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Association of Psoriasis With Inflammatory Bowel Disease
A Systematic Review and Meta-analysis

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IMPORTANCE Patients with psoriasis may experience comorbidities involving cardiovascular diseases, chronic kidney disease, uveitis, psychiatric disturbances, and metabolic syndrome. However, the association between psoriasis and inflammatory bowel disease (IBD) has been largely unclear.

OBJECTIVE To investigate the association of psoriasis with IBD.

DATA SOURCES For this systematic review and meta-analysis, MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched for relevant studies from inception to January 17, 2018.

STUDY SELECTION Case-control, cross-sectional, or cohort studies that examined either the odds or risk of IBD in patients with psoriasis were included. No geographic or language limitations were used in the search.

DATA EXTRACTION AND SYNTHESIS The PRISMA and MOOSE guidelines were followed for data extraction. The Newcastle-Ottawa Scale was used to evaluate the risk of bias of included studies. Crohn disease and ulcerative colitis were analyzed separately and random-effects model meta-analysis was conducted. A subgroup analysis was performed on psoriatic arthritis.

MAIN OUTCOMES AND MEASURES The risk and odds of IBD, Crohn disease, and ulcerative colitis in patients with psoriasis.

RESULTS A total of 5 case-control or cross-sectional studies and 4 cohort studies with 7 794 087 study participants were included. Significant associations were found between psoriasis and Crohn disease (odds ratio, 1.70; 95% CI, 1.20-2.40) and between psoriasis and ulcerative colitis (odds ratio, 1.75; 95% CI, 1.49-2.05). Patients with psoriasis had an increased risk of Crohn disease (risk ratio, 2.53; 95% CI, 1.65-3.89) and ulcerative colitis (risk ratio, 1.71; 95% CI, 1.55-1.89).

CONCLUSIONS AND RELEVANCE These findings suggest that psoriasis is significantly associated with IBD. Gastroenterology consultation may be indicated when patients with psoriasis present with bowel symptoms.

Supplemental content

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Psoriasis is a chronic systemic immune-mediated disorder affecting approximately 0.5% to 11.4% of adults and approximately 1.4% of children worldwide.[1,2] Psoriasis has been characterized by sharply demarcated erythematous scaling plaques with a typical relapsing and remitting course.[3,4] Even with proper treatments, psoriasis can only be controlled but cannot be cured.[5] Genetic and environmental factors are considered involved in the possible causes of psoriasis.[6] Previous genome-based analysis revealed that specific genes (eg, *PSORS1* [OMIM 177900], *IL12B* [OMIM 161561], and *IL23R* [OMIM 607562]) are predisposing factors for psoriasis.[7] Psoriasis has been linked with a variety of comorbidities including cardiovascular diseases, chronic kidney disease, uveitis, psychiatric disturbances, and metabolic syndrome and its relevant components (obesity, hypertension, dyslipidemia, and type 1 and 2 diabetes), resulting in impaired quality of life and shortening of life expectancy.[8-18]

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disease of the gastrointestinal tract that requires long-term management.[19] Crohn disease (CD) and ulcerative colitis (UC) are the 2 main forms of IBD.[20] During the past 2 decades, the incidence of IBD has increased in developing countries, with an annual increase of 11.1% for CD and an annual increase of 14.9% for UC.[21] Accumulating evidence indicates that genetic susceptibility may play an essential role in the dysregulated inflammatory reaction of IBD.[22,23] Crohn disease frequently causes the infiltration and destruction of all intestinal wall layers along the digestive tract, while UC primarily involves the colon and rectum, with mucosal and submucosal invasion.[24] Patients with IBD often experience recurrent loss of appetite, vomiting, diarrhea, abdominal pain, rectal bleeding, and body weight loss.[25-27]

Previous studies have shown common genotypes, clinical course, and immunologic features shared by psoriasis and IBD.[7] Genetic correlation between psoriasis and IBD, including chromosomal locus 6p21 and the *IL23R* and *IL12B* genes, has been identified.[7,28-30] As to the shared immunologic features, increased levels of IL-17 were found in both IBD and psoriasis.[31-33] However, the association between psoriasis and IBD was largely unclear. In this study, we aimed to systematically analyze the association of psoriasis with IBD.

Key Points

Question Is there an association between psoriasis and inflammatory bowel disease?

Findings This meta-analysis included 5 case-control or cross-sectional studies with 1 826 677 individuals; patients with psoriasis had 1.70-fold increased odds of Crohn disease and 1.75-fold increased odds for ulcerative colitis. The meta-analysis also included 4 cohort studies with 5 967 410 individuals; patients with psoriasis had a 2.53-fold increased risk of developing Crohn disease and a 1.71-fold increased risk of developing ulcerative colitis.

Meaning Psoriasis appears to be associated with inflammatory bowel disease; gastroenterology consultation may be indicated when patients with psoriasis present with bowel symptoms.

Methods

We conducted a systematic review and meta-analysis of observational studies (including case-control, cross-sectional, and cohort studies) on the association of psoriasis with IBD. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[34] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[35]

Literature Search

We searched MEDLINE, the Cochrane Central Register of Controlled Trials, and Embase from inception to January 17, 2018, for relevant studies. The search strategy is shown in the eTable in the Supplement. No language or geographic restrictions were imposed.

Study Selection

We included studies that met the following inclusion criteria: (1) observational studies examining the association of psoriasis with IBD, including cross-sectional, case-control, or cohort studies; (2) the study participants were humans; and (3) the case group was composed of patients with psoriasis and the control group was composed of individuals without psoriasis. Two of us (Y.F. and C.-H.L.) independently screened the search results and assessed their eligibility by scanning the titles and abstracts of citations. We checked the full text of potentially eligible studies and included studies that met the inclusion criteria. Disagreement was resolved by consulting another one of us (C.-C.C.).

Data Extraction and Risk of Bias Assessment

The following data were extracted from the included studies: first author, year of publication, country, study design, and quantitative estimates including odds ratio (OR) and risk ratio (RR) with 95% CIs on the association of psoriasis with IBD. We used the Newcastle-Ottawa Scale to assess the risk of bias of included studies.[36] The following 8 domains were evaluated for included case-control studies: adequacy of case definition, representativeness of cases, selection of controls, definition of controls, comparability of cases and controls, ascertainment of exposure, same method of ascertainment for cases and controls, and nonresponse rate. The following 8 domains were evaluated for included cohort studies: the representativeness of exposed cohort, selection of nonexposed cohort, ascertainment of exposure, outcome of the interest not present at start of study, comparability of cohorts, assessment of outcome, follow-up duration, and adequacy of follow up of cohorts.

Statistical Analysis

All analyses were conducted by using the Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration). We calculated the pooled OR with 95% CI for included case-control and cross-sectional studies, and calculated the pooled RR with 95% CI for included cohort studies. If

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there were multiple risk estimates provided in the study report, we adopted the risk estimates with the most adjusted confounders. The statistical heterogeneity across the included studies was assessed by using the I^2 statistic. We considered an I^2 of greater than 50% to represent substantial heterogeneity. We adopted the random-effects model in conducting meta-analyses as we anticipated clinical heterogeneity. We conducted a subgroup analysis on patients with psoriatic arthritis.

Results

Characteristic of Included Studies

The PRISMA study flowchart is shown in **Figure 1**. Our search identified 1109 records after removing duplicates. After scanning the titles and abstracts, 1083 citations were excluded. After examining the full text, 5 case-control or cross-sectional studies and 4 cohort studies with a total of 7 794 087 study participants were included in this study.[37-45] The characteristics of the included case-control or cross-sectional studies are listed in **Table 1**,[37-40,43] and the characteristics of the cohort studies are listed in **Table 2**.[41,42,44,45]

Risk of Bias of Included Studies

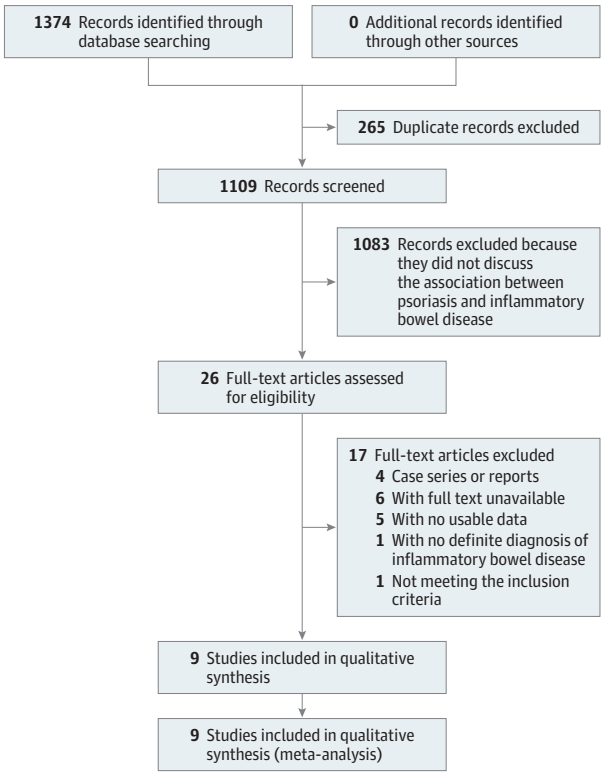
The risk of bias of included case-control and cohort studies was summarized in **Figure 2**[37-45] and **Figure 3**.[37-45] Of 5 included case-control studies, 4 studies were rated with unclear risk in the domains of adequacy of case definition and ascertainment of exposure domains.[38-40,43] The main reason for an unclear risk in the adequacy of case definition domain was that most studies defined the case group by using corresponding *International Classification of Diseases* diagnosis codes. Moreover, the reason for an unclear risk of bias in the ascertainment of exposure domain was that most studies used the medical record as their only reference for ascertainment of exposure. We rated the study by Augustin et al[38] at high risk in the comparability of cases and controls domain because there was no controlling for confounders. All 4 included cohort studies were rated at low risk of bias in the adequacy of follow-up of cohorts domain, as the length of follow-up exceeded 1 year in all 4 studies.[41,42,44,45] We rated the study by Li et al[41] at high risk in the domain of representativeness of exposed cohort because the study participants were from a specific group limited to nurses. We also rated the study by Manos et al[44] at high risk of bias in the domain of outcome of the interest not present at start of the study because the study did not report relevant information.

Association of Psoriasis With IBD

Except for the study by Tsai et al,[39] all of the other 4 case-control studies demonstrated an increased odds of CD in association with psoriasis.[37,38,40,43] We identified substantial statistical heterogeneity across these 5 studies (I^2 = 92%). As shown in Figure 3A,[37-40,43] the meta-analysis illustrates a significant association of psoriasis with CD (pooled OR, 1.70; 95% CI, 1.20-2.40).

Four included case-control studies provided data regarding the association of psoriasis with UC.[37,38,40,43] Significant statistical heterogeneity was identified across the 4 studies (I^2 = 54%). As illustrated in Figure 3B,[37,38,40,43] the meta-analysis revealed a significant association of psoriasis with UC (pooled OR, 1.75; 95% CI, 1.49-2.05).

Figure 1. PRISMA Study Flowchart



All 4 included cohort studies illustrated an increased risk of CD and UC in patients with psoriasis.[41,42,44,45] The meta-analysis revealed that patients with psoriasis had a significantly increased risk of CD (pooled RR, 2.53; 95% CI, 1.65-3.89) (Figure 3C)[41,42,44,45] and UC (pooled RR, 1.71; 95% CI, 1.55-1.89) (Figure 3D).[41,42,44,45] Substantial statistical heterogeneity was found in the risk estimate for CD (I^2 = 55%) (Figure 3C)[41,42,44,45] but not for UC (I^2 = 0%) (Figure 3D).[41,42,44,45]

Subgroup Analysis on Patients With Psoriatic Arthritis

One case-control study and 2 cohort studies investigated the association of psoriatic arthritis with CD and UC.[43-45] The case-control study found significant associations of psoriatic arthritis with CD (OR, 2.20; 95% CI, 1.59-3.03) and UC (OR, 1.91; 95% CI, 1.21-3.00).[43] As illustrated in Figure 3E,[44,45] the meta-analysis on the 2 cohort studies demonstrated a significantly increased risk of CD (RR, 2.74; 95% CI, 1.41-5.32; I^2 = 0%) and a nonsignificant increase in the risk of UC (RR, 1.74; 95% CI, 0.72-4.17; I^2 = 34%) in patients with psoriatic arthritis.

Discussion

To our knowledge, this study is the first meta-analysis to examine the association of psoriasis with IBD. We found that

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Table 1. Characteristics of Included Case-Control and Cross-Sectional Studies

Source	Study Design	Case Group	Control Group	OR (95% CI)	
				Crohn Disease	Ulcerative Colitis
Cohen et al,[37] 2009	Case-control	12 502 Patients with psoriasis (6516 males and 5986 females)	24 285 Age- and sex-matched controls (12 197 males and 12 088 females)	2.49 (1.71-3.62)	1.64 (1.15-2.33)
Tsai et al,[39] 2011	Case-control	51 800 Patients with psoriasis (31 923 males and 19 877 females)	207 200 Controls matched for age, sex, and urbanization level of residential area	0.70 (0.52-0.94)	NA
Augustin et al,[38] 2010	Cross-sectional	33 981 Patients with psoriasis	1 310 090 Healthy controls	2.06 (1.83-2.31)	1.95 (1.76-2.17)
Zohar et al,[43] 2016	Case-control	3161 Patients with psoriatic arthritis	31 610 Age- and sex-matched randomly selected patients	2.20 (1.59-3.03)	1.91 (1.21-3.00)
Wu et al,[40] 2012	Case-control	25 341 Patients with ≥2 diagnosis codes for any psoriatic disease	126 705 Controls matched for age, sex, and length of enrollment	1.80 (1.50-2.16)	1.53 (1.30-1.80)

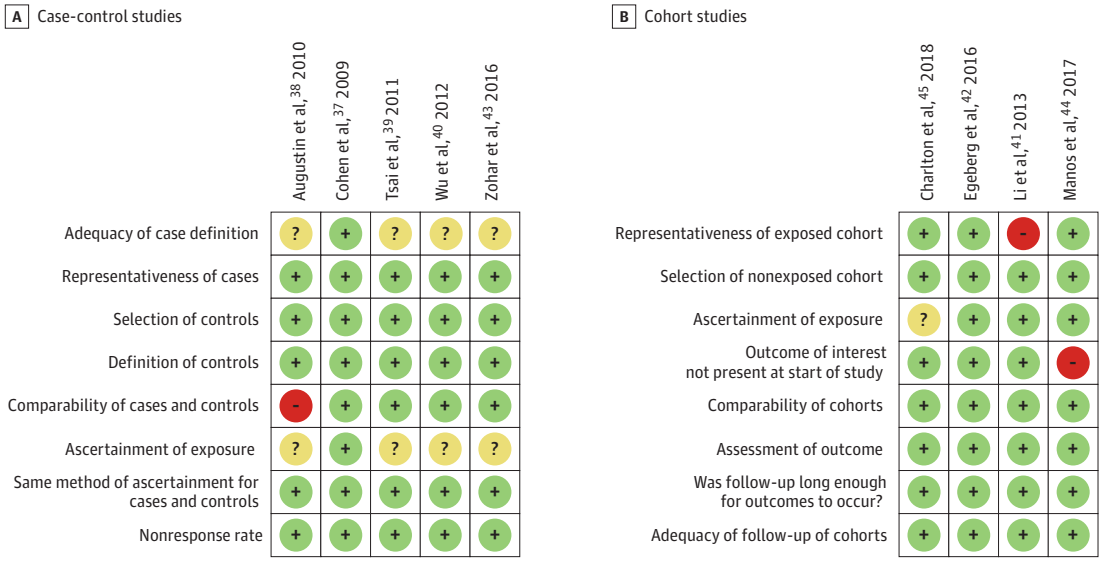
Abbreviations: NA, not available; OR, odds ratio.

Table 2. Characteristics of Included Cohort Studies

Source	Study Design	Exposed Group	Control Group	RR (95% CI)	
				Crohn Disease	Ulcerative Colitis
Egeberg et al,[42] 2016	Cohort study	75 209 Patients with psoriasis (36 212 males and 38 997 females)	5 478 891 Individuals in the reference population	1.94 (1.66-2.26)	1.72 (1.56-1.90)
Charlton et al,[45] 2018	Cohort study	6783 Patients with psoriatic arthritis	27 132 Individuals in the general population	2.96 (1.46-6.00)	1.30 (0.66-2.56)
Li et al,[41] 2013	Cohort study	2755 Women with psoriasis	171 721 Women without psoriasis	3.86 (2.23-6.67)	1.17 (0.41-3.36)
Manos et al,[44] 2017	Cohort study	1012 Children with psoriatic arthritis	203 907 Controls matched for age, sex, and date of psoriasis or psoriatic arthritis diagnosis	1.50 (0.21-10.68)	3.45 (0.86-13.90)

Abbreviation: RR, risk ratio.

Figure 2. Risk of Bias of Included Studies



A, Risk of bias of included case-control studies. B, Risk of bias of included cohort studies. A green dot denotes low risk of bias, yellow for unclear risk of bias, and red for high risk of bias.

patients with psoriasis were prone to have comorbid IBD. The evidence from case-control studies indicates that patients with psoriasis had 1.70-fold increased odds of developing CD and 1.75-fold increased odds of developing UC when compared with controls. Meanwhile, the evidence from cohort studies revealed that patients with psoriasis had a 2.53-fold increased risk of developing CD and a 1.71-fold increased risk of developing UC when compared with controls. The subgroup analysis on patients with psoriatic arthritis showed similar results. Patients with psoriatic arthritis had a 2.74-fold

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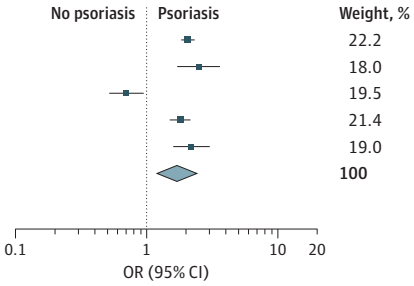
Figure 3. Forest Plots of the Association of Psoriasis With Crohn Disease and Ulcerative Colitis, and Subgroup Analysis of Psoriatic Arthritis

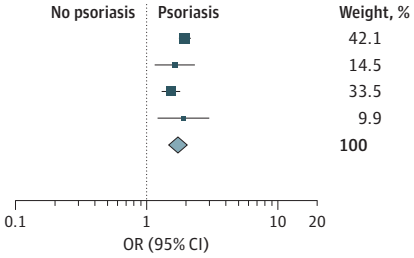
A Case-control studies on the association of psoriasis with Crohn disease

Study or Subgroup	Log (OR)	SE	OR (95% CI)
Augustin et al,[38] 2010	0.72	0.06	2.06 (1.83-2.31)
Cohen et al,[37] 2009	0.91	0.19	2.49 (1.71-3.62)
Tsai et al,[39] 2011	-0.36	0.15	0.70 (0.52-0.94)
Wu et al,[40] 2012	0.59	0.09	1.80 (1.50-2.16)
Zohar et al,[43] 2016	0.79	0.16	2.20 (1.59-3.03)
Total			**1.70 (1.20-2.40)**
Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 48.09$; $P < .001$; $I^2 = 92\%$			
Test for overall effect: $z = 2.98$; $P = .003$			



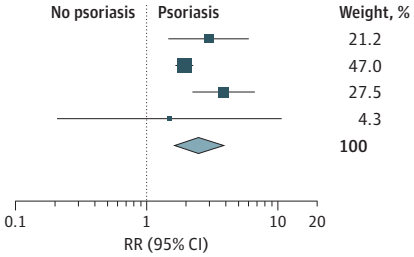
B Case-control studies on the association of psoriasis with ulcerative colitis

Study or Subgroup	Log (OR)	SE	OR (95% CI)
Augustin et al,[38] 2010	0.67	0.05	1.95 (1.76-2.17)
Cohen et al,[37] 2009	0.49	0.18	1.64 (1.15-2.33)
Wu et al,[40] 2012	0.43	0.08	1.53 (1.30-1.80)
Zohar et al,[43] 2016	0.64	0.23	1.91 (1.21-3.00)
Total			**1.75 (1.49-2.05)**
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 6.53$; $P = .09$; $I^2 = 54\%$			
Test for overall effect: $z = 6.92$; $P < .001$			



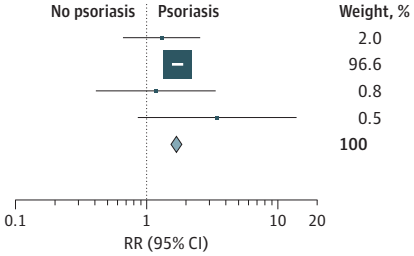
C Cohort studies on the association of psoriasis with Crohn disease

Study or Subgroup	Log (RR)	SE	RR (95% CI)
Charlton et al,[45] 2018	1.09	0.36	2.96 (1.46-6.00)
Egeberg et al,[42] 2016	0.66	0.08	1.94 (1.66-2.26)
Li et al,[41] 2013	1.35	0.28	3.86 (2.23-6.67)
Manos et al,[44] 2017	0.41	1.00	1.50 (0.21-10.68)
Total			**2.53 (1.65-3.89)**
Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 6.74$; $P = .08$; $I^2 = 55\%$			
Test for overall effect: $z = 4.26$; $P < .001$			



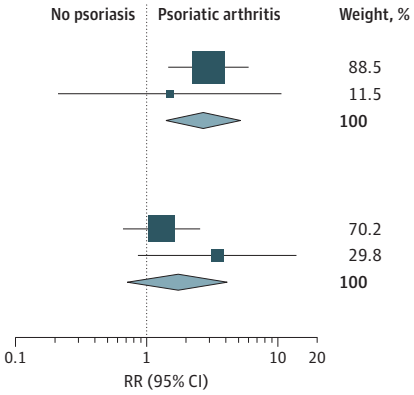
D Cohort studies on the association of psoriasis with ulcerative colitis

Study or Subgroup	Log (RR)	SE	RR (95% CI)
Charlton et al,[45] 2018	0.26	0.35	1.30 (0.66-2.56)
Egeberg et al,[42] 2016	0.54	0.05	1.72 (1.56-1.90)
Li et al,[41] 2013	0.16	0.54	1.17 (0.41-3.36)
Manos et al,[44] 2017	1.24	0.71	3.45 (0.86-13.90)
Total			**1.71 (1.55-1.89)**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.11$; $P = .55$; $I^2 = 0\%$			
Test for overall effect: $z = 10.87$; $P < .001$			



E Subgroup analysis of psoriatic arthritis

Study or Subgroup	Log (RR)	SE	RR (95% CI)
Crohn disease			
Charlton et al,[45] 2018	1.09	0.36	2.96 (1.46-6.00)
Manos et al,[44] 2017	0.41	1.00	1.50 (0.21-10.68)
Subtotal			**2.74 (1.41-5.32)**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.41$; $P = .52$; $I^2 = 0\%$			
Test for overall effect: $z = 2.97$; $P = .003$			
Ulcerative colitis			
Charlton et al,[45] 2018	0.26	0.35	1.30 (0.66-2.56)
Manos et al,[44] 2017	1.24	0.71	3.45 (0.86-13.90)
Subtotal			**1.74 (0.72-4.17)**
Heterogeneity: $\tau^2 = 0.16$; $\chi^2 = 1.52$; $P = .22$; $I^2 = 34\%$			
Test for overall effect: $z = 1.24$; $P = .22$			



A, Case-control studies on the association of psoriasis with Crohn disease. B, Case-control studies on the association of psoriasis with ulcerative colitis. C, Cohort studies on the association of psoriasis with Crohn disease. D, Cohort studies on the association of psoriasis with ulcerative colitis. E, Subgroup analysis of psoriatic arthritis. The size of the data markers reflects the weight. Data were pooled separately by study design type using random-effects models; the inverse variance technique was used for pooling of measures of effect.

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risk of developing CD and a 1.74-fold risk of developing UC when compared with controls.

Only 1 case-control study evaluated the association of psoriasis with CD in Asians; it showed a negative association of psoriasis with CD in Asians (OR, 0.70; 95% CI, 0.52-0.94). By contrast, all the other studies were conducted in Western countries and Israel, and found a significant association of psoriasis with CD (pooled OR, 2.02; 95% CI, 1.84-2.22; I^2 = 3%).

Most of the included studies were rated as low risk of bias according to the Newcastle-Ottawa Scale. Three included studies were rated as high risk of bias for the following reasons: no control for confounders,[38] study participants from a specific group,[41] and lack of relevant information on the outcome interest not present at the start of the study.[44] These points in study design should be considered in future studies.

The possible explanations for the identified association of psoriasis with IBD include genetic abnormalities, immune dysfunction, systemic inflammation, and dysregulation of gut microbiota. A few studies have explored the genetic link between psoriasis and IBD. Chromosomal locus 6p21, an area encompassing the major compatibility complex (MHC)-related genes, is the most extensively studied genetic region.[46] Psoriasis and IBD shared same the genetic susceptibility loci on chromosome 6p21, which corresponds to *PSORS1* in psoriasis and *IBD3* in IBD.[7] Furthermore, genes not related to major compatibility complex, including *IL23R* and *IL12B*, have been identified in the pathogenesis of both psoriasis and IBD.[28-30] The *IL23R* gene encodes a subunit of the IL-23 receptor and affects the binding capability of IL-23. Interleukin-23 is essential for the differentiation and activation of T_H17 lymphocytes that produce IL-17. Binding of IL-17 to its receptor stimulates hyperproliferation and differentiation of keratinocytes, maturation of myeloid dendritic cells, and recruitment of neutrophils and macrophages in psoriatic lesions.[31,32] In the gastrointestinal system, increased expression of IL-17 in the mucosa of the gut and serum in patients with IBD in comparison with healthy controls has been found.[33] The evidence supports the possibility that IL-17 plays an important role in the pathogenesis of IBD. Moreover, the *IL12B* gene encodes the p40 subunit that participates in the signaling pathways of both IL-12 and IL-23.[47] Therefore, IL-12B is an essential cytokine subunit in the pathogenesis of both psoriasis and IBD.

On the other hand, the skin and gut show similarities in IBD and psoriasis, including immense microbial diversity and bountiful blood supply.[48] Microbiota affect the physiology and immune response of the epithelium of the skin and gut by regulating biological metabolites.[49,50] In addition, the microbiota may lead to expression of antimicrobial particles, elevated cytokine levels, and, consequently, regulation of activity and differentiation of T cells.[51] Therefore, microbiota dysfunction may cause systemic immune dysregulation. The emerging evidence supports the gut-skin axis theory that describes the close association between intestinal dysbiosis and cutaneous manifestations.[52] Patients with psoriasis have been found to present with decreased diversity and abundance of gut microbiota that was similar to patients with IBD.[53]

Limitations

This study has several limitations. First, we found that only 1 cohort study reported the association between different severity of psoriasis and IBD.[42] Second, only 1 case-control study provided data on the association of psoriasis with IBD in Asians.[39] More studies are warranted to confirm if psoriasis is inversely associated with IBD in this population. Third, owing to the variation in sample size across the included studies, the relative weight of studies varied in different subgroup analyses. Nevertheless, the overall direction of effects was consistent.

Conclusions

The evidence to date supports an association of psoriasis with IBD. Patients with psoriasis should be informed about the increased risk of IBD. Gastroenterology consultation is indicated for patients with psoriasis presenting with bowel symptoms.

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Concept and design: Chi.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Fu, Lee.
Critical revision of the manuscript for important intellectual content: Chi.
Statistical analysis: All authors.
Administrative, technical, or material support: Chi.
Supervision: Chi.

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