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

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Editorial page 1005

Supplemental content

IMPORTANCE Hidradenitis suppurativa (HS) and inflammatory bowel disease (IBD) are inflammatory diseases that share common genetic susceptibility and immunologic features. However, the link between HS and IBD has been largely unclear.

OBJECTIVE To conduct a meta-analysis to investigate the association between HS and IBD.

DATA SOURCES A search of the MEDLINE, Cochrane Central Register of Controlled Trials, and Embase databases yielded 397 relevant studies from inception to June 10, 2018. Two additional studies were supplied by one of the investigators.

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

DATA EXTRACTION AND SYNTHESIS The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. The Newcastle-Ottawa Scale was used to assess the risk of bias of included studies. Crohn disease and ulcerative colitis were analyzed separately, and a random-effects model meta-analysis was conducted.

MAIN OUTCOMES AND MEASURES The odds ratios (ORs) and hazard ratios (HRs) of IBD, Crohn disease, and ulcerative colitis in association with HS.

RESULTS Five case-control studies, 2 cross-sectional studies, and 1 cohort study with a total of 93 601 unique participants were included. The meta-analysis of case-control and cross-sectional studies showed significant associations of HS with Crohn disease (pooled OR, 2.12; 95% CI, 1.46-3.08) and ulcerative colitis (pooled OR, 1.51; 95% CI, 1.25-1.82). Two case-control studies found significant association of HS with IBD (ORs, 2.16 [95% CI, 1.40-3.34] and 10.00 [95% CI, 1.94-51.50]). One cohort study found an increased risk of IBD in patients with HS (HR, 5.6; 95% CI not reported; $P < .002$).

CONCLUSIONS AND RELEVANCE The evidence to date supports an association of HS with IBD. These results suggest that consultation with gastroenterologists should be sought when patients with HS present with recurrent abdominal pain, chronic diarrhea, bloody stool, and body weight loss.

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Hidradenitis suppurativa (HS) or acne inversa is defined as "a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillary, inguinal, and anogenital regions" (Dessau definition).[1(p619)] The etiology is largely unclear, but dysregulated inflammatory response of cytokines, follicular occlusion, obstruction and dilatation of the pilosebaceous unit, and altered microbiota may be involved in the pathogenesis of HS.[2-5]

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disease of the intestinal tract. Inflammatory bowel disease consists of 2 predominant types: Crohn disease (CD) and ulcerative colitis (UC).[6] Accumulating evidence indicates that genetic susceptibility to dysregulated inflammatory reaction and altered microbiota may play crucial roles in the pathogenesis of IBD.[7-9]

Hidradenitis suppurativa shares common clinical manifestations, genetic susceptibility, and immunologic features with IBD.[5,10] Both diseases have similar clinical manifestations in the skin and gut, characterized by sterile abscesses in the perineal and inguinal areas, scarring, and sinus tract formation.[1,7,11,12] Hidradenitis suppurativa and IBD have been associated with an increased prevalence of spondyloarthropathy, and both diseases respond well to tumor necrosis factor inhibitors.[1,13-17] Moreover, smoking and obesity are known common risk factors for HS and IBD.[18-21]

Although some studies have suggested a link between HS and IBD,[22-25] data on the association remain inconsistent and unclear. For example, one recent study[26] failed to find a significant association between HS and CD, whereas another study[27] did not detect a significant increase of UC in patients with HS. In this study, we aimed to systematically examine the evidence of an association of HS with IBD.

Key Points

Question Is hidradenitis suppurativa associated with inflammatory bowel disease?

Findings This systematic review and meta-analysis included 5 case-control studies, 2 cross-sectional studies, and 1 cohort study with a total of 93 601 unique participants with hidradenitis suppurativa who had 2.12-fold increased odds for Crohn disease and 1.51-fold increased odds for ulcerative colitis. One cohort study found a 5.6-fold increased risk of inflammatory bowel disease in patients with hidradenitis suppurativa.

Meaning Gastrointestinal tract symptoms, such as recurrent abdominal pain and chronic diarrhea, should not be overlooked in patients with hidradenitis suppurativa, and consultation with gastroenterologists should be sought.

Methods

Eligibility Criteria and Evidence Search

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline,[28] we conducted a meta-analysis of observational studies on the association of HS with IBD. The types of eligible studies included case-control, cross-sectional, and cohort studies.

The MEDLINE, Cochrane Central Register of Controlled Trials, and Embase databases were searched for relevant studies from the respective inception of these databases to June 10, 2018. We did not impose any language or geographic restrictions. Our search strategy is listed in the eTable in the Supplement.

Selection of Studies

Studies that met the following inclusion criteria were included: (1) observational studies examining the association of HS with IBD, including cross-sectional, case-control, or cohort studies; (2) human study participants; and (3) a case group consisting of patients with HS and a control group composed of people without HS. Both authors independently selected relevant studies by scanning the titles and abstracts of search results. The full text of potential studies was obtained and examined for eligibility. Disagreement was resolved by discussion.

Data Extraction and Risk of Bias Assessment

We extracted the following data from the included studies: study design, first author, year of publication, country, and risk estimates, including odds ratios (ORs) and hazard ratios (HRs) with corresponding 95% CIs on the association of HS with IBD. We used the Newcastle-Ottawa Scale to assess the risk of bias of included studies.[29]

Statistical Analysis

We used Review Manager software, version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration), to conduct meta-analyses when at least 3 studies provided usable data for 1 outcome.[30] We calculated a pooled OR with 95% CI for case-control and cross-sectional studies and a pooled HR with 95% CI for cohort studies. The I^2 statistic was calculated for examining statistical heterogeneity across the included studies. An I^2 of greater than 50% was considered substantial heterogeneity.[31] The random-effects model was chosen for meta-analyses because clinical heterogeneity was anticipated.

Results

Characteristics of Included Studies

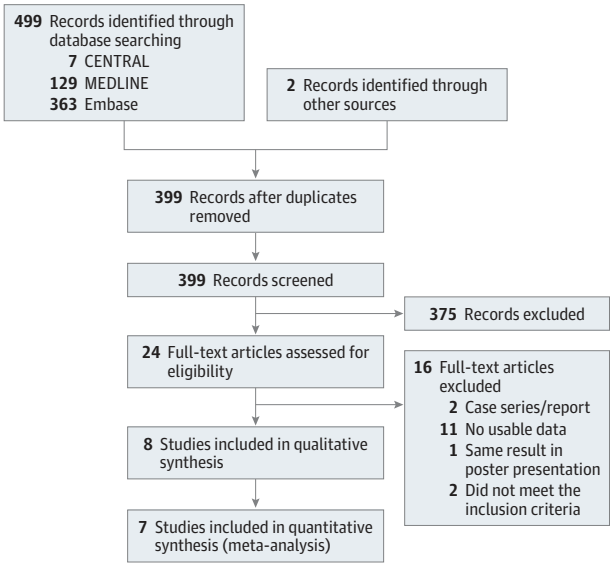
The PRISMA study flow diagram is shown in **Figure 1**. After removing duplicates, 397 records were identified by our search. Two additional relevant studies were provided by 1 author (C.-C.C.).[26,32] We excluded 375 citations after scanning the titles and abstracts. After examination of the full text, we included 5 case-control studies,[26,33-36] 2 cross-sectional studies,[27,32] and 1 cohort study[37] with a total of 93 601 unique study participants. One study was conducted in Asia,[26] and the other 7 were conducted in the West.[27,32-37] The characteristics of the included case-control studies are shown in **Table 1**.

Risk of Bias of Included Studies

The risk of bias among included case-control and cohort studies is summarized in **Figure 2**. No studies were rated with

a high risk of bias in any item. As to the adequacy of case definition, 5 studies[26,32-34,36] were rated with an unclear risk of bias because only codes from the *International Classification of Diseases, Eighth Revision*, and *Ninth Revision*, and *Tenth Revision* were used for identification of cases. Five case-control and cross-sectional studies[26,33-36] and 1 cohort study[37] were rated with an unclear risk of bias in the comparability of cases and controls or cohorts because the analyses controlled for age and sex but not body mass index and smoking. As to ascertainment of exposure, 6 case-control and cross-sectional studies[26,32-36] and 1 cohort study[37] were rated with an unclear risk of bias because only *International Classification of Diseases* codes were used.

Figure 1. PRISMA Study Flowchart



CENTRAL indicates Cochrane Central Register of Controlled Trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Association of HS With IBD

Five studies with a combined 91 917 study participants, including 2 cross-sectional studies[27,32] and 3 case-control studies,[26,34,35] provided data on the association of HS with CD. Substantial statistical heterogeneity was found across these studies (I^2 = 92%). As illustrated in **Figure 3**A, the meta-analysis illustrated a significantly increased odds of CD in patients with HS (pooled OR, 2.12; 95% CI, 1.46-3.08).

Four studies with a combined 39 497 study participants, including 1 cross-sectional study[27] and 3 case-control studies,[26,34,35] provided data on the association of HS with UC. We found no substantial statistical heterogeneity across these studies (I^2 = 28%). As demonstrated in Figure 3B, the meta-analysis showed a significantly increased odds of UC in patients with HS (pooled OR, 1.51; 95% CI, 1.25-1.82).

Two case-control studies[33,36] with a combined 1642 study participants provided data on the association of HS with IBD and found significantly increased odds of IBD in subjects with HS (ORs, 2.16 [95% CI, 1.40-3.34] and 10.00 (95% CI, 1.94-51.50]). One cohort study[37] with 14 136 study participants found an increased risk of IBD in patients with HS (HR, 5.6; 95% CI not reported; P < .002).

Discussion

To the best of our knowledge, this study is the first meta-analysis to illustrate a significant association of HS with IBD. The evidence from case-control studies indicates that patients with HS had 2.12-fold odds of CD and 1.51-fold odds of UC when compared with controls. Meanwhile, the evidence from 1 cohort study[37] reveals that patients with HS had a 5.6-fold HR of IBD when compared with controls.

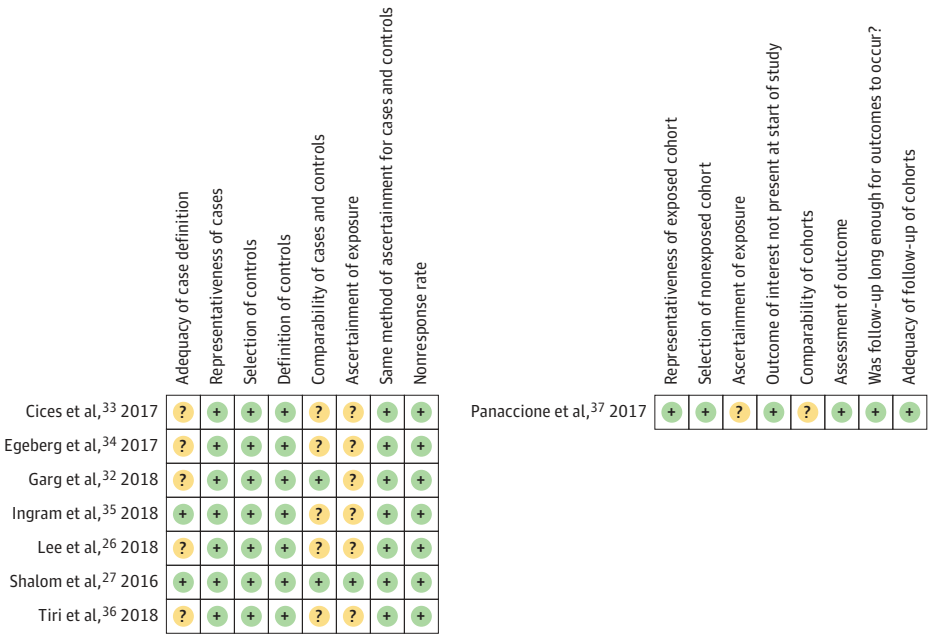
Hidradenitis suppurativa and IBD share many characteristics, including clinical manifestations, genetic susceptibility, and immunologic features. There are several explanations of the link between HS and IBD. First, genetic susceptibility

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

Source (Country)	Study Design	Group		OR (95% CI)		
		No. of Patients With HS	No. of Controls	Inflammatory Bowel Disease	Crohn Disease	Ulcerative Colitis
Shalom et al,[27] 2016 (Israel)	Cross-sectional	3207	6412	NA	2.03 (1.14-3.62)	1.82 (0.81-4.05)
Cices et al,[33] 2017 (United States)	Case-control	1489 (22.7% Male and 77.3% female)	871 398 (38.5% Male and 61.4% female)	2.16 (1.40-3.34)	NA	NA
Egeberg et al,[34] 2017 (Denmark)	Case-control	7732	4 354 137	NA	2.04 (1.59-2.62)	1.75 (1.44-2.13)
Garg et al,[32] 2018 (United States)	Cross-sectional	52 340 (31.8% Male and 68.2% female)	18 404 260 (44.1% Male and 55.7% female)	NA	3.05 (2.87-3.25)	NA
Ingram et al,[35] 2018 (United Kingdom)	Case-control	122	187	NA	2.65 (1.89-3.72)	NA
	Case-control	42	129	NA	NA	1.24 (0.79-1.94)
Lee et al,[26] 2018 (Korea)	Case-control	28 516 (61.3% Male and 38.7% female)	142 580 (61.3% Male and 38.7% female)	NA	1.23 (0.92-1.63)	1.32 (1.04-1.69)
Tiri et al,[36] 2018 (Finland)	Case-control	153	612 Patients with melanocytic nevi	10.0 (1.94-51.5)	NA	NA

Abbreviations: HS, hidradenitis suppurativa; NA, not available; OR, odds ratio.

Figure 2. Risk of Bias Among Included Studies



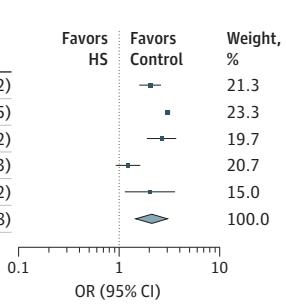
The Newcastle-Ottawa Scale was used to access the risk of bias. A green dot denotes low risk of bias; yellow, unclear risk of bias.

Figure 3. Forest Plots of the Association of Hidradenitis Suppurativa (HS) With Crohn Disease and Ulcerative Colitis

A Crohn disease

Source	Logarithm OR (SE)	Total No. HS Group	Total No. Control Group	IV Randomized OR (95% CI)	Weight, %
Egeberg et al,[34] 2017	0.7135 (0.1274)	7732	4354137	2.04 (1.59-2.62)	21.3
Garg et al,[32] 2018	1.1165 (0.0317)	52340	18404260	3.05 (2.87-3.25)	23.3
Ingram et al,[35] 2018	0.9752 (0.1727)	122	187	2.65 (1.89-3.72)	19.7
Lee et al,[26] 2018	0.2035 (0.1442)	28516	142580	1.23 (0.92-1.63)	20.7
Shalom et al,[27] 2016	0.7088 (0.2948)	3207	6412	2.03 (1.14-3.62)	15.0
Total		91917	22907576	2.12 (1.46-3.08)	100.0

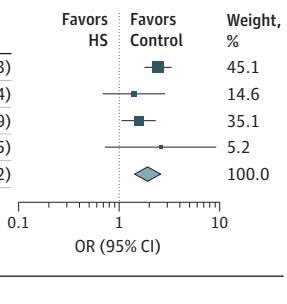
Heterogeneity: $\tau^2 = 0.15$, $\chi^2_4 = 47.36$ ($P < .001$); $I^2 = 92\%$
Test for overall effect: $z = 3.96$ ($P < .001$)



B Ulcerative colitis

Source	Logarithm OR (SE)	Total No. HS Group	Total No. Control Group	IV Randomized OR (95% CI)	Weight, %
Egeberg et al,[34] 2017	0.5604 (0.0999)	7732	4354137	1.75 (1.44-2.13)	45.1
Ingram et al,[35] 2018	0.2135 (0.2292)	42	129	1.24 (0.79-1.94)	14.6
Lee et al,[26] 2018	0.281 (0.1258)	28516	142580	1.32 (1.04-1.69)	35.1
Shalom et al,[27] 2016	0.5965 (0.4093)	3207	6412	1.82 (0.81-4.05)	5.2
Total		39497	4503258	1.51 (1.25-1.82)	100.0

Heterogeneity: $\tau^2 = 0.01$, $\chi^2_3 = 4.16$ ($P = .24$); $I^2 = 28\%$
Test for overall effect: $z = 4.31$ ($P < .001$)



Data were pooled separately by study design using random-effects model; the inverse variance (IV) technique was used for pooling of measures of effects. OR indicates odds ratio; SE, standard error.

loci shared by HS and IBD have been found. Certain genes, for example *SULT1B1* (OMIM 608436) and *SULT1E1* (OMIM 600043), have been associated with HS as well as IBD.[5,38,39] Second, emerging studies have shown that HS and IBD are diseases of immune dysregulation. Cytokine abnormalities, such as elevation of interleukin 1 (IL-1), IL-6, IL-17, IL-23, and tumor necrosis factor, are involved in HS and IBD.[40-42] Third, altered microbiota with dysregulated immune responses may play an important role in HS and IBD.[5,43] Microbiota affect the immunologic and physiologic homeostasis of the epithelia of

skin and mucosa of gut by activation of toll-like receptors to recognize pathogens and repair damage.[44-46] However, a variety of environmental factors can alter microbial balance with a resultant decrease in microbial diversity.[7] Such alterations of microbiota may cause immune dysregulation and susceptibility to diseases, including HS and IBD.[47] Altered microbiota have been found in the lesional and nonlesional skin of patients with HS when compared with healthy control individuals.[48] Increasing evidence shows that altered intestinal microbiota may be involved in the pathogenesis of IBD, with decreases in specific *Firmicutes* species and a concomitant increase in *Bacteroidetes* species and facultative anaerobes such as *Enterobacteriaceae*.[49] The alterations of microbiota may lead to systemic immune impairment. Such a close interplay between alterations of microbiota, cytokines, and dermatoses has been proposed as the gut-skin axis theory.[50]

We detected high statistical heterogeneity for the association of HS with CD (I^2 = 92%) (Figure 3A). However, no significant statistical heterogeneity was present when we excluded 3 studies[26,34,35] that did not control for body mass index and smoking habit (I^2 = 47%; P = .17). Therefore, uncontrolled confounding may account for the high statistical heterogeneity detected in Figure 3A.

Limitations

This study has some limitations. First, no studies examined the association between different severity of HS and IBD. Second, most of the included studies were from Western countries (United States and Europe),[27,32-37] with only 1 from Asia.[26] More studies are warranted to confirm whether HS is associated with IBD in Asian or other racial/ethnic groups.

Conclusions

The evidence to date supports an association of HS with IBD. Patients with HS should be informed about the increased risk of IBD. Consultation with gastroenterologists should be sought when patients with HS present with recurrent abdominal pain, chronic diarrhea, bloody stool, and body weight loss.

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

Conflict of Interest Disclosures: None reported.

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