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ORIGINAL ARTICLE

The relationship between inflammatory bowel disease and rosacea over the lifespan: A meta-analysis



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KEYWORDS

Inflammatory bowel disease;
Rosacea;
Meta-analysis

Summary

Backgrounds and aims: It has been argued that the relationship between inflammatory bowel disease (IBD) and rosacea is bi-directional, but this hypothesis has not been explicitly tested. This systematic review examines the bi-directional prospective relationships between IBD and rosacea.

Methods: A comprehensive search through PubMed and EMBASE was undertaken for studies investigating the association between two mainly forms of IBD [ulcerative colitis (UC) and Crohn's disease (CD)] and rosacea published in English until Jan 2018. Reviewers assessed the eligibility of each report by exposure/outcome measurement and study design. Two sets of pooled risk estimates were calculated using fixed or random effects: the direction from IBD to rosacea and rosacea to IBD.

Results: Five publications on 13 separate study results involving 5,051,356 participants were eligible for this meta-analysis. A total of 6 outcomes established the direction of association from IBD to rosacea, and 7 outcomes examined the direction of association from rosacea to IBD. Compared to a non-rosacea population, the pooled RR (95% CI) for overall IBD, UC and CD were 1.32 (1.18–1.49), 1.19 (1.02–1.38) and 1.52 (1.25–1.84), respectively ($P < 0.05$). Meanwhile, the summary RR (95% CI) of rosacea in overall IBD, UC and CD patients were 1.66 (1.50–1.84), 1.69 (1.48–1.93) and 2.08 (1.26–3.46), respectively ($P < 0.05$).

Conclusion: Our meta-analysis confirmed a significant bi-directional association in occurrence of IBD and rosacea. Future studies should specifically investigate possible shared pathophysiological mechanisms between the two disorders.

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Introduction

Inflammatory bowel disease (IBD), mainly including ulcerative colitis (UC) and Crohn's disease (CD), is a group of

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IBD	inflammatory bowel disease
UC	ulcerative colitis
CD	Crohn's disease
RR	risk ratio
ROS	reactive oxygen species

chronic relapsing inflammatory conditions of the gastrointestinal tract [1]. A deal of studies indicated IBD affected nearly 1.5 million Americans and 3 million Europeans, with peak incidence in the second and third decades of life [2,3]. Rosacea is a common chronic inflammatory skin condition characterized primarily by transient or persistent centro-facial erythema, pustules, and telangiectasia [4–6]. Rosacea is not life-threatening, but severely affects quality of life [7,8]. Furthermore, the incidence and prevalence of IBD and rosacea are increasing with time and in different regions around the world [9,10].

Observational studies have examined the potential association between IBD and rosacea. However, the published results were inconsistent. The positive association were found both in rosacea with incident CD and CD with incident rosacea [11,12], whereas this has not been confirmed in rosacea and UC by other studies [13,14]. In sum, evidence suggested that the exposure/outcome relationship between these conditions was bi-directional and might change over the life course. Previous reviews have explored the relationship between IBD and rosacea using retrospective and prospective studies, but none have assessed this relationship from a lifespan perspective by simultaneously examining its bi-directionality. Thus, we performed a meta-analysis to further investigate whether an association or bi-directional association existed between IBD and rosacea.

Methods

Search strategy and selection criteria

A comprehensive search was performed for relevant articles through Jan. 2018 using the following databases:

- PubMed;
- Web of Science (ISI);
- Cochrane library;
- EMBASE;
- Google Scholar.

Search terms included “inflammatory bowel disease (IBD)”, “ulcerative colitis (UC)” and “Crohn’s disease (CD)” and “rosacea”. Moreover, we identified studies not captured by our database by reviewing reference lists from retrieved articles to search for further relevant articles. We followed standard criteria for conducting meta-analyses and reporting the results [15].

Each identified study was independently reviewed by two investigators to determine whether an individual study was eligible for inclusion in this meta-analysis. The inclusion criteria are as follows:

- studies written in English with observational design;
- reported the outcome of IBD (CD and/or UC) or rosacea;
- the exposure was IBD (CD and/or UC) or rosacea;
- odds ratio (OR) or relative risk (RR) estimates with 95% confidence intervals (CIs) were reported.

If data were duplicated in more than one study, we included the study with the largest number of cases. If there was disagreement between the two investigators about eligibility of the article, it was resolved by consensus with a third reviewer.

The following data were collected from all studies: the first author’s name, year of publication, country where the study was performed, sex, number of participants, variables adjusted for in the analysis, as well as multivariate adjusted RRs (ORs for case-control studies) and 95% CIs. For studies that reported results from various covariates analyses, we abstracted the estimates based on the model that included the most potential confounders. The quality of the studies were assessed by using the Newcastle-Ottawa Scale (NOS) based on three perspectives: selection, comparability, and ascertainment of outcome [16]. Full score is nine stars, and studies with more stars were considered to be of higher quality.

Statistical analysis

Pooled measure was calculated as the inverse variance-weighted mean of the natural logarithm of multivariate adjusted ORs or RRs with 95% CIs to assess the association of IBD and rosacea. The Q test and I^2 of Higgins and Thompson were used to assess heterogeneity among studies [17]. I^2 describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance. In the presence of substantial heterogeneity ($I^2 > 50%$) [18], the DerSimonian and Laird random effect model (REM) was adopted as the pooling method; otherwise, the fixed effect model (FEM) was used as the pooling method. The ‘leave one out’ sensitive analysis [19] was carried out using $I^2 > 50%$ as the criteria to evaluate the key studies with substantial impact on between-study heterogeneity. An analysis of influence was conducted [20], which describes how robust the pooled estimator is to removal of individual studies. An individual study is suspected of excessive influence, if the point estimate of its omitted analysis lies outside the 95% CIs of the combined analysis. Publication bias was estimated using Egger’s regression asymmetry test [21].

All statistical analyses were performed with STATA version 12 (Stata Corporation, College Station, Texas, USA). All reported probabilities (P -values) were two-sided, with $P < 0.05$ considered statistically significant.

Results

Study Characteristics

According to the aforementioned search strategy and terms, 175 potentially relevant reports were found. The study identification and selection progression was summarized in Fig. 1. General characteristics in the studies included in this

Table 1 The main characteristics of the included studies.

First author (year of publication)	Country	Sex	Study size	Exposure	Outcome	Adjusted RR (95% CI)	Adjustment for Covariates
Egeberg et al. [11] 2016	Danish	F/M	4,361,688	IBD	Rosacea	Female: UC: 1.24 (1.03–1.48); CD: 1.36 (1.06–1.73) Male: UC: 1.09 (0.81–1.48); CD: 1.71 (1.19–2.43)	Age, sex, socioeconomic status, smoking, alcohol abuse, and healthcare consumption
Li et al. [14] 2016	USA	F	96,314	IBD	Rosacea	Female: UC: 0.94 (0.45–1.95); CD: 2.2 (1.15–4.18)	Age, BMI, alcohol consumption, physical activity, physical examination, multi-vitamin use, smoking, oral contraceptive use, menopausal status, menopausal hormone therapy, use of NSAIDs and use of medications
Wu et al. [22] 2017	China	F/M	268,068	IBD	Rosacea	Female/Male: IBD: 1.94 (1.04–3.63)	Gender, hypertension, diabetes mellitus, interactions among strata of matched cohorts
Spoendlin et al. [12] 2016	United Kingdom	F/M	161,914	Rosacea	IBD	Female/Male: UC: 1.65 (1.43–1.90); CD: 1.49 (1.25–1.77)	Smoking, body mass index, and alcohol consumption
Kim et al. [13] 2017	Korea	F/M	163,372	Rosacea	IBD	Female: UC: 1.49 (0.89–2.49); CD: 2.59 (1.31–5.14) Male: UC: 2.59 (1.59–4.25); CD: 3.03 (1.57–5.83)	Age

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; RR: risk ratio; CI: confidence interval; F/M: female/male.

Table 2 Subgroup analysis of inflammatory bowel disease and rosacea.

Study	Rosacea patients				IBD patients			
	No. of results	RR (95% CI)	I ² (%)	P	No. of results	RR (95% CI)	I ² (%)	P
Overall	7	1.32 (1.18–1.49)	31.60	0.19	6	1.66 (1.50–1.84)	48.30	0.09
Types of IBD								
UC	3	1.19 (1.02–1.38)	0.00	0.29	3	1.69 (1.48–1.93)	38.20	0.20
CD	3	1.52 (1.25–1.84)	19.10	0.63	3	2.08 (1.26–3.46)	67.70	0.04
Study design								
Study design								
Cohort	7	1.32 (1.18–1.49)	31.60	0.19	—	—	—	—
Cross-sectional	—	—	—	—	4	2.25 (1.70–2.99)	19.70	0.29
Case-control	—	—	—	—	2	1.58 (1.42–1.77)	0.00	0.00
Sex								
Total	1	1.94 (1.04–3.62)	—	—	2	1.58 (1.42–1.77)	0.00	0.37
Female	4	1.29 (1.13–1.49)	18.80	0.30	2	1.82 (1.21–2.75)	37.70	0.21
Male	2	1.35 (1.16–1.59)	72.00	0.06	2	2.74 (1.85–4.06)	0.00	0.71
Nations								
USA	2	1.47 (0.64–3.39)	65.7	0.88	—	—	—	—
Europe	4	1.29 (1.14–1.46)	24.20	0.27	2	1.58 (1.42–1.77)	0.00	0.37
Asia	1	1.94 (1.04–3.62)	—	—	4	2.25 (1.69–2.99)	19.70	0.29

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; RR: risk ratio; CI: confidence interval.

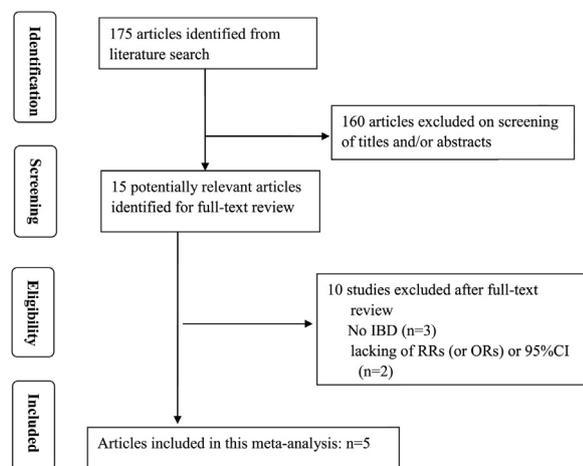


Figure 1 Flowchart of search strategies to identify relevant studies investigating association between inflammatory bowel diseases and rosacea.

meta-analysis were shown in Table 1. A total of 5 publications [11–14,22] with 13 separate study results were eligible for this study. Two publications [12,13] with 6 study results [1 conducted by Spoenclin et al. [12] reported 2 separate results in both sexes (UC and CD), and 1 conducted by Kim et al. [13] reported 4 separate results (men (UC and CD) and women(UC and CD))] explored the association between IBD patients and subsequent of rosacea risk. Three publications [11,14,22] with 7 independent study results [1 conducted by Egeberg et al. [11] reported 4 separate results (men (UC and CD) and women(UC and CD)), 1 conducted by Li et al. [14] reported 2 separate results in women (UC and CD)] suggested a possible association between personal history of rosacea and the risk of IBD. All studies were published in 2016 and 2017, with a total of 5,051,356 participants.

Mean age of all participants of these studies was range from 30–60 years. The variables adjusted in the regression models mainly included age, sex, smoking, body mass index, and alcohol consumption. Of these studies, 2 were conducted in Europe, 1 in America and 2 in China. The overall methodological quality of studies was summarized in Supplementary Tables 1 and 2. Using the Newcastle-Ottawa scale (NOS) quality tool, the score of all the studies ranged from 7 to 8, indicating moderate to high quality.

Rosacea risks in IBD patients

There were two publications with six separate study results on the risks of rosacea in IBD patients. Compared to non-IBD patients, personal history of IBD was significantly associated with an elevated risk of rosacea (RR=1.66, 95% CI: 1.50–1.84), test for overall effect $Z = 9.66$, $P < 0.05$ (Fig. 2). There was no statistically significant heterogeneity among studies ($P_{\text{heterogeneity}} > 0.05$, $I^2 = 48.30\%$). Moreover, similar increased risks of rosacea were also found in UC (RR=1.69, 95% CI: 1.48–1.93) and CD (RR=2.08, 95% CI:1.26–3.46) patients.

IBD risks in Rosacea patients

There were 3 publications with 7 separate study results on the risks of IBD in rosacea patients. The obtained pool RR estimation was 1.32 (95% CI: 1.18–1.49), test for overall effect $Z = 4.67$, $P < 0.05$ (Fig. 2). There was no statistically significant heterogeneity among studies ($P_{\text{heterogeneity}} > 0.05$, $I^2 = 31.6\%$). Besides, rosacea was also significantly associated with increased risks of subsequent UC (RR=1.19, 95% CI: 1.02–1.38) and CD (RR=1.52, 95% CI: 1.25–1.84).

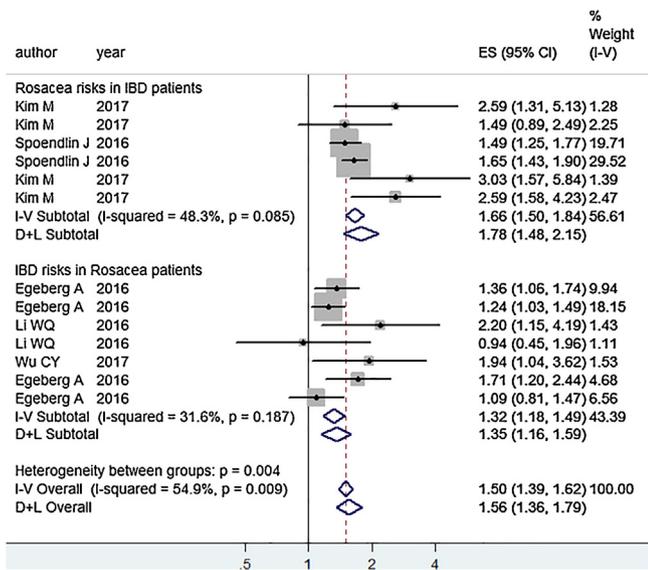


Figure 2 Forest plot of the association between inflammatory bowel diseases and rosacea.

Influence analysis and publication bias

Sensitivity analysis suggested that no individual study had excessive influence on the above-mentioned pooled effect. The Egger test showed no evidence of significant publication bias for the analysis between IBD and rosacea ($P > 0.05$).

Discussion

Based on the limited evidence from observational studies, our meta-analysis supported the hypothesis that a significant bi-directional association between IBD (mainly including UC and CD) and rosacea. That is to say, significant positive associations were found both in the direction from IBD to rosacea and in the direction from rosacea to IBD.

The current evidence associating IBD with rosacea must be interpreted conservatively, because observed relative risks do not necessarily translate into large absolute numbers or a clinically relevant increased risk of disease. The strength of the association was found to be stronger in the direction of association from IBD to rosacea than for rosacea leading to IBD, IBD was associated with a 66% increased risk of rosacea, and rosacea was associated with only modest increased risk of IBD. However, this might be affected by the study design. The two studies [12,13] established the association from IBD to rosacea were case-control and cross-sectional studies, recall bias and selection bias were common shortcomings.

The mechanism underlying the association between IBD and rosacea has not been completely resolved. The two diseases are both chronic inflammatory condition of gastrointestinal tract and skin, which leads to the hypothesis that they are somehow linked [6]. Rosacea was related to both innate and adaptive immune activation, and IBD share common innate inflammatory elements with rosacea. For instance, macrophages and macrophage-derived mediators ROS, matrix metalloproteinases, IL-1b, and tumor necrosis factor contribute pathologically to rosacea and IBD [23–26].

Adaptive immune activation is also a common link between rosacea and IBD. TH1, TH17, and B cells are pathogenic in rosacea and IBD through production of interferon- γ , IL-17, and immunoglobulins [27,28].

This analysis has strengths and limitations. The primary strengths are the expansive literature search and the explicit assessment of the bi-directionality of the IBD-rosacea relationship, which previous reviews have not systematically evaluated. The primary limitation stems from the quantity and quality of the included studies. First, insufficient number of studies was included in this study, which limited us to perform subgroup analysis and meta-regression to explore the probable source of heterogeneity, however, no significant heterogeneity was found among the studies. Despite the number of including studies was relatively small, the total number of participants was very large (5,051,356 participants and 1397 interesting outcomes). Second, because of the observational design, the possibility that other factors may account for the observed association could not be ruled out. Nevertheless, most studies in this meta-analysis adjusted for potential confounders, including age, sex, smoking, alcohol drinking and BMI. Besides, it has been hypothesized that systemic treatment with corticosteroids is associated with risk of rosacea [29,30]. However, among including studies assessing the risk of rosacea in patients with IBD, Spoendlin et al. [12] assessed current use of systemic corticosteroids irrespective of the underlying diagnosis and found that systemic corticosteroids was not associated with a materially increased risk of rosacea. Further studies are needed to evaluate the role of corticosteroids in the development of rosacea. Third, the influence of rosacea subtypes or severity and IBD phenotypes or severity were also not consistently evaluated. Therefore, additional studies are required to validate reported associations. Forth, although we performed a comprehensive search for relevant articles, unpublished studies (grey literature) cannot be ruled out entirely. Egger's regression asymmetry test was conducted to explore possible publication bias, however, no evidence of significant publication bias was indicated by the Egger test ($P < 0.05$).

Conclusion

We suggested an interesting bi-directional association between IBD and rosacea. Further controlled and prospective studies are still needed to completely elucidate this possible bi-directional association between IBD and rosacea.

Author contributions

All authors had access to the data and a role in writing the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found, in the online version, at <https://doi.org/10.1016/j.clinre.2018.09.009>.

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