

The Bidirectional Association between Inflammatory Bowel Disease and Atopic Dermatitis: A Systematic Review and Meta-Analysis

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Keywords

Atopic dermatitis · Inflammatory bowel disease · Crohn's disease · Ulcerative colitis · Meta-analysis

Abstract

Background: Previous investigations have suggested a significant association between inflammatory bowel disease (IBD) and atopic dermatitis (AD). Yet, outcomes published remain inconsistent. **Objective:** To explore the association between IBD and AD by a systematic review and meta-analysis. **Methods:** A comprehensive search of studies published from March 1, 1968, to July 26, 2019, was performed in electronic databases as follows: PubMed, Embase, Cochrane Library, and Web of Science. Methodological quality was assessed based on the Newcastle-Ottawa Scale. Data analysis was conducted using R version 3.6.1 (meta package version 4.9-7). **Results:** A total of 14 studies were eligible for exploring the association between IBD and AD. Statistically significant differences were found on the risk of AD comorbidity among patients with IBD (risk ratio [RR] 1.83, 95% CI 1.39–2.40), Crohn's disease (CD; RR 2.06, 95% CI 1.61–2.64), and ulcerative colitis (UC; RR 1.66, 95% CI 1.23–2.24). Compared with non-AD subjects, patients with AD were 48% ($p = 0.019$), 44% ($p = 0.002$), and 38% ($p = 0.000$) more likely to exhibit

IBD, CD as well as UC, respectively. **Discussion:** Our evidence supported a significant bidirectional association between IBD and AD. Future prospective studies are warranted to explore underlying mechanisms linking them.

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Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is recognized as a chronic idiopathic disorder that causes inflammation of the gastrointestinal tract [1]. Over the past decade, IBD has emerged as a public health challenge around the world [2]. The exact pathogenesis of IBD remains poorly understood. Nevertheless, increasing evidence suggested that immune dysregulation could be a potential mechanism [3]. In addition, genetic factors, presence of microorganisms, and environmental factors may also play a vital role in promoting the clinical features of IBD [4]. To date, more investigations found that IBD is not merely restricted to the excessive immune response within the digestive system but is also expected to be connected with

X.S. and Q.C. contributed equally to this study.

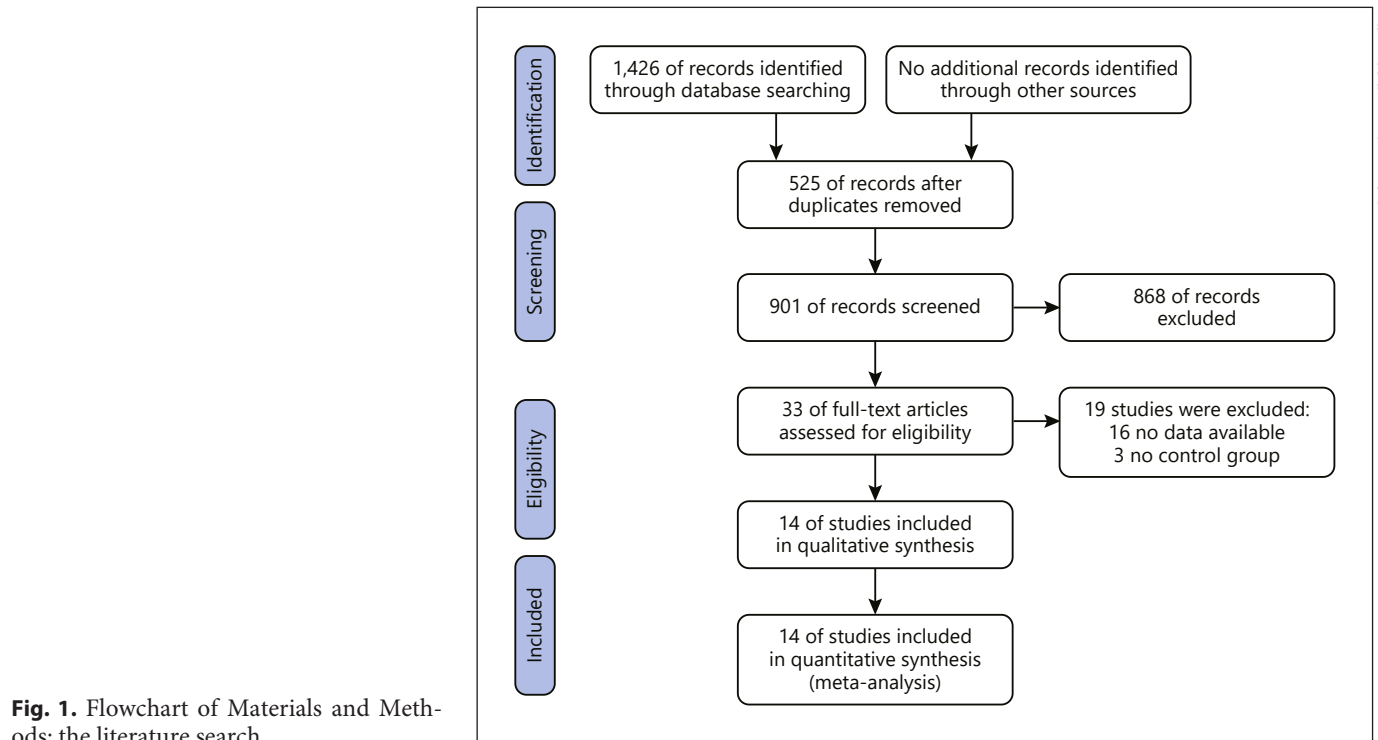


Fig. 1. Flowchart of Materials and Methods: the literature search.

various extraintestinal manifestations, especially inflammatory skin diseases like rosacea, atopic dermatitis (AD), and psoriasis [5–8].

AD is regarded as a chronic relapsing inflammatory disorder predominantly attributed to the dysfunction of the epidermal barrier and immune system-mediated inflammation, which affects up to 20% of the pediatric population and 3% of the adult population in Western countries [9, 10]. A growing group of systemic diseases has been reported to be associated with AD, including vitiligo, alopecia areata, IBD, and attention deficit/hyperactivity disorder (ADHD) [11].

Given several genes, microorganisms and environment are suggested to be involved in the possible predisposing factors shared by IBD and AD, it is urgent for physicians of gastroenterology and dermatology to pinpoint the truth and put forward a better therapy for patients suffering from both diseases [12].

Although numerous observational studies have argued that there is a significant relationship between AD and IBD, outcomes published remain inconsistent. For instance, findings from Rahier et al. [13] indicated a significant prevalence of AD in patients with IBD. A cross-sectional study carried out in the USA found that patients with AD had a significantly increased risk of IBD, compared with a control group [14]. In contrast, Treudler et

al. [15] found no significance with regard to the association between IBD and AD. As such, the objective of our study was to perform a meta-analysis and systematic review in order to convincingly and thoroughly evaluate the bidirectional association between IBD and AD.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000505290 for all online suppl. material) (Fig. 1) [16–29].

Results

Literature Search

A total of 1,426 references including 229 articles from PubMed, 498 articles from Embase, 27 articles from Cochrane Library, and 672 articles from Web of Science were retrieved. After removing 525 duplicates, we excluded 901 citations based on scanning the titles and abstracts. Nineteen possible full-text studies were carefully reviewed, of which 16 studies and 3 studies were excluded due to no usable data and no control groups, separately. Finally, 14 eligible studies met the inclusion criteria for

Table 1. Eligible studies in the meta-analysis

First author, year	Country	Study design	Primary disease		diagnostic basis	Concomitant disease		Controls	
			primary disease	number (sex, female %; age, years, mean $\pm$ SD or range)		concomitant disease	n	number (sex, female %; age, years, mean $\pm$ SD, range)	diagnostic basis
Wasieleska [21], 2019	Poland	Case-control	IBD CD UC	60 (57; 14.72 $\pm$ 2.92) 36 (42; 15.0 $\pm$ 3.08) 24 (42; 14.3 $\pm$ 3.89)	Clinical, endoscopic and histopathological and radiological criteria	AD	15 6 7	60 (57; 14.85 $\pm$ 2.92) 60 (57; 14.85 $\pm$ 2.92) 60 (57; 4.85 $\pm$ 2.92)	Questionnaires Questionnaires Questionnaires
Kim [8], 2017	Korea	Case-control	IBD CD UC	40,843 (39.8; 41.2 $\pm$ 17.2) 12,646 (31; 32.5 $\pm$ 16.1) 28,197 (44; 45.1 $\pm$ 16.1)	ICD-10	AD	826 314 512	122,529 (n.a.; 41.2 $\pm$ 17.2) 122,529 (n.a.; 41.2 $\pm$ 17.2) 122,529 (n.a.; 41.2 $\pm$ 17.2)	ICD-10 ICD-10 ICD-10
Kappelman [29], 2011	USA	Cross-sectional	IBD CD UC	1,242 (45; 15.0 $\pm$ 3.4) 737 (44; 15.0 $\pm$ 3.2) 488 (47; 14.8 $\pm$ 3.7)	ICD-9	AD	51 31 20	3,353 (45; 15 $\pm$ 3.5) 1,997 (44; 15.1 $\pm$ 3.4) 1,310 (48; 14.9 $\pm$ 3.7)	ICD-9 ICD-9 ICD-9
Baron [22], 2005	Germany	Case-control	CD	222 (46; 13.5)	Two expert gastroenterologists	AD	35	222 (n.a.; 13.5)	Questionnaires
Myrelid [23], 2004	Sweden	Case-control	CD	280 (52; 18–50)	Clinical, radiological, endoscopic, and histological criteria	AD	72	779 (53; 18–50)	Questionnaires
Nasu [24], 1999	Japan	Case-control	IBD CD UC	58 (n.a.) 26 (19; 19–55) 32 (34; 18–68)	Clinical, radiological, endoscopic, and histological criteria	AD	12 7 5	58 (n.a.) 26 (19; 19–55) 32 (34; 18–68)	Questionnaires Questionnaires Questionnaires
Gilat [25], 1987	9 countries	Case-control	IBD CD UC	499 (50; 20 $\pm$ 5.2) 302 (n.a.) 197 (n.a.)	Questionnaires	AD	64 44 20	998 (n.a.) 604 (n.a.) 394 (n.a.)	Questionnaires Questionnaires Questionnaires
Pugh [26], 1979	England	Case-control	IBD CD UC	500 (n.a.) 200 (n.a.) 300 (n.a.)	Histological, radiological, and pathological criteria	AD	110 47 63	500 (n.a.) 200 (n.a.) 300 (n.a.)	Questionnaires Questionnaires Questionnaires
Jewell [27], 1972	England	Case-control	IBD CD UC	58 (n.a.) 19 (n.a.) 39 (n.a.)	Barium enema, clinical, endoscopic, and histological criteria	AD	5 2 3	20 (n.a.) 20 (n.a.) 20 (n.a.)	n.a. n.a. n.a.
Hammer [28], 1968	France	Case-control	IBD CD UC	243 (n.a.) 45 (n.a.) 198 (n.a.)	Clinical, radiological, and histological criteria	AD	41 15 26	319 (n.a.) 319 (n.a.) 319 (n.a.)	Questionnaires Questionnaires Questionnaires
Narla [14], 2019	USA	Cross-sectional	AD	44,605 (63.9; >18)	ICD-9	IBD CD UC	523 308 215	341,176,608 (n.a.)	ICD-9 or CCS codes ICD-9 or CCS codes ICD-9 or CCS codes
Egeberg [30], 2017	Denmark	Case-control	AD	7,032 (64.5; 45.5 $\pm$ 12.1)	Dermatologists	IBD CD UC	167 37 96	3,587,974 (51.1; 54.0 $\pm$ 15.3)	n.a. n.a. n.a.
Schmitt [31], 2016	Germany	Case-control	AD	49,847 (58.64; 0–40)	ICD-10	IBD CD UC	242 130 112	605,968 (48.77; 0.40)	ICD-10 ICD-10 ICD-10
Wu [32], 2014	China	Case-control	AD	41,950 (54.29; 34.71 $\pm$ 23.79)	ICD-9	IBD	37	167,800 (54.29; 34.70 $\pm$ 23.79)	ICD-9

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; ICD, International Statistical Classification of Disease; AD, atopic dermatitis; CCS, clinical classification software; SD, standard deviation; n.a., not available.

Table 2. Newcastle-Ottawa Scale (NOS) quality assessment table

First author, year	Selection	Comparability	Exposure	Total NOS score
Wasielewska [21], 2019	****	**	***	9
Kim [8], 2017	****	*	**	7
Kappelman [29], 2011	****	**	**	8
Baron [22], 2005	***		**	5
Myrelid [23], 2004	****	**	**	8
Nasu [24], 1999	****	**	**	8
Gilat [25], 1987	**	**	**	6
Pugh [26], 1979	****	*	***	8
Jewell [27], 1972	***		*	4
Hammer [28], 1968	****	**	***	9
Narla [14], 2019	****	**	**	8
Egeberg [30], 2017	**	*	**	5
Schmitt [31], 2016	****	**	**	8
Wu [32], 2014	****	**	**	8

this study. The flow diagram of the literature search is shown in Figure 1.

Study Characteristics and Quality Assessment

The diagnosis of IBD was mainly based on clinical, radiological, endoscopic, and histological criteria, International Classification of Diseases, ninth/tenth revision (ICD-9/10), or by expert dermatologists. AD was mainly diagnosed using the International Classification of Diseases, ninth/tenth revision (ICD-9/10), or by expert dermatologists (Table 1).

For 10 studies assessing the risk of AD in patients with IBD, the total population of the recruited articles consisted of 43,503 patients with IBD and 127,837 control subjects, 14,513 patients with CD and 126,756 control subjects, along with 29,466 patients with UC and 123,562 control subjects. Nine of the included studies were case-control studies [8, 21–28], the remaining a cross-sectional study [29]. As for the study continent, 6 studies were conducted in Europe [21–23, 26–28], 2 in Asia [8, 24], 1 in North America [29], and another 1 in 9 countries covering all of them [25].

In another 4 reverse directional articles involving 143,434 participants, one was a cross-sectional study [14] while 3 of them were case-control studies [30–32]. As for the study continent, 2 studies were conducted in Europe [30, 31], 1 in Asia [32], 1 in North America [14]. The detailed characteristics of these articles are summarized in Table 1.

As for the included studies, the median (interquartile range) modified NOS score was 8 (5.5–8.0). The quality of the eligible studies based on the NOS was high overall (score of 7 or greater; Table 2).

AD Risks in Patients with IBD

All of these 10 studies provided data on the association of AD in patients with CD (14,513 participants) [8, 18–26]. We found that patients with CD were significantly more likely to suffer from AD compared to controls (risk ratio, RR, 2.06, 95% confidence interval, CI, 1.61–2.64, $p < 0.01$; Fig. 2). The heterogeneity was moderate ($I^2 = 66\%$, $p < 0.01$; Fig. 2). In order to explore the sources of heterogeneity, sensitivity analysis was performed by excluding studies sequentially. The results showed that after omitting the study by Hammer et al. [28], the RR significantly decreased to 1.80 (95% CI 1.49–2.17), which suggested the main source of the heterogeneity (online suppl. Appendix 2, Fig. S1). A symmetrical funnel plot and an insignificant Egger's test showed a limited publication bias and no small-study effects ($p = 0.1284$) among these studies (online suppl. Appendix 3, Fig. S1A/B).

Eight studies investigating UC were enrolled (29,472 participants) [9, 14, 22, 25–29]. Statistically significant associations were observed for AD in patients with UC (RR 1.66, 95% CI 1.23–2.24, $p < 0.01$; Fig. 2). Heterogeneity across trials was moderate ($I^2 = 59\%$, $p = 0.02$; Fig. 2). We noticed that by excluding the study conducted by Pugh et al. [26], RR decreased to 1.35 (95% CI 1.12–1.62), suggesting the main source of the heterogeneity (online suppl. Appendix 2, Fig. S2). The funnel plot showed notable publication bias by visual inspection, and Egger's test indicated mild publication bias ($p = 0.044$; online suppl. Appendix 3, Fig. S2A/B).

We included a total of 8 studies regarding the risk of AD in unspecified IBD (43,503 participants) [8, 18, 21–26]. Our meta-analysis illustrated an obvious increased RR of IBD in AD patients (RR 1.83, 95% CI 1.39–2.40, $p < 0.01$; Fig. 2). Moderate heterogeneity was reported ($I^2 = 74\%$, $p < 0.01$; Fig. 2). The results showed that after omitting the study by Pugh et al. [26], RR decreased to 1.54 (95% CI 1.28–1.86), suggesting the main source of the heterogeneity (online suppl. Appendix 2, Fig. S3). No major publication bias was evaluated using funnel plot and Egger's test ($p = 0.065$; online suppl. Appendix 3, Fig. S3A/B).

IBD Risks in Patients with AD

Of the 4 studies, 3 reported the outcomes of both CD (101,484 participants) and UC (101,484 participants),

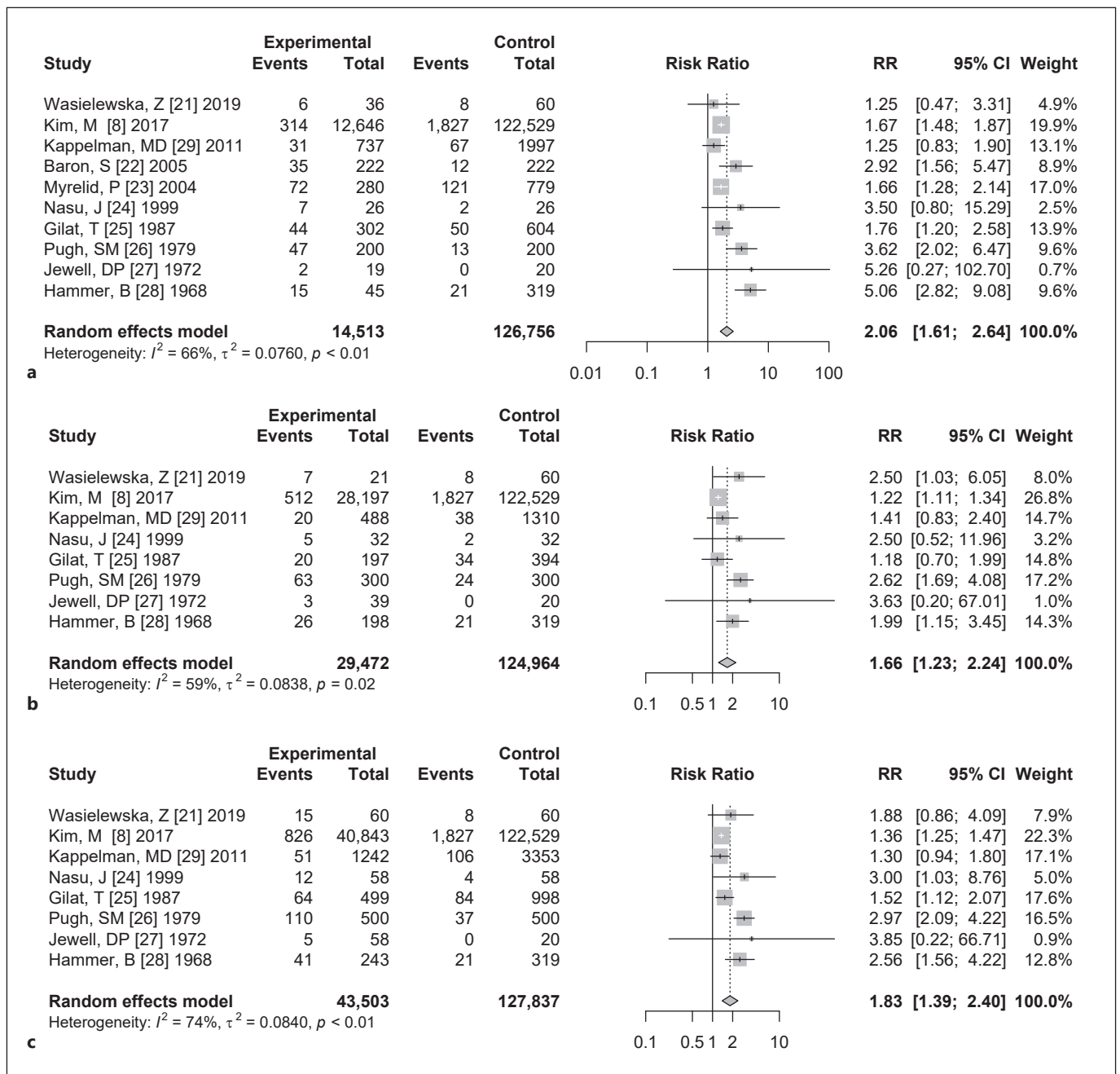


Fig. 2. Forest plot of atopic dermatitis in patients with inflammatory bowel disease. The squares indicate individual studies. The diamonds represent pooled effect sizes. The dashed lines represent the 95% CIs. RR, risk ratio. **a** Crohn's disease. **b** Ulcerative colitis. **c** Inflammatory bowel disease.

and all of them investigated the risk of unspecified IBD (143,434 participants) in AD patients. We calculated a pooled RR of 1.38 (95% CI 1.22–1.57, $p < 0.01$), 1.48 (95% CI 1.06–2.04, $p < 0.05$), and 1.44 (95% CI 1.14–1.82, $p < 0.01$), for CD, UC, and IBD in AD populations, respectively (Fig. 3). Heterogeneity in CD, UC, and IBD groups

was low ($I^2 = 35\%$, $p = 0.22$; Fig. 3), high ($I^2 = 91\%$, $p < 0.01$; Fig. 3), and high ($I^2 = 90\%$, $p < 0.01$; Fig. 3), respectively. It is not likely to accomplish the assessment of publication bias with funnel plots due to the finite numbers of studies in each subgroup, suggesting that no conclusion was able to be drawn from visual examination.

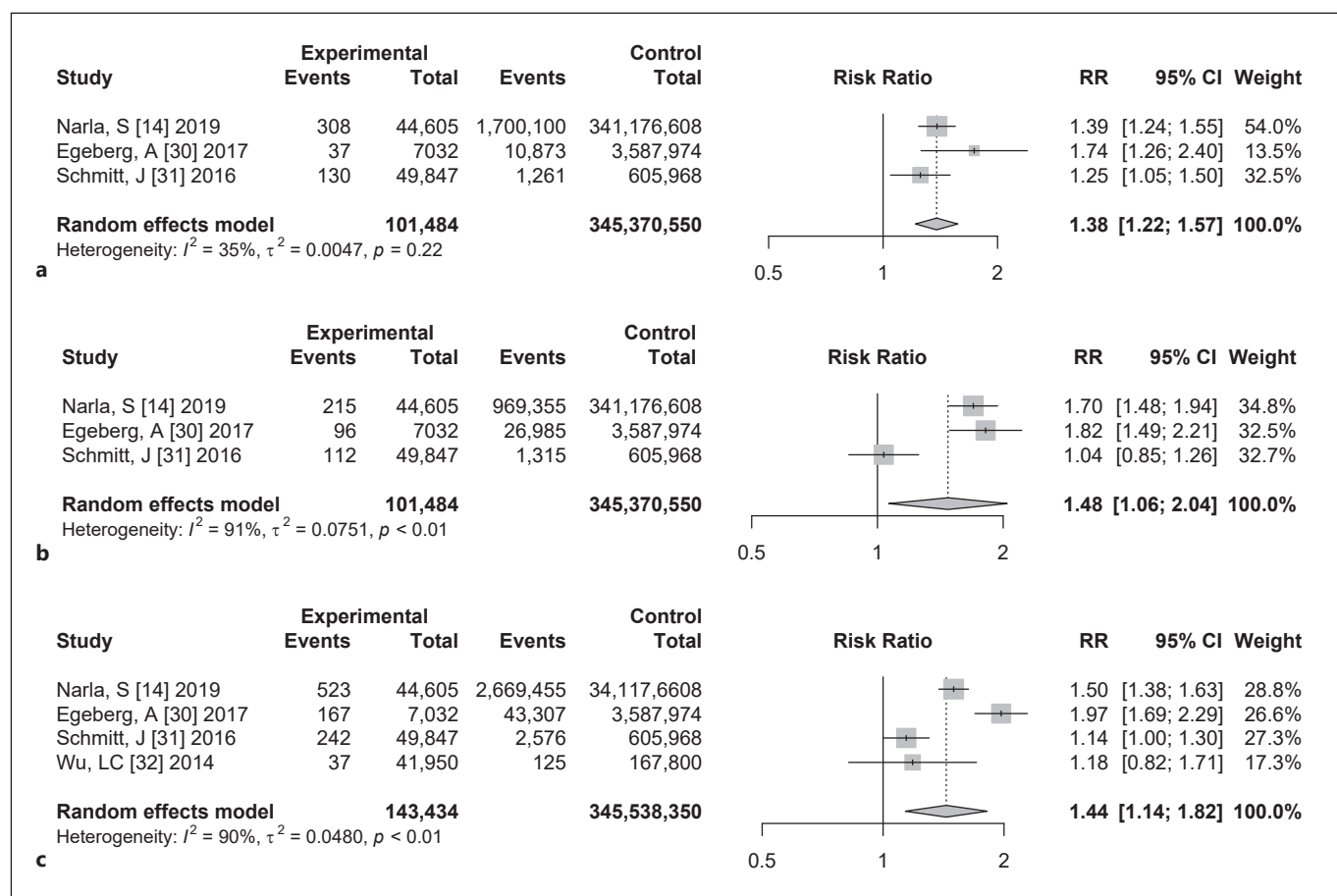


Fig. 3. Forest plot of IBD in patients with AD. The squares indicate individual studies. The diamonds represent pooled effect sizes. The dashed lines represent the 95% CIs. RR, risk ratio. **a** Crohn's disease. **b** Ulcerative colitis. **c** Inflammatory bowel disease.

Discussion

To the best of our knowledge, this study was the first meta-analysis to summarize the bidirectional association between IBD and AD. Our data revealed the relative risks of AD were 1.83-, 2.06-, and 1.66-fold in patients with IBD, CD, and UC compared with control groups, respectively. Compared with non-AD subjects, patients with AD were 44, 38, and 48% more likely to exhibit IBD, CD, and UC, respectively.

Most of the involved studies were rated as high quality based on the Newcastle-Ottawa Scale. Four trials were regarded as moderate risk of bias and primarily result from deficient comparability of cases and controls (no control for confounders) or explicit clinical criteria for IBD or AD [22, 25, 27, 30].

IBD and AD are diseases induced by chronic inflammation, and the resemblances in their pathophysiology may be attributed to genetic abnormalities, aberrant inflammatory responses along with intestinal microbiome-regulated disorders [33]. Primarily, genetic susceptibility loci shared by IBD and AD have been unmasked. Current experimental data suggested that 5 IBD risk loci, which incorporated genes important for adaptive immune regulation (IL1RL1/IL18R1/IL18RAP, RTEL1/TNFRSF6B, STAT3, and IL2/IL21) and tissue response (LRRC32), were significantly associated with AD [31]. Intriguingly, investigators revealed that AD symptoms in BALB/c mice were alleviated by antagonizing C-C motif chemokine receptor 4 (CCR4), which was significantly increased in UC patients, as well [34–36]. Additionally, there are strong signs that C-C motif ligand 17 (CCL17), the chemokine

ligand of CCR4, was a necessary factor to induce colitis in mice [37]. Similarly, a study by Stutte et al. [38] addressed that CCL17 expression was significantly increased in the occurrence of AD. Accordingly, CCR4/CCL17 might be a vital ligament connecting AD and UC with underlying value.

On the other hand, accumulating evidence reported that IBD and AD were commonly accompanied with cytokine abnormalities such as elevated tumor necrosis factor α [24]. Furthermore, absence of short-chain fatty acids (SCFA) was a potential contributing factor of IBD. An analysis of the intestinal microbiome in AD patients found that changes in components of *Faecalibacterium prausnitzii* could result in a decreased level of SCFA, which was shared by IBD [39]. Also, it is indicated from a study in infants that probiotics were temporarily likely to improve symptoms of AD, which was possibly related to the production of SCFA [40].

There are a few limitations worth noting. First, inherent shortcomings of observational studies are inevitable, such as unmeasured confounding factors [21, 22, 27], heterogeneity between different studies, as well as indemonstrable causality between IBD and AD. Second, parts of the enrolled studies are of small size with relatively low methodological quality [22, 27]. Third, it is possible to increase the risk of misdiagnosis of these 2 disorders via simple questionnaires [21, 26, 28]. Ultimately, several cases might be missed as a result of hesitation to seek medical attention among AD patients with milder symptoms [23, 29].

Conclusions

Considered together, our evidence supported a significant bidirectional association between IBD and AD. It is recommended that consultation with medical professionals should be sought when patients with IBD presented with recurrent skin inflammation such as epidermal dryness, itching, redness and roughness, in order to accept the diagnosis and appropriate treatment in the early stage. Equally, patients with AD should also be informed about the increased risk of IBD to obtain an early diagnosis and treatment. Future prospective studies are warranted to explore the underlying mechanisms linking IBD and AD.

Key Message

Our evidence supported a significant bidirectional association between inflammatory bowel disease and atopic dermatitis.

Acknowledgments

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Statement of Ethics

Not applicable (all data are fully available from published articles: no humans are involved in our study).

Disclosure Statement

The authors declare that they have no conflict of interests.

Funding Sources

There are no funding sources to declare.

Author Contributions

X.S. and Q.C. made equivalent contributions to this study. X.S. and Q.C. designed the research, searched the literature; extracted data, evaluated the quality of evidence, and wrote the paper. F.W. made a critical revision of the manuscript for important intellectual content and study supervision.

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