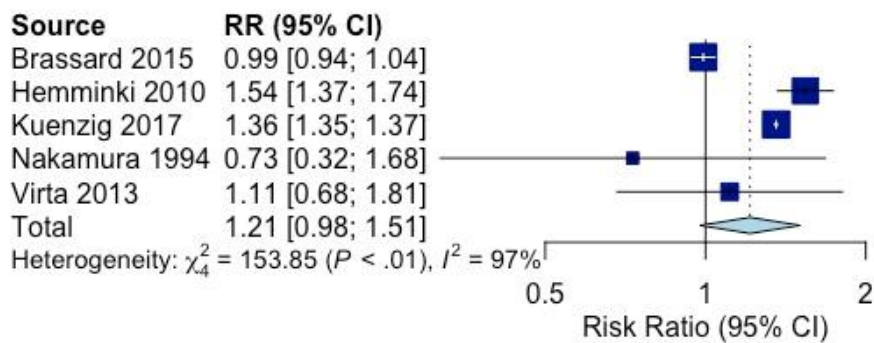
^bThe rate of inflammatory bowel disease (IBD) among people with asthma was compared to the rate of asthma in the general population

^cPatients with asthma were recruited from a tertiary-care respiratory centre

Supplementary Figure 1. Sensitivity analysis restricted to studies in which the diagnosis of asthma preceded the diagnosis of Crohn's disease

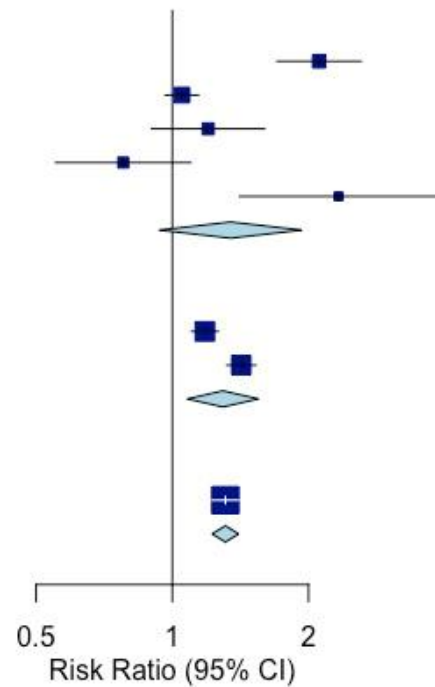


Supplementary Figure 2. Sensitivity analysis restricted to studies in which the diagnosis of asthma preceded the diagnosis of ulcerative colitis

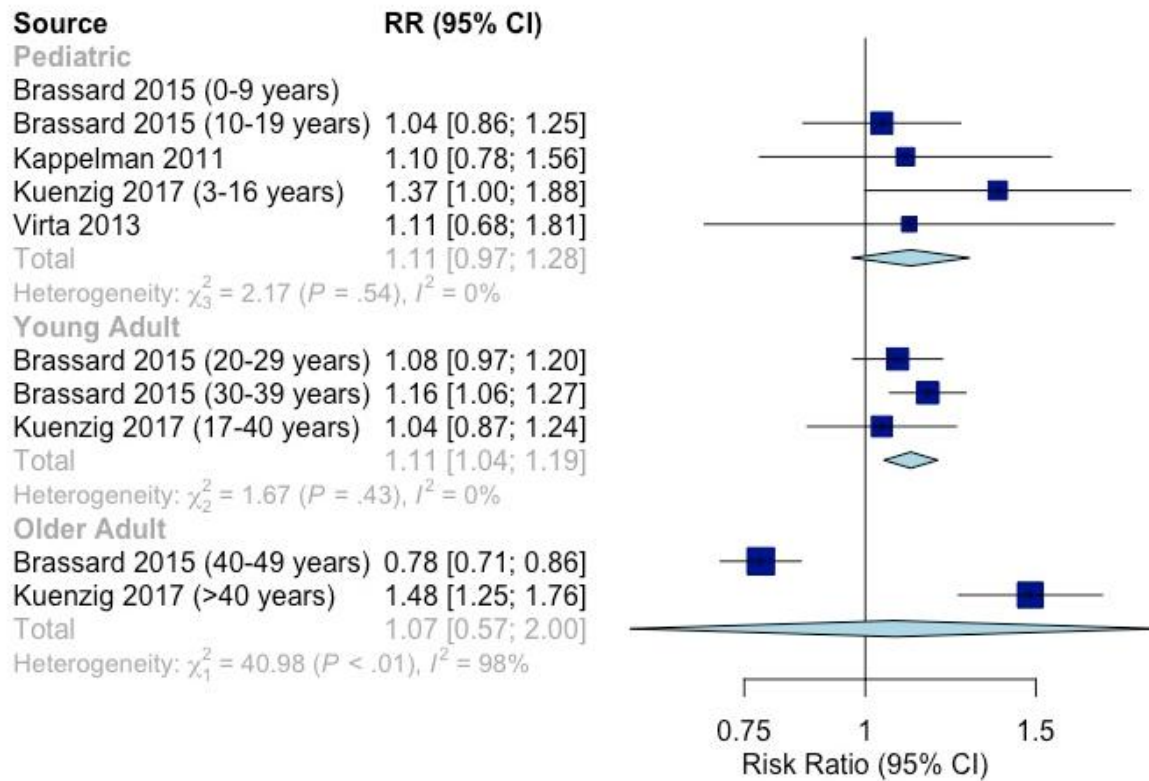


Supplementary Figure 3. Association between asthma and Crohn's disease stratified by age at IBD diagnosis

Source	RR (95% CI)
Pediatric	
Brassard 2015 (0-9 years)	2.11 [1.70; 2.61]
Brassard 2015 (10-19 years)	1.05 [0.96; 1.14]
Kappelman 2011	1.20 [0.90; 1.60]
Livnat 2012	0.78 [0.55; 1.10]
Virta 2013	2.33 [1.41; 3.86]
Total	1.35 [0.94; 1.93]
Heterogeneity: $\chi^2_4 = 47.74$ ($P < .01$), $I^2 = 92\%$	
Young Adult	
Brassard 2015 (20-29 years)	1.18 [1.10; 1.26]
Brassard 2015 (30-39 years)	1.42 [1.32; 1.53]
Total	1.29 [1.08; 1.55]
Heterogeneity: $\chi^2_1 = 13.09$ ($P < .01$), $I^2 = 92\%$	
Older Adult	
Brassard 2015 (40-49 years)	1.31 [1.22; 1.40]
Total	1.31 [1.22; 1.40]
Heterogeneity: not applicable	



Supplementary Figure 4. Association between asthma and ulcerative colitis stratified by age at IBD diagnosis



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