Bidirectional relationship between atopic dermatitis and inflammatory bowel disease: A systematic review and meta-analysis

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Background: Recently, atopic dermatitis has been suggested as a systemic inflammatory disorder that can accompany other inflammatory diseases, including inflammatory bowel disease. However, comprehensive reviews that specifically focus on the association between inflammatory bowel disease and atopic dermatitis are lacking.

Objective: To determine the association between inflammatory bowel disease and atopic dermatitis.

Methods: We searched for relevant studies from MEDLINE, EMBASE, and the Cochrane Library from inception to November 22, 2019. Considering a potential bidirectional relationship, studies reporting inflammatory bowel disease in patients with atopic dermatitis and atopic dermatitis in patients with inflammatory bowel disease were evaluated separately.

Results: We included 10 studies with 95,291,110 patients (4 studies on the prevalence of atopic dermatitis in inflammatory bowel disease, 2 on the prevalence and incidence of inflammatory bowel disease in atopic dermatitis, and 4 on either the prevalence or incidence of inflammatory bowel disease in atopic dermatitis). Meta-analyses revealed a statistically significant association between inflammatory bowel disease and atopic dermatitis in both directions (4 studies on atopic dermatitis prevalence in inflammatory bowel disease, odds ratio 1.39, 95% confidence interval 1.28-1.50; 5 on inflammatory bowel disease prevalence in atopic dermatitis, odds ratio 1.35, 95% confidence interval 1.05-1.73; and 3 studies on inflammatory bowel disease incidence in atopic dermatitis, relative risk 1.46, 95% confidence interval 0.98-2.17).

Limitations: A small number of observational studies were reviewed.

Conclusion: Published literature suggests a bidirectional relationship between inflammatory bowel disease and atopic dermatitis. (J Am Acad Dermatol 2020;83:1385-94.)

Key words: atopic dermatitis; Crohn's disease; inflammatory bowel disease; ulcerative colitis.

INTRODUCTION

Inflammatory bowel disease, which includes ulcerative colitis and Crohn's disease, is a chronic inflammatory disease involving the gastrointestinal tract. Although traditionally regarded as a disease prevalent in Western countries, the global burden of

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Funding sources: Supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2019R1C1C1002243) and Basic Science Research Program through the NRF, funded by the Ministry of Education (NRF-2016R1D1A1B03931961 and NRF-2020R1A1F10666419).

Conflicts of interest: None disclosed.

IRB approval status: Exempted by the IRB of SMG-SNU Boramae Medical Center (07-2020-01).

Accepted for publication May 23, 2020.

Reprints not available from the authors.

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Published online June 1, 2020.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.05.130

this disease is increasing, with an increasing incidence in newly industrialized countries.[1] The pathogenesis of inflammatory bowel disease is still incompletely understood, but the current available evidence highlights an inappropriate immunoresponse to commensal microbes in the intestine as a key factor in the development of inflammatory bowel disease.[2,3] Inflammatory bowel disease and atopic dermatitis, which seem clinically unrelated, have been approached separately for a long time. However, recently, a similar immunodysregulation mechanism of inflammatory bowel disease has been implicated in atopic dermatitis.[4,5] Considering that the skin and the gut represent 2 main barriers that protect the body from harmful exogenous substances, the functional and etiologic similarities between atopic dermatitis and inflammatory bowel disease are not surprising. Physicians should be especially aware of this type of newly found association between the 2 disorders because it may be translated into better patient management. Nevertheless, compared with other studies that reported the clinical relevance of inflammatory bowel disease in relation to other immunomediated skin disorders, such as psoriasis,[6,7] comprehensive epidemiologic understanding of the association between inflammatory bowel disease and atopic dermatitis is still limited. In this study, we sought to review the existing evidence in the literature by performing a systematic review and meta-analysis.

CAPSULE SUMMARY

- Recent evidence has revealed that atopic dermatitis may be a systemic inflammatory disease that can accompany other inflammatory diseases.
- Our systematic review and meta-analysis suggest that there is a bidirectional association between inflammatory bowel disease and atopic dermatitis. A multidisciplinary approach may be required for these patients.

METHODS

A systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses and the Meta-analyses of Observational Studies in Epidemiology guidelines.[8,9] All relevant studies that reported the association between inflammatory bowel disease and atopic dermatitis, in either direction, were planned to be searched. The primary outcomes of interest were the prevalence and incidence as well as the odds and risks (if applicable) of atopic dermatitis in patients with inflammatory bowel disease and vice versa.

Search strategy

MEDLINE (accessed with PubMed), EMBASE, and the Cochrane Library were searched from inception to November 22, 2019, by 2 of the investigators (H.L. and H.P.). An experienced medical librarian helped optimize the search strategy. The search terms (for PubMed) were as follows: (dermatitis, atopic[MeSH Terms] OR atopic dermatit*[Title/Abstract] OR atopic neurodermatit*[Title/Abstract] OR disseminated neurodermatit*[Title/Abstract] OR atopic eczema*[Title/Abstract] OR infantile eczema*[Title/Abstract] OR atopic disease*[Title/Abstract]) AND (inflammatory bowel disease[MeSH Terms] OR enterocolitis [MeSH Terms] OR proctitis [MeSH Terms] OR ileitis [MeSH Terms] OR inflammatory bowel disease*[Title/Abstract] OR ulcerative colit* [Title/Abstract] OR crohn* [Title/Abstract] OR enterocolit*[Title/Abstract] OR proctit* [Title/Abstract] OR ileit* [Title/Abstract]).

Study selection

Studies were selected according to the following inclusion criteria: (1) observational studies examining the association between atopic dermatitis and inflammatory bowel disease, including cross-sectional studies, prospective or retrospective cohort studies, and case-control studies; (2) participants of all age groups and both sexes; (3) reports of prevalence or incidence of atopic dermatitis in inflammatory bowel disease, and vice versa, or presence of sufficient information to estimate the crude odds ratio (OR) or relative risk (RR); (4) atopic dermatitis diagnosed and evaluated clinically or through medical database, survey, or questionnaire; (5) inflammatory bowel disease diagnosed and evaluated clinically or histologically (with endoscopy and biopsy), or through medical database, survey, or questionnaire; (6) published from inception to November 22, 2019, with any study period; and (7) published in English and based on human subjects. Exclusion criteria were as follows: duplicate publications; the use of an umbrella term "eczema" for the study group, without clearly defining it as atopic dermatitis or distinguishing it from other skin disorders; and conference proceedings, case reports ($n < 10$), reviews, or unpublished studies.

Data extraction

Two investigators (H.L. and H.P.) independently screened the titles and abstracts of the relevant articles. A full-text evaluation was performed to determine eligibility if the abstract did not provide enough information. The reference lists of the identified articles were

manually screened for additional relevant studies. Then, both investigators independently extracted relevant details from the selected studies, including country, study setting, study period, incidence or prevalence of inflammatory bowel disease or atopic dermatitis, age, and sex. Any discrepancy was resolved through discussion among the 3 investigators (H. L., S.-J.K., and H. P.). The study design was evaluated and reclassified according to the Design Algorithm for Medical Literature on Intervention for classifying study designs,[10] regardless of the author-reported study designs, because there can be substantial misclassification, especially in observational studies.[11]

Meta-analysis

Separate meta-analyses were conducted for the prevalence of atopic dermatitis in inflammatory bowel disease, the prevalence of inflammatory bowel disease in atopic dermatitis, and the incidence of inflammatory bowel disease in atopic dermatitis. For the studies that reported the prevalence of either disease, a pooled OR with 95% confidence interval (CI) was calculated. For the incidence of inflammatory bowel disease, a pooled RR with 95% CI was calculated. Moreover, subgroup meta-analyses were conducted for ulcerative colitis and Crohn's disease separately. The selected studies were evaluated by the Newcastle-Ottawa Scale.[12] For cross-sectional studies, an adapted form of the Newcastle-Ottawa cohort scale for cross-sectional studies was used.[13] Statistical heterogeneity was calculated with I^2 statistics, and a random-effects model was used to account for study heterogeneity. The statistical analysis was performed with R statistical software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Search results and description of the included studies

After a comprehensive database search, a total of 29 studies were assessed (the full text) for eligibility (Fig 1). Finally, 10 studies with a total of 95,291,110

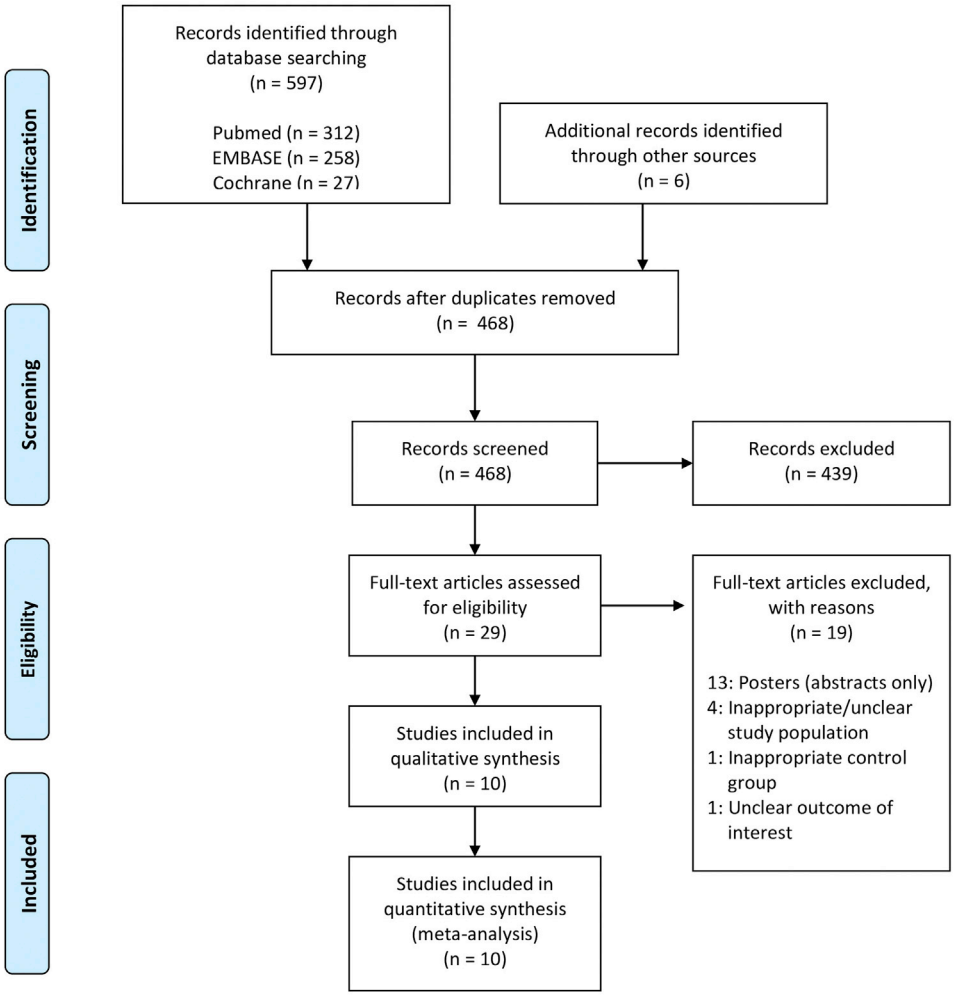

Fig 1. Flow diagram of the included reports.

Table I. Characteristics of the studies included in the systematic review and meta-analysis

						Study population				Control			
Study	Year	Country	Setting	Study design	Study period	Total, n	Events, n	Mean age (range), y	Male ratio, %	Total, n	Events, n	Mean age (range), y	Male ratio, %
Prevalence of AD in patients with IBD													
Wasielewska et al	2019	Poland	Hospital	Cross-sectional study	2015-2016	60 (UC 24, CD 36)	13 (21.7%; UC 7, 29%; CD 6, 17%)	14.72 (4.75—19.25)	58	60	8 (13.3%)	14.85 (6.58—18.71)	43
Kim et al	2017	South Korea	Population	Cross-sectional study	2009-2013	40,843 (UC 28,197, CD 12,646)	826 (2.0%; UC 512, 1.8%; CD 314, 2.5%)	41.2 (NS)	60.2	122,529	1,827 (1.5%)	41.2 (NS)	60.2
Boneberger et al	2012	Chile	Hospital	Cross-sectional study‡	2009-2010	UC 52	10 (19.2%)	27.4 (6—45)	44	174	29 (16.7%)	26.2 (NS)	33
Myrelid et al	2004	Sweden	Population	Cross-sectional study‡	2000	CD 278	72 (25.8%)	NS	NS	738	121 (16.4%)	NS	NS
Prevalence of IBD in patients with AD													
Krishna et al*	2019	United Kingdom	Population	Cohort study	1990-2018	1,393,570	7,848 (0.56%)	29.8 (NS)	45.9	2,170,618	9,537 (0.44%)	32.7 (NS)	46.2
Narla et al†	2019	United States	Population	Cross-sectional study	2002-2012	19,486	133 (0.68%; UC 58, CD 75)	NS	NS	87,033,669	578,588 (0.66%; UC 210,640, CD 367,948)	NS	NS
Egeberg et al*	2017	Denmark	Population	Cohort study	2008-2012	7,032	167 (2.4%; UC 96, CD 37, unspecified 34)	45.5 (NS)	35.5	3,587,974	43,307 (1.3%; UC 26,985, CD 10,873, unspecified 5,449)	54.0 (NS)	48.9
Wu et al	2014	Taiwan	Population	Cross-sectional study‡	1997-2010	41,950	37 (0.09%)	34.71 (NS)	45.7	167,800	125 (0.07%)	34.70 (NS)	45.7
Niwa et al	2004	Japan	Hospital	Cross-sectional study‡	1992-2003	47,862	118 (0.25%; UC 112, CD 6)	NS	53.3	600	0	NS	50.0
Incidence of IBD in patients with AD													
Krishna et al*	2019	United Kingdom	Population	Cohort study	1990-2018	1,393,570	3,512 (0.25%)	29.8 (NS)	45.9	2,170,618	2,876 (0.13%)	32.7 (NS)	46.2

Egeberg et al*	2017	Denmark	Population	Cohort study	2008-2012	7,032	33 (0.47%; UC 22, CD 8, unspecified 3)	45.5 (NS)	35.5	3,587,974	11,919 (0.33%; UC 8,232, CD 2,991, unspecified 696)	54.0 (NS)	48.9
Schmitt et al	2016	Germany	Population	Cohort study	2005-2011	49,847	242 (0.49%; UC 112, CD 130)	NS	31.4	605,968	2,576 (0.44%; UC 1,315, CD 1,261)	NS	51.2

AD, Atopic dermatitis; *CD*, Crohn's disease; *IBD*, inflammatory bowel disease; *NS*, not specified; *UC*, ulcerative colitis.
†The study design was evaluated and reclassified according to the Design Algorithm for Medical Literature on Intervention for classifying study designs regardless of the author-reported study designs.
*These studies reported both the baseline prevalence and incidence of inflammatory bowel disease in patients with atopic dermatitis.
†The missing crude numbers were estimated with the given data in the study.

patients were included (Table I).[14-23] Seven studies were population based and 3 were hospital based. Six studies were conducted in Europe, 3 in East Asia, and 1 in the United States. Four studies reported the prevalence of atopic dermatitis in patients with inflammatory bowel disease.[14-17] Two studies reported both the prevalence and incidence of inflammatory bowel disease in patients with atopic dermatitis.[18,19] The remaining 4 studies reported either the prevalence or incidence of inflammatory bowel disease in patients with atopic dermatitis.[20-23] We did not find any study that reported the incidence of atopic dermatitis in patients with inflammatory bowel disease. The risks of bias of the selected studies are reported in Table II.

Prevalence of atopic dermatitis in patients with inflammatory bowel disease

Among the 4 cross-sectional studies regarding the prevalence of atopic dermatitis in inflammatory bowel disease, 2 failed to demonstrate a statistically significant association between the 2 disease entities,[14,16] whereas the other 2 revealed increased odds of atopic dermatitis in association with inflammatory bowel disease.[15,17] Three of these 4 studies reported adjusted ORs,[15-17] whereas the other study provided only a crude OR.[14] The ORs were adjusted for different sets of parameters, and the difference between the crude OR and adjusted OR in each applicable study was minimal. Because the 4 studies all provided raw data and there was a lack of uniformity among the adjusted ORs, we pooled a crude OR to evaluate the overall odds of atopic dermatitis in inflammatory bowel disease. The meta-analysis revealed a synthesized OR of 1.39 (95% CI 1.28-1.50) (Fig 2, *A*). There was minimal statistical heterogeneity (I^2 = 0%; P = .43).

Prevalence of inflammatory bowel disease in patients with atopic dermatitis

In total, 5 studies reported the prevalence of inflammatory bowel disease in patients with atopic dermatitis.[18-20,22,23] A cross-sectional study conducted in Japan did not show a statistically significant association between inflammatory bowel disease and atopic dermatitis.[20] The study claimed that the patients with atopic dermatitis had increased odds of ulcerative colitis compared with the Japanese population, but the population data were not provided in detail. A cross-sectional study conducted in Taiwan also failed to show a significant association between the 2 disease entities.[22] Another cross-sectional study that was conducted in the Unites States reported a meaningful association between atopic dermatitis and inflammatory bowel disease in

Table II. Risk of bias assessed with the Newcastle-Ottawa Scale

Study	Study design	Representativeness of the samples	Sample size	Nonrespondents	Ascertainment of exposure*	Comparability of cross-sectional studies*	Assessment of outcome*	Statistical test
Narla et al 2019	Cross-sectional study	+	+	+	+	+	+	+
Wasielewska et al 2019	Cross-sectional study	+	−	+	+	+	+	+
Kim et al 2017	Cross-sectional study	+	+	+	+	+	+	+
Wu et al 2014	Cross-sectional study	+	+	+	+	+	+	+
Boneberger et al 2012	Cross-sectional study	+	−	−	+	+	+	+
Myrelid et al 2004	Cross-sectional study	+	+	+	+	+	+	+
Niwa et al 2004	Cross-sectional study	+	−	−	+	+	+	+

Study	Study design	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts*	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts
Krishna et al 2019	Cohort study	+	+	+	+	+	+	+	+
Egeberg et al 2017	Cohort study	+	+	+	+	+	+	+	+
Schmitt et al 2016	Cohort study	+	+	+	+	+	+	+	+

+, Low risk of bias; −, high risk of bias.
*These criteria were evaluated as either satisfactory (1 point or more) or nonsatisfactory instead of having 2 or 3 maximum points.

adults and a significant crude association between atopic dermatitis and ulcerative colitis in children.[23] However, the combined data from the 2 age groups that were analyzed for our meta-analysis showed increased, but not statistically significant, odds of prevalent inflammatory bowel disease. Two cohort studies, which reported the baseline prevalence of inflammatory bowel disease, in addition to the incident inflammatory bowel disease, showed a statistically significant association between inflammatory bowel disease and atopic dermatitis.[18,19] The meta-analysis was conducted on these 5 studies, and the synthesized OR was 1.35 (95% CI 1.05-1.73), with high interstudy heterogeneity (I^2 = 89%; $P < .01$) (Fig 2, *B*).

Incidence of inflammatory bowel disease in patients with atopic dermatitis

Three cohort studies reported the incident inflammatory bowel disease in patients with atopic dermatitis.[18,19,21] Each of these 3 studies evaluated the risk of inflammatory bowel disease differently, according to a rate ratio, hazard ratio, and RR, respectively. However, because all the studies also reported raw numbers of incidents, we could calculate a pooled RR. The meta-analysis revealed a synthesized RR of 1.46 (95% CI 0.98-2.17) (Fig 2, *C*). Again, high interstudy heterogeneity was observed (I^2 = 96%; $P < .01$).

Subgroup analyses on ulcerative colitis and Crohn's disease

Except for the 2 studies[18,22] that provided only the number of patients with inflammatory bowel disease as a whole, the remaining 8 of the 10 included studies reported the number with Crohn's disease as well as the number with ulcerative colitis, in addition to the number with inflammatory bowel disease; 2 of these studies had study populations consisting of patients with only ulcerative colitis or Crohn's disease.[16,17] Subgroup meta-analyses showed that ulcerative colitis also has a bidirectional association with atopic dermatitis, with increased odds of atopic dermatitis in ulcerative colitis (OR 1.23; 95% CI 1.11-1.35) and increased odds of ulcerative colitis in atopic dermatitis (OR 1.53; 95% CI 1.07-2.18) (Fig 3, *A* and *B*). An increased risk of ulcerative colitis in atopic dermatitis was not statistically significant (RR 1.11; 95% CI 0.88-1.41) (Fig 3, *C*). The other set of subgroup meta-analyses revealed increased odds of atopic dermatitis in Crohn's disease (OR 1.69; 95% CI 1.51-1.89), but the odds of Crohn's disease in atopic dermatitis were not statistically significant (OR 1.14; 95% CI 0.60-2.15) (Fig 3, *D* and *E*). The risk of

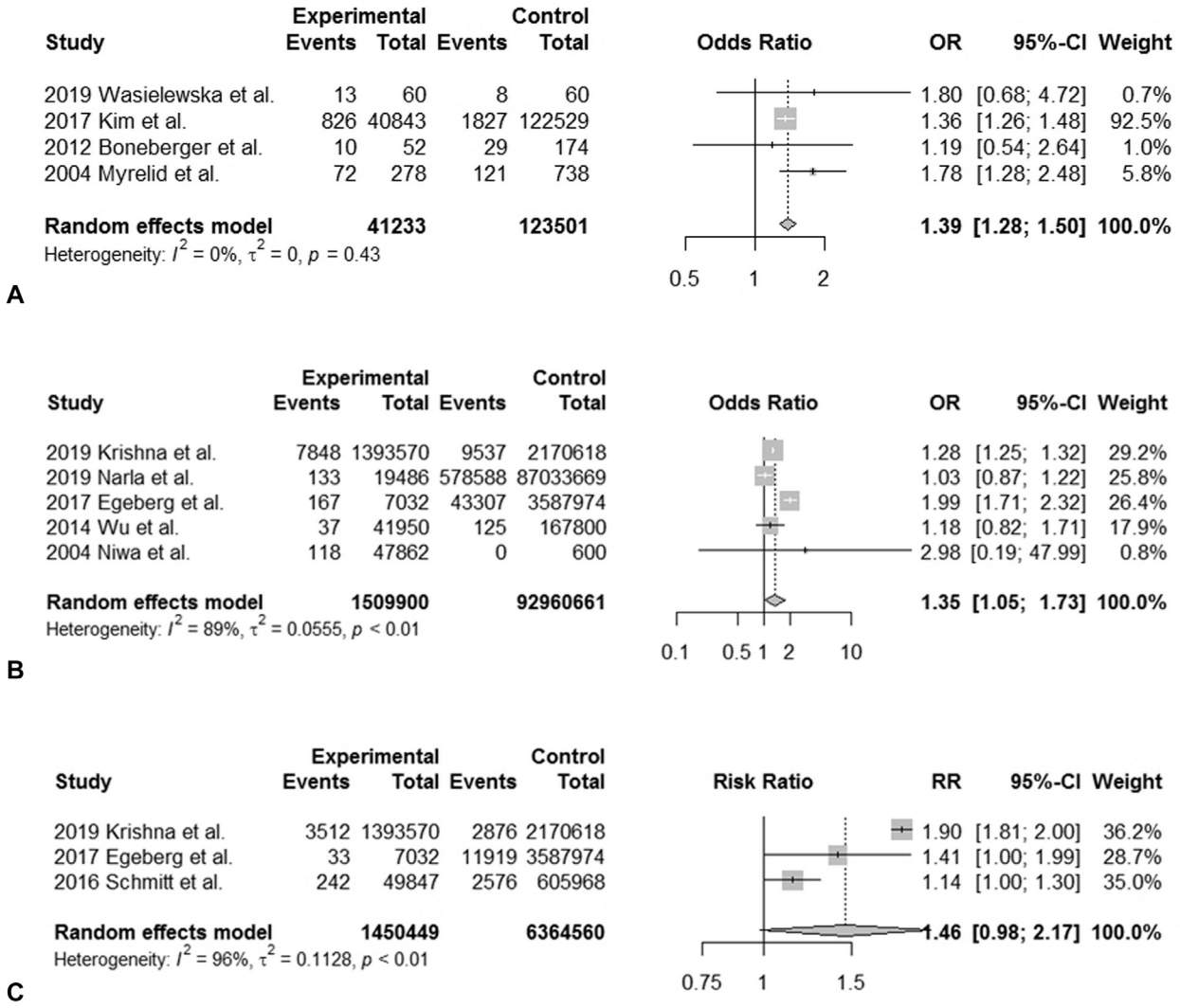

Fig 2. Forest plots assessing the prevalence of atopic dermatitis in inflammatory bowel disease (**A**), prevalence of inflammatory bowel disease in atopic dermatitis (**B**), and incidence of inflammatory bowel disease in atopic dermatitis (**C**). *CI*, Confidence interval; *OR*, odds ratio; *RR*, relative risk.

Crohn's disease in atopic dermatitis was significant, with an RR of 1.26 (95% CI 1.06-1.50) (Fig 3, *F*).

DISCUSSION

Atopic dermatitis has long been considered simply a chronic inflammatory disease that predominantly affects the skin. However, evidence has been obtained that it may be a systemic inflammatory disease and can accompany various other systemic diseases, including inflammatory bowel disease, autoimmune diseases, and metabolic diseases.[24] In comparison, inflammatory bowel disease is well known for its extraintestinal manifestations, which are common in both Crohn's disease and ulcerative colitis.[25] Especially cutaneous manifestations, such as erythema nodosum and pyoderma gangrenosum, are commonly found in patients with inflammatory bowel disease; psoriasis may also occur.[26,27] The association between inflammatory bowel disease and allergic diseases has been recognized only recently. Few recent studies have investigated the co-occurrence of asthma and inflammatory bowel disease[28] or atopic dermatitis and autoimmune disease.[29] The recent meta-analysis by Shi et al[30] also suggested an association between atopic dermatitis and inflammatory bowel disease. Although the study is valuable and noteworthy, the authors used the concepts of prevalence and incidence interchangeably in their meta-analysis. Furthermore, it appears that their analysis included studies that used a

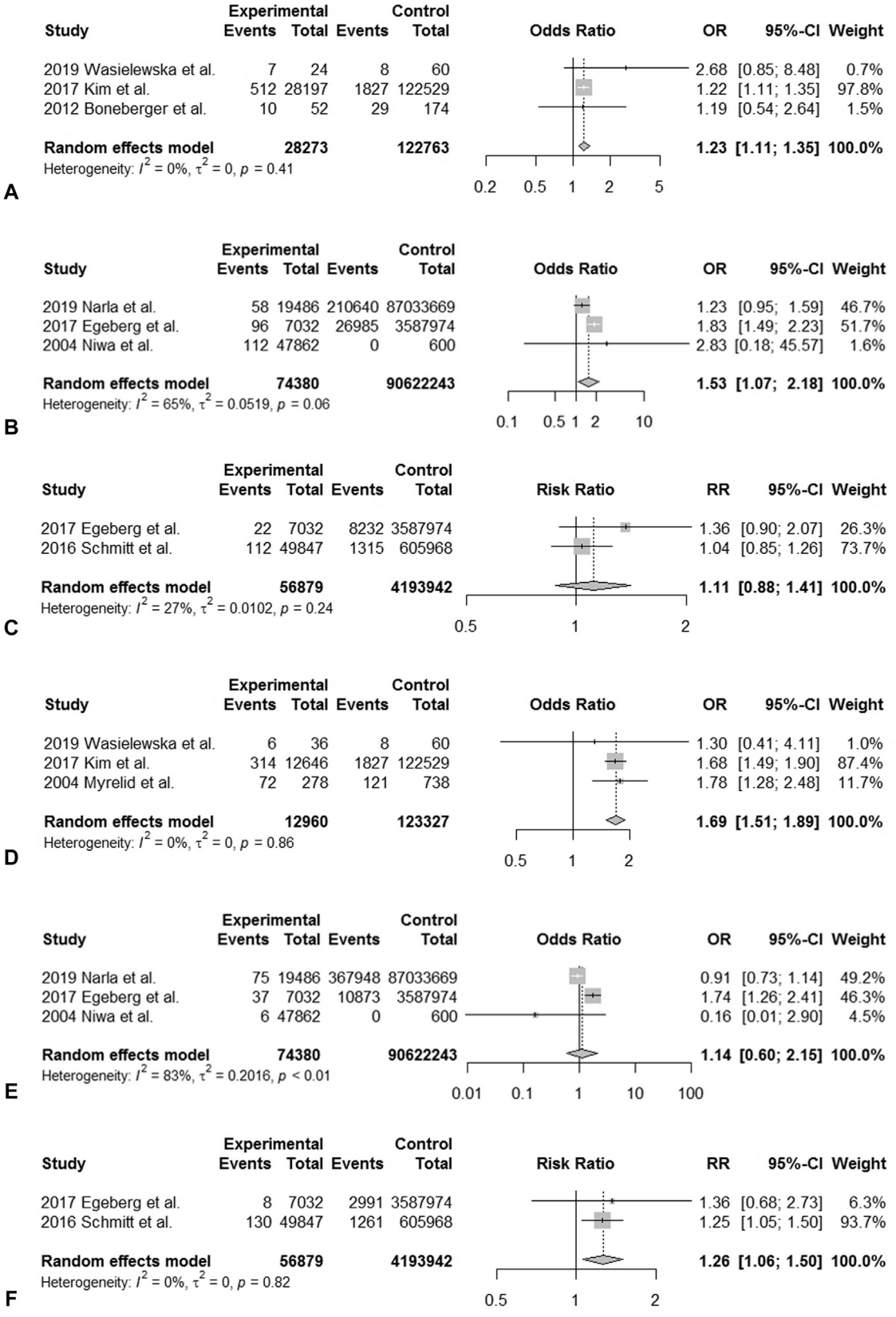

Fig 3. Forest plots assessing the prevalence of atopic dermatitis in ulcerative colitis (**A**), prevalence of ulcerative colitis in atopic dermatitis (**B**), incidence of ulcerative colitis in atopic dermatitis (**C**), prevalence of atopic dermatitis in Crohn's disease (**D**), prevalence of Crohn's disease in atopic dermatitis (**E**), and incidence of Crohn's disease in atopic dermatitis (**F**). *CI*, Confidence interval; *OR*, odds ratio; *RR*, relative risk.

general umbrella term "eczema" for the study group without clearly defining it as atopic dermatitis, which should be distinguished from other broad ranges of eczematous skin disorders. Overall, there is a lack of comprehensive reviews that specifically focus on the association between atopic dermatitis and inflammatory bowel disease.

Our meta-analysis demonstrated a bidirectional association between atopic dermatitis and inflammatory bowel disease. Synthesized ORs based on the prevalence of atopic dermatitis in inflammatory bowel disease, and vice versa, were statistically meaningful. Subgroup analyses were also conducted for the 2 subtypes of inflammatory bowel disease. The meta-analyses on patients with ulcerative colitis showed a bidirectional association between the 2 disease entities. In contrast, the association between Crohn's disease and atopic dermatitis was confirmed only from the pooled odds of atopic dermatitis in Crohn's disease, but not vice versa. Overall, the subgroup analysis also supports the general association between atopic dermatitis and inflammatory bowel disease. The lower heterogeneity found in the subgroup meta-analyses compared with the main meta-analysis between atopic dermatitis and inflammatory bowel disease indicates that there might be a considerable difference between ulcerative colitis and Crohn's disease in terms of their specific associations with atopic dermatitis. However, considering the small number of included studies, our overall findings must be interpreted with caution.

The identified association between atopic dermatitis and inflammatory bowel disease can be explained by the shared pathogenesis of the 2 diseases. First, many of the genes that confer risk of atopic dermatitis *(IL1RL1, IL18R1, IL18RAP, ADAD1, KIAA1109, LRRC32, STAT3, RTEL1, ZGPAT, SLC9A4, IL13, C11orf30, TNFRSF6B,* and *IL2/IL21)* are also implicated in inflammatory bowel disease[31]; the shared genetic risk may contribute to the comorbidity of atopic dermatitis and inflammatory bowel disease. Second, atopic dermatitis and inflammatory bowel disease are disorders implicated in a disturbed barrier function, which may lead to an aberrant interface permeability, passage of pathogens, and subsequent inflammation. Third, recent studies highlight that inability to maintain a homeostatic relationship with the microbiota is strongly implicated in the pathogenesis of both inflammatory bowel disease and atopic dermatitis.[32-34] Fourth, they may share similar immunodysregulation mechanisms. Although the pathogenesis of atopic dermatitis is strongly correlated with the T helper cell type 2 immune pathway, increasing evidence suggests that T helper cell types 1, 17, and 22 also play a considerable role.[35,36] Similarly, whereas inflammatory bowel disease is a mixture of T helper cell type 1– and T helper cell type 2–mediated disorders, interleukin 17 and 22 are also recognized in the pathogenesis of inflammatory bowel disease.[37] Fifth, they may share predisposing environmental factors, such as an urban lifestyle, obesity, reduced breastfeeding, or stress. In summary, clinicians should be aware of a potential bidirectional relationship between these 2 disease entities. A multidisciplinary approach may be required for patients with atopic dermatitis who present with bowel symptoms, or vice versa, and therapeutic options beneficial for both diseases may be primarily considered.

LIMITATIONS

Our study has some limitations. First, there were only a small number of studies that focused on the association between inflammatory bowel disease and atopic dermatitis. Second, there was considerable interstudy heterogeneity in terms of age, sex, and the ratio between ulcerative colitis and Crohn's disease. Third, there might be some diagnostic discrepancies among the included studies, and selection and reporting biases are possible. Fourth, the chronologic sequence between inflammatory bowel disease and atopic dermatitis is unclear because most of the data used in the meta-analyses were the cross-sectional prevalence of each disease. Despite the limitations, we believe that our study is meaningful because it provides a comprehensive review of the existing evidence on the association between inflammatory bowel disease and atopic dermatitis in the published literature to date. Although only a small number of studies were included in this meta-analysis, the association was statistically significant in both directions and the population-based studies with large numbers of subjects supported the same conclusion.

CONCLUSION

Our meta-analysis suggests that there is a bidirectional relationship between inflammatory bowel disease and atopic dermatitis. This pooled epidemiologic evidence is reasonable and logical, considering the shared immunologic pathways between the 2 diseases emphasized in the recent studies. Further data with more well-controlled, population-based studies are warranted to confirm our findings.

We would like to thank Professor Pär Myrelid, MD, PhD, for providing supplementary data regarding his study, Eunsun Park for helping us optimize the literature search process, and Jungyoon Ohn, MD, for helping us classify the study design. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2019R1C1C1002243) and

Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2016R1D1A1B03931961 and NRF-2020R1A1F10666419).

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