Meta-Analysis of Observational Studies in Epidemiology

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Association of rosacea with inflammatory bowel disease

A MOOSE-compliant meta-analysis

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Abstract

Rosacea has been reported with several systemic comorbidities, but its relationship with inflammatory bowel disease (IBD) is unclear. Thus, our objective is to conduct a meta-analysis on the association of rosacea with IBD.

We conduct a meta-analysis and searched MEDLINE, CENTRAL, and Embase databases for case-controlled and cohort studies that assessed the association of rosacea with IBD from inception to July 2nd, 2018. Two authors independently selected studies, extracted data, and assessed the risk of bias of included studies. Disagreement was resolved by discussion. We performed random-effects model meta-analysis to obtain the pooled risk estimates for Crohn disease (CD) and ulcerative colitis (UC) in patients with rosacea.

We included three case-control and three cohort studies. The risk of bias of included studies was generally low. The meta-analysis on case-control studies showed marginally increased odds of CD (pooled odds ratio (OR) 1.30, 95% confidence interval (CI) 0.99–1.69) and a significantly increased odds of UC (pooled OR 1.64, 95% CI 1.43–1.89) in patients with rosacea. The meta-analysis on cohort studies demonstrated significant increased risk of CD (pooled hazard ratio (HR) 1.58, 95% CI 1.14–2.20) and UC (pooled HR 1.18, 95% CI 1.01–1.37) in patients with rosacea.

The evidence indicates an association of rosacea with IBD. If patients with rosacea suffer from prolonged abdominal pain, diarrhea, and bloody stool, referral to gastroenterologists may be considered.

Abbreviations: BTNL2 = butyrophilin-like 2, CD = Crohn disease, CI = confidence interval, GST = glutathione S-transferases, HLA = human leukocyte antigen, HR = hazard ratio, IBD = inflammatory bowel disease, ICD = International Classification of Disease, MOOSE = Meta-analysis of Observational Studies in Epidemiology, NOS = Newcastle-Ottawa Scale, OR = odds ratio, SIBO = small intestinal bacterial overgrowth, UC = ulcerative colitis.

Keywords: Crohn disease, inflammatory bowel disease, rosacea, ulcerative colitis

1. Introduction

Rosacea is a prevalent chronic inflammatory disease characterized by flushing, persistent erythema, telangiectasia, inflammatory papules and pustules on the central face.[1] Rosacea was estimated to affect 5.46% of adults, especially those aged 45 to 60 years.[2] Although rosacea most commonly involves women after the age of 30,[3,4] both men and women may be affected.[2] The pathogenesis of rosacea is unclear and has been proposed to relate to dysregulation of neurovascular and neuroimmune communication.[5–7] Both innate and adaptive immune system activation have been implicated in the pathogenesis of rosacea.[6,8] In addition to genetic factors and fair skin types predisposition,[6,9] environmental factors including alcohol consumption, ultraviolet light, cold and hot may exacerbate rosacea. Microorganisms such as Demodex mites,[10,11] *Bacillus oleronius*,[12] and small intestinal bacterial overgrowth (SIBO)[13] have also been associated with rosacea. Various comorbidities of rosacea have been reported recently, including cardiovascular disease,[14] migraine,[15] and mood disorders.[16]

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of gastrointestinal tract which includes 2 main types: Crohn disease (CD) and ulcerative colitis (UC). UC is a relapsing non-transmural inflammatory disease restricted to the mucosa of the colon. By contrast, CD usually causes more persistent transmural inflammation of the gastrointestinal mucosa with skip lesions and can involve the entire gastrointestinal tract, resulting in sinus tracts, perforations, and fistulae.[17,18] The clinical manifestations of IBD include prolonged diarrhea with abdominal pain, weight loss, fatigue, fever, and bloody stool.[18] The prevalence of IBD is about 0.3% and appears to be lower in Asia and the Middle East.[19] Recently, a rising incidence of IBD has been found in newly industrialized countries.[19] Various risk factors for IBD have been proposed,[20] including age,[21] gender,[22,23] smoking,[24,25] obesity,[26,27] microorgan-

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isms,[28,29] and medications.[30,31] IBD usually needs long-term medical control and is associated with an increased mortality of affected patients.[32]

Although the pathogenesis remains unclear, rosacea and IBD, same as chronic inflammatory diseases, share some commonalities including genetic susceptibility, immunological features, microbiota, and trigger factors.[6,13,33] A few cases of simultaneous occurrence of rosacea and IBD have been reported.[34–38] However, conflicting results have been reported. The objective of this study was to systematically examine the evidence on the association of rosacea with IBD.

2. Methods

2.1. Literature search

We conducted a meta-analysis on the association of rosacea with IBD. Therefore, ethical approval was not necessary. The reporting of this study was in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline[39] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guideline.[40] The protocol for this study has been registered with PROSPERO (CRD42018102922). The MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and Embase databases were searched from inception to July 2nd, 2018. The search terms included rosacea, IBD, Crohn disease (CD), and ulcerative colitis (UC). The detailed search strategy is listed in the Supplement, http://links.lww.com/MD/D214. We did not apply any language or geographic limitations.

2.2. Study selection

Studies were included if they met the following criteria:

1. observational studies assessing the association of rosacea with IBD;
2. study design being case-control or cohort studies; and
3. the study subjects were humans.

Two authors (FW and CC) 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 by the 2 authors. After resolving disagreement by discussion, the 2 authors decided which studies to beincluded.

2.3. Data extraction and risk of bias assessment

We extracted the following data from the included studies: first author, publication year, study design, country, study settings, and risk estimates. The quantitative estimates included odds ratio (OR) for case-control studies and hazard ratio (HR) for cohort studies with 95% confidence intervals (CI). Two authors evaluated the risk of bias of the included studies by using the Newcastle-Ottawa Scale (NOS).[41] Disagreement was resolved by discussion. For case-control studies, we examined the risk of bias in the following 8 items, including 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 non-response rate. On the other hand, for cohort studies, we evaluated the following eight items, including the representativeness of exposed cohort, selection of non-exposed cohort, ascertainment of exposure, outcome of the interest not present at start of study, assessment of outcome, comparability of cohorts, follow-up duration, as well as adequacy of follow up of cohorts.

2.4. Statistical analysis

We conducted meta-analyses to calculate a pooled OR with 95% CI for case-control studies and a pooled HR with 95% CI for cohort studies. We assessed heterogeneity across the studies by using the I^2 statistic. An I^2 of >50% was considered substantial statistical heterogeneity.[42] We decided a priori to use the random-effects model for meta-analyses because we assumed clinical heterogeneity across the included studies. All the meta-analyses were conducted by using the Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3. Results

3.1. Characteristics of included studies

The process of identification and selection of relevant studies is shown in Figure 1. We obtained 198 records after searching the MEDLINE, CENTRAL, and Embase databases. After removing 6 duplicates, the titles and abstracts of the remaining 192 records were independently scanned by 2 authors, and 179 articles were excluded. After examining the full text, we included 3 cohort studies and 3 case-control studies with a total of 5,149,963 study subjects. Apart from one Asian study conducted in Taiwan,[43] the remaining 5 studies were carried out in the West.[44–48] The characteristics of the included cohort and case-control studies are reported in Table 1.

3.2. Risk of bias of included studies

The risk of bias of included case-control and cohort studies are summarized in Figure 2A and B, respectively. None of our included studies were rated with a high risk of bias in any item of the NOS. All of the 3 cohort studies were as associated with unclear risk of bias in the 'ascertainment of exposure' item because rosacea was identified by using corresponding International Classification of Disease (ICD) codes or self-reports of clinicians' diagnosis, lacking independent validation.[43–45] From the same reason, 2 included case-control studies were rated unclear risk in the 'adequacy of case definition' item.[46,48] Two case-control and 2 cohort studies were judged as unclear risk of bias in the 'comparability' of cases and controls or of cohorts because they only adjusted for 2 or 3 of the most important confounding factors of IBD, which include age, gender, smoking, and obesity.[43,44,46,47]

3.3. Association of rosacea with IBD in case-control studies

All the included 3 case-control studies with a total of 423,893 subjects provided data regarding the association of rosacea with CD.[46–48] As shown in Figure 3A, the meta-analysis demonstrated marginally increased odds of prevalent CD in patients with rosacea (pooled OR 1.30, 95% CI 0.99–1.69). We identified substantial statistical heterogeneity across the three studies ($I^2 = 74\%$).

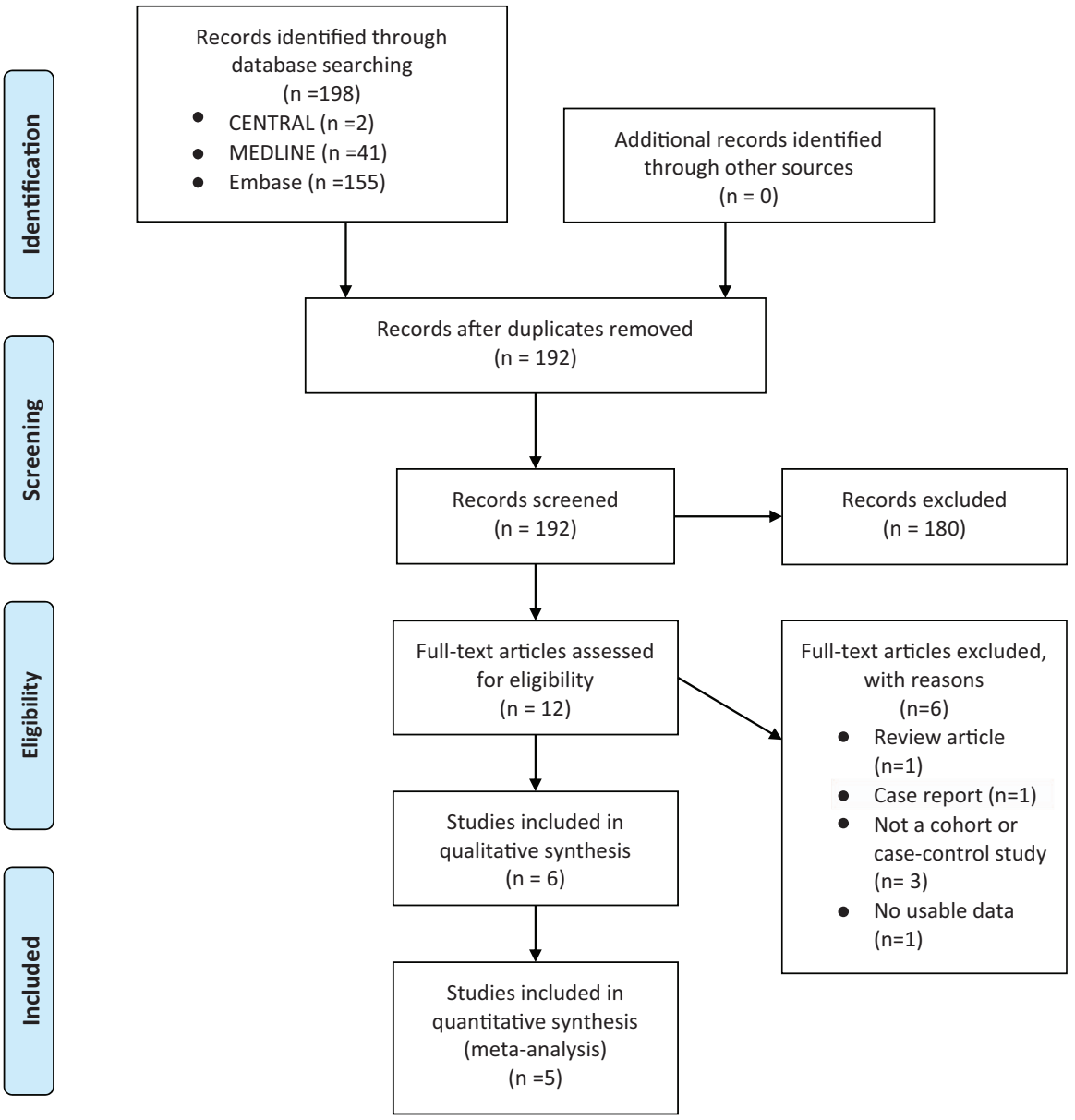

Figure 1. PRISMA study flow diagram.

As illustrated in Figure 3B, 2 out of the 3 included case-control studies contributed data to the association of rosacea with UC.[47,48] No statistical heterogeneity was found across the 2 studies ($I^2 = 0\%$). The meta-analysis found a significantly increased odds of prevalent UC in relation to rosacea (pooled OR 1.64, 95% CI 1.43–1.89).

3.4. Association of rosacea with IBD in cohort studies

Two included cohort studies with a total of 4,458,002 subjects supplied usable data on the HR estimates of CD and UC in patients with rosacea.[44,45] As displayed in Figure 4A, the meta-analysis of cohort studies demonstrated a significantly increased risk of incident CD in rosacea patients (pooled HR 1.58, 95% CI 1.14–2.20). Moreover, as shown in Figure 4B, the meta-analysis of cohort studies demonstrated a significantly increased risk of incident UC in rosacea patients (pooled HR 1.18, 95% CI 1.01–1.37). No statistical heterogeneity was detected across these studies for both CD and UC ($I^2 = 30\%$ and 0%, respectively).

The only Asian study included 268,068 subjects and showed significantly increased HR of incident IBD in rosacea (HR 1.94, 95% CI 1.04–3.63).[43] We contacted the authors for respective data on CD and UC; however, they decided not to conduct further calculations because of a very limited number of events (16 and 37 incident cases of IBD in the rosacea and reference cohorts, respectively).[43]

4. Discussion

Our study indicates patients with rosacea are associated with an increase in prevalent CD and UC. The evidence from case-control studies indicates 1.30-fold odds of prevalent CD and 1.64-fold

Table 1

Characteristics of included cohort and case-control studies.

First author, publication year	Study design	Exposed/case group	Control group	HR/OR with 95% CI for IBD	HR/OR with 95% CI for CD	HR/OR with 95% CI for UC	Notes
Egeberg, 2017	Cohort study	49,475 patients with rosacea	4,312,213 general population controls	NA	HR 1.45 (1.19–1.77)	HR 1.19 (1.02–1.39)	Country: Denmark Setting: nationwide
Wu, 2017	Cohort study	89,356 patients with rosacea	178,712 controls without rosacea matched by age, gender, hospital visits, and comorbidities including diabetes, hypertension, psoriasis, and rheumatoid arthritis.	HR 1.94 (1.04–3.63)	NA	NA	Country: Taiwan Setting: nationwide
Li, 2016	Cohort study	1,127 female nurses with rosacea	95,187 female nurses	NA	HR 2.20 (1.15–4.18)	HR 0.94 (0.45–1.95)	Country: US. Setting: 14 states
Spoendlin, 2016	Case-control study	80,957 patients with rosacea	80,957 controls matched by age, sex, general practice, index date, recorded years before index date		OR 1.49 (1.25–1.77)	OR 1.65 (1.43–1.90)	Country: UK. Setting: nationwide
Marks, 1967	Case-control study	62 patients with rosacea	62 control patients with other skin disorder matched by age, sex and occupation	NA	OR 5.17 (0.24–109.83)	OR 0.33 (0.01–8.2)	Country: UK. Setting: one hospital
Lim, 2017	Case-control study	39,982 patients with rosacea	221,873 patients with seborrheic keratosis matched by age	NA	OR 1.13 (1.01–1.26)	NA	Country: US. Setting: nationwide

CD = Crohn disease, CI = confidence interval, HR = hazard ratio, IBD = inflammatory bowel disease, NA = not available, OR = odds ratio, UC = ulcerative colitis.

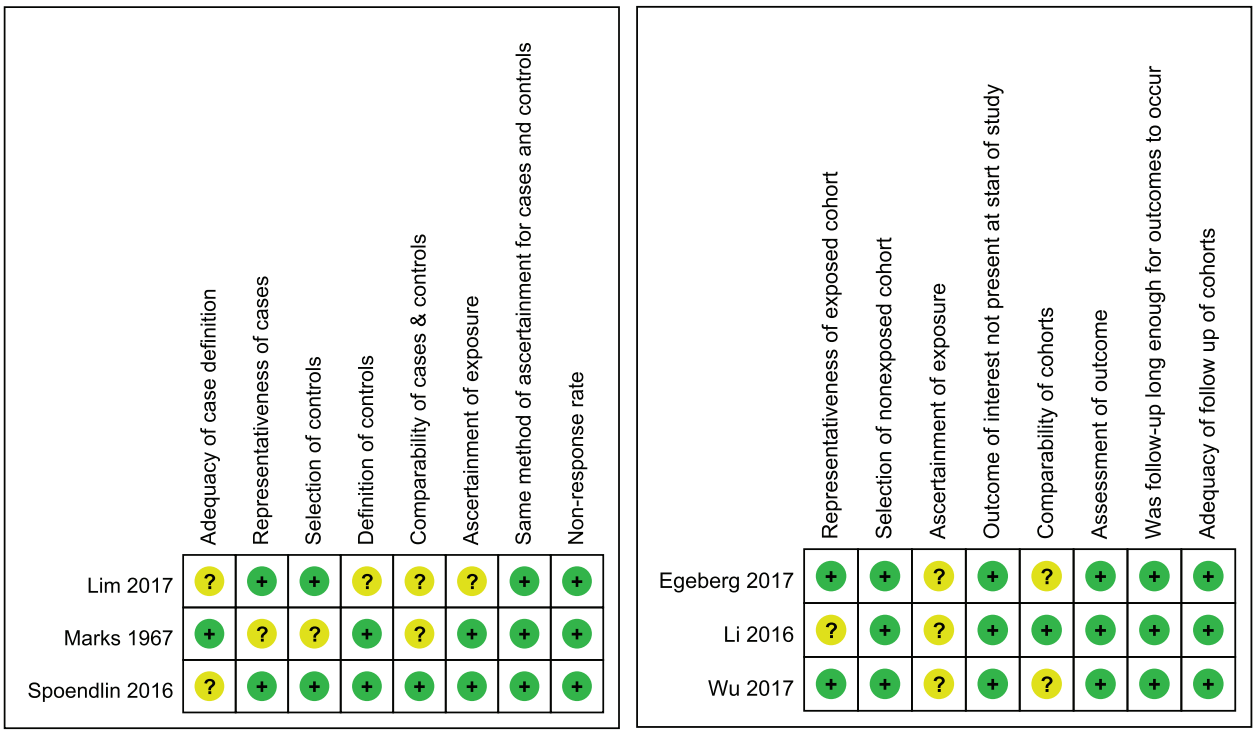

Figure 2. A. Risk of bias of included case-control studies. B. Risk of bias of included cohort studies.

odds of prevalent UC in rosacea patients when compared to controls. On the other hand, the evidence from cohort studies reveals a 1.58-fold risk of incident CD and a 1.18-fold risk of incident UC in rosacea patients when compared to controls. We identified statistical heterogeneity in the association of rosacea with Crohn disease ($I^2 = 74\%$; Fig. 3A); however, the direction of all the three case-control studies was consistent and indicated a positive association between the 2 diseases. Therefore, the evidence supports an association of rosacea with Crohn disease and the statistical heterogeneity merely represents variations between these studies.[49] Due to the lack of further detailed data from the included studies, we were unable to conduct a subgroup analysis to explore the origin of variations.

The mechanism underlying the association between rosacea and IBD is unclear. Rosacea and IBD are both chronic inflammatory diseases involving the interplay between genetic and immunological elements. Familial history has been reported as a risk factor, suggesting that genetic predisposition may be critical in the 2 diseases.[9,50] Rosacea was identified to involve human leukocyte antigen (HLA)-DRB1*03:01,

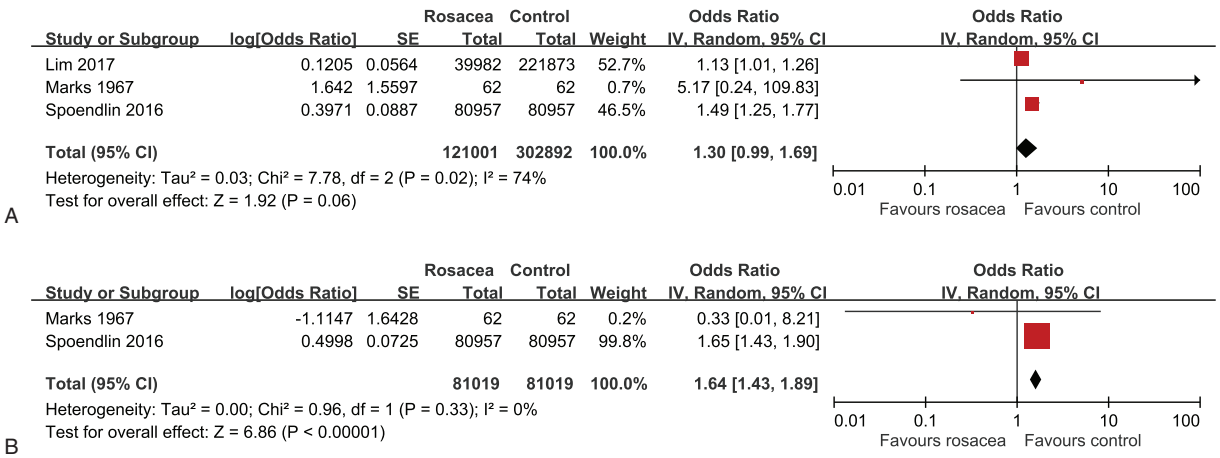

Figure 3. A. Forest plot for the association of rosacea with Crohn disease in case-control studies. B. Forest plot for the association of rosacea with ulcerative colitis in case-control studies.

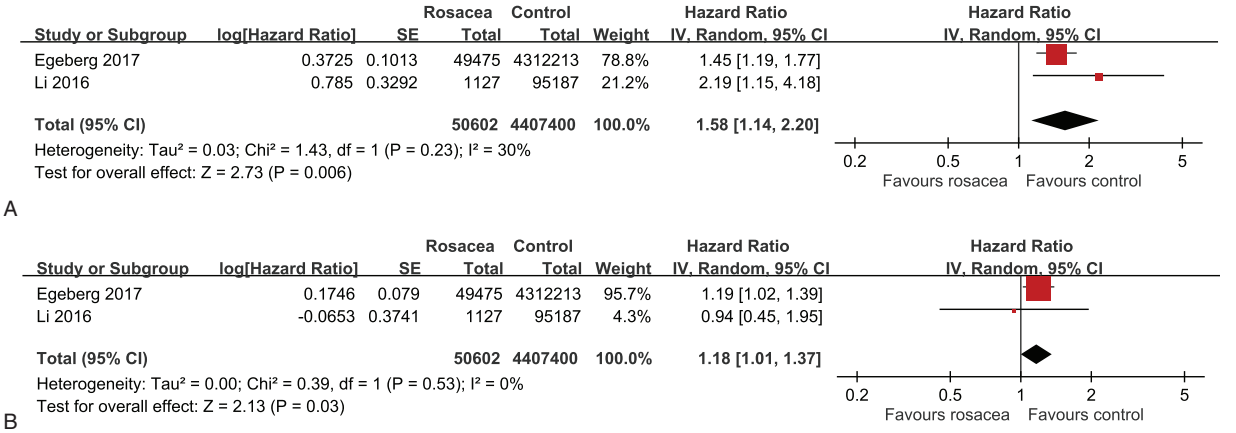

Figure 4. A. Forest plot for the association of rosacea with Crohn disease in cohort studies. B. Forest plot for the association of rosacea with ulcerative colitis in cohort studies.

HLA-DQB1*02:01, and HLA-DQA1*05:01 as well as the intergenic single-nucleotide polymorphism between HLA-DRA and butyrophilin-like 2 (BTNL2).[51] BTNL2 possesses an immunomodulatory function by regulation of T cell activation and tolerance.[52] Interestingly, previous studies have detected strong overdominance of HLA-DRB1*03:01 in UC,[53] and BTNL2 was linked to an increased risk for IBD.[54,55] Furthermore, glutathione S-transferases (GST) plays a major role in cellular defense against reactive oxygen species, providing photoprotection.[56] GSTT1 null genotype has been found significantly increased in rosacea patients[57] and was associated with increased susceptibility to CD and UC.[58] These common genetic factors may contribute to the association between rosacea and IBD.

Both rosacea and IBD are associated with alterations in innate and adaptive immunity.[6] Dysfunction of the innate immune system may contribute to the development of chronic inflammation and vascular abnormalities. For example, activation of macrophages and toll-like receptor 2, dysregulations of mast cells, fibroblasts, and production of reactive oxygen species, matrix metalloproteinases, tumor necrosis factor and interleukin-1β contribute to inflammation of rosacea and IBD.[6,59] As to adaptive immunity, T helper type 1 and 17 cells as well as B cells are pathogenic in both rosacea and IBD through production of interferon-gamma, tumor necrosis factor, interleukin-17, and multiple immunoglobulins.[6,59,60]

Rosacea and IBD share common risk factors. Obesity is a risk factor for IBD,[26,27] while a higher body-mass index has been associated with increased severity of rosacea in twins.[61] On the other hand, previous smoking status is a risk factor for rosacea.[9] Interestingly, active smoking appears to be associated with a reduced risk for rosacea, with risk increasing about 1 year after smoking cessation.[3,6,62] Similar influence of smoking was also noted in UC.[63] In the present study, only 1 included case-control studies and 2 included cohort studies had considered smoking as a confounding factor.[44,45,48] In these studies, only 1 case-control and one cohort studies had adjusted for body-mass index additionally.[45,48]

A significantly increased prevalence of SIBO has been found in patients with rosacea.[13] Remarkably higher SIBO has been observed in both CD and UC patients, and eradication of SIBO substantially improved clinical symptoms of IBD.[33,64,65] Higher SIBO has also been found in rosacea patients, and eradication of SIBO led to complete resolution of rosacea and maintained remission.[13] It has been speculated that SIBO increases intestinal permeability, with resultant translocation of bacterial components and proinflammatory cytokine into the blood flow and triggering inflammation of the skin.[13,66] The observed association between rosacea and IBD is compatible with the newly emerging concept of 'skin-gut axis', which proposed gastrointestinal dysbiosis affects the skin through complicated communications between immune, metabolic, and nervous systems.[67]

The present study has several limitations. First, we originally planned to assess publication bias, but the limited number of included studies prevented us from drawing a funnel plot. However, the total sample size was large and the risk of bias of included studies was generally low. Second, the included studies were primarily from Western countries, especially the US and UK. The only Asian study provided data on the association of rosacea with IBD but lacked respective data of CD and UC for meta-analysis.[43] More studies for rosacea patients in different ethnic groups are needed. Third, we did not find studies that examined the association between rosacea of different severity or phenotypes and IBD. Whether the strength of association differs among patients of different rosacea severity or phenotypes remains unclear.

In conclusion, our study demonstrates a modest association of rosacea with prevalent and incident IBD. Conversely, another study has shown that IBD is associated with an increase in rosacea.[68] Putting together the evidence, rosacea and IBD are related to each other. When rosacea patients suffer from chronic abdominal pain, prolonged diarrhea, and bloody stool, the possibility of comorbid IBD should be considered.

Author contributions

Conceptualization: Ching-Chi Chi.
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Investigation: Fang-Ying Wang, Ching-Chi Chi.
Methodology: Ching-Chi Chi.
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Software: Fang-Ying Wang, Ching-Chi Chi.

Supervision: Ching-Chi Chi.
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