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REVIEW ARTICLE

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Risk of allergic rhinitis in patients with inflammatory bowel disease: A systematic review and meta-analysis

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KEYWORDS
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Abstract
Background: Numerous parallels exist between inflammatory bowel disease (IBD) and allergic rhinitis (AR), which include risk factors (such as environmental and genetic factors), pathogenesis (immune disorders, epithelial cell barriers, etc.), and treatment (immunosuppressants and immunomodulators, such as cyclosporine and steroids). However, the risk of AR in IBD patients is unknown.
Objective: In this systematic review and meta-analysis, patients with IBD are examined for their risk of AR.
Methods: Several databases are accessible in both Chinese and English, including PubMed, BioRXiv, WanFang, the China National Knowledge Infrastructure (CNKI), Web of Science, METSTR, and MedRxiv. Findings presented at allergy, rhinology, thoracic, and gastrointestinal conferences were analyzed. Based on the inclusion and exclusion criteria, two evaluators independently retrieved data, read the literature, and evaluated bias risk. The data analysis was conducted using RevMan 5.4. Case-control and cohort studies were eligible study designs for this research.
Results: There were 10 case-control studies and 1 cohort study included in the meta-analysis. The experimental group consisted of 65,687 IBD patients, of whom 5838 had AR. A total of 345,176 participants without IBD were included in the control group, of whom 24,625 developed AR. The outcomes demonstrated that IBD patients had a higher risk of developing AR (odds ratio [OR] = 1.48, 95% confidence interval [CI] [1.12, 1.95], Z = 2.78, P = 0.005) than those without IBD.
Conclusion: The risk of AR is higher in IBD patients. Further investigation is required to determine the mechanism behind the association between AR and IBD.

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Introduction

A chronic condition referred to as allergic rhinitis (AR) is described as the inflammatory changes in mucous membranes in the nose caused by exposure to allergens found in the air.[1] There is actually a significant prevalence of AR. Studies have shown that AR affects 40% of the global population, with differences between adults and children and between different countries in the world.[2] In the International Study of Asthma and Allergies in Childhood (ISAAC) Phase III, the prevalence of AR in Turkey population aged 10–18 year is 2.9%, while in Nigeria the prevalence of AR in population aged 13–14 years is 54.1%.[3] In adults, the prevalence of AR ranges from 9 to 42% in the United States. In Europe, the prevalence of AR in adults is 17% in Italy, 28.5% in Belgium, 24.5% in France, 21.5% in Spain, 20.6% in Germany, and 26% in the United Kingdom.[4] A total of € 961.1 per person was spent on AR in Sweden in 2015.[5] Costs will continue to rise due to an increase in disease severity and comorbidities.

Researchers have discovered that AR in children is caused by environmental and genetic risk factors,[6] such as antibiotic usage, air pollution, cigarette smoking, intense physical activity, and epigenetic alterations.[7] However, there is still much to learn about the risk factors of AR. Recognizing the comorbidities of AR may help with early diagnosis, therapy, and further research in the pathophysiology of AR.

Inflammatory bowel disease (IBD) occurs when there is an abnormal immune response in the mucosal lining, which can be triggered by infection with a particular pathogen or the breakdown of the mucosal barrier.[8-10] It manifests as abdominal pain and diarrhea, and in the case of ulcerative colitis as blood in the stool. It consists of Crohn's disease (CD), ulcerative colitis (UC), and IBD-unspecified (IBDU).[10] About 25% of IBD patients develop the disease before the age of 20, about 18% before the age of 10, and about 4% before the age of 5, and the prevalence continues to rise.[11] Although the incidence of IBD may be lower than AR, it is also a common disease within the population.

Many investigations have been performed on the comorbidity of IBD with other disorders, particularly allergies. These diseases share many similarities in terms of risk factors (such as environment and genetics), pathogenesis (including the microbiome, epithelial cell barrier, and immune disorders), and therapeutic approaches (which may involve immunomodulators and immunosuppressants such as steroids and cyclosporine).[12-17] The overactive immune response of the digestive system is regarded as the root cause of IBD. Additionally, they have been linked to numerous extraintestinal symptoms, such as common allergy illnesses (asthma, atopic dermatitis, AR, etc.).[18,19] IBD patients, however, are unknown to be at risk for AR. Therefore, we performed a meta-analysis of individuals with and without IBD to ascertain whether there is a connection between IBD and AR and whether IBD patients may be at more risk for AR.

Methods

This meta-analysis followed PRISMA standards.[20] INPLASY has registered the meta-analysis protocol (Registration No. INPLASY202350077).

Eligibility standards

The following eligibility standards were used: (1) The study had a specific publication year and was a case-control or cohort study. (2) The research intended to investigate the risk of AR in people with IBD. (3) Subjects had IBD or were without IBD (IBD was diagnosed by clinical manifestations and the history of attacks, supplemented by gastrointestinal sampling, colonoscopy, endoscopy, etc.). (4) The diagnosis criterion of AR based on clinical manifestations and related examinations. The clinical manifestations are sneezing, nasal congestion, runny and itchy nose. Relevant tests include allergen excitation, skin prick test, enzyme allergy absorption test, and serum total IgE. (5) Chinese or English publications were used for the study.

The exclusion standards were as follows: (1) In IBD or non-IBD populations, patients with AR were not mentioned in the studies, or the data that were provided were duplicated. (2) Neither the experimental nor control groups met the study standards. (3) The sample information was insufficient. (4) The essay was a review of previously published works. (5) Drug or animal studies were reported.

Non-IBD population was the control group, while IBD population was the experimental group.

Information sources

To locate pertinent research, literature searches were carried out in the following databases: PubMed, WanFang, BioRXiv, China National Knowledge Infrastructure (CNKI), Web of Science, METSTR, and MedRxiv. Additionally, major allergy conferences, such as the World Allergy Organization, Eurasian Respiratory and Allergy Consortium, American Academy of Allergy, Asthma, and Immunology, European Academy of Allergy and Clinical Immunology, were referred. Major nasal conferences, such as American Rhinologic Society, European Rhinologic Society, and major gastroenterological meetings such as the European Joint Gastroenterological Week, American Gastroenterological Association, and Digestive Disease Week were included along with thoracic meetings such as the European Respiratory Society, American Thoracic Society, and American College of Chest Physicians. The retrieval period was from database inception to July 2023, and either Chinese or English was used as the publication language.

Search strategy

The following search terms were combined: "Crohn's Disease," "Ulcerative Colitis," "IBD-unspecified (IBDU)," "Inflammatory bowel disease," "hay fever," and "allergic rhinitis."

Extraction of data and quality evaluation

Two investigators individually examined the literature using the same search strategy and screened it using the criteria for inclusion or exclusion. Studies that were peer-reviewed and unreviewed were both included. Reading the papers' titles and abstracts served as the first screening, and reading the entire texts of the articles served as the second screening. Studies that satisfied the criteria as a whole were chosen and included. Discussions or third-party assistance were used if there was a dispute. Author, year, country, research type, sample size, age, sex, the total number of experimental and control groups, and the number of AR cases were the primary contents of the data extraction.

Quality assessment

Ten case-control studies and one cohort study were included in the meta-analysis; hence, the Newcastle-Ottawa Scale (NOS) served to analyze the quality of the studies.[21] Three criteria were used to evaluate the studies: case selection, group comparability, and exposure factor assessment. Scores for studies might range from 0 to 9, with $\geq$ 6 points indicating reliability. Two researchers assessed the literature separately, and they settled disagreements through discussions and the help of a third party.

Analysis of statistics

In this research, with Review Manager version 5.4, heterogeneity tests, odds ratios (ORs), and 95% confidence intervals (CIs) were calculated. The chi-square test was used to assess interstudy heterogeneity. The I^2 statistic, which showed the percentage of heterogeneity in the overall range of effect size, was used to assess and express the heterogeneity of the included literature. $I^2 > 50\%$ showed blatant heterogeneity. If $P > 0.1$ and $I^2 < 50\%$, the fixed effect model was used for merging. If $P \leq 0.1$ and $I^2 \geq 50\%$, the random effects model was used for merging. Sensitivity analysis and subgroup analysis were also employed to examine the steady combined results and investigate potential causes of heterogeneity when the heterogeneity of test results was high.

Results

Study search results

Characteristics of included studies

From the initial database search, 866 articles were found. There were 716 references left after deleting duplicates. 11 publications altogether from the 24 studies that were chosen for full-text examination were used in the meta-analysis. 13 papers were excluded: 3 lacked any particular data, 1 did not have the entire text available, and 9 studies did not disclose a control group. All the included studies were from peer-reviewed journal, with no study from preprints. Figure 1 shows the flowchart detailing the procedure for choosing research.

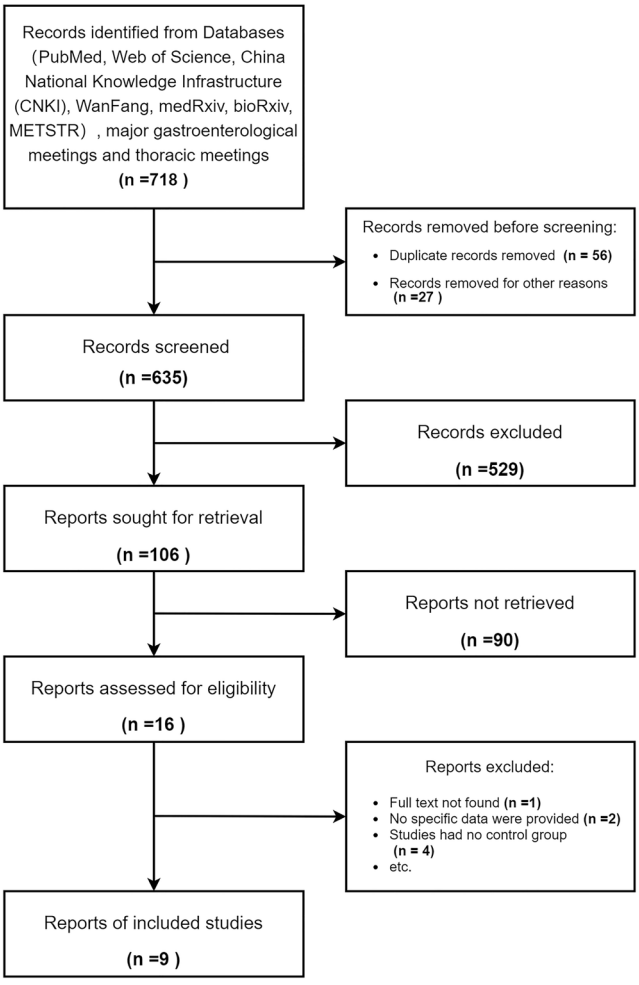

Figure 1 PRISMA flow diagram showing the selection of clinical studies included in the review.

Information about the included studies

Overall, there were 345,176 controls without IBD and 65,687 patients with IBD in the 11 studies. Of these, 5838 IBD patients had AR, and 24,625 controls without IBD had AR. The details of the study are provided in Table 1. The studies were published between 1968 and 2023. In this paper, only the study by Alenezy et al. was a cohort study,[22] while other studies were case-control studies.[17,23-32] All patients in the experimental group suffered from IBD, and patients without IBD were included in the control group. However, all studies differed in age, location, and time; and some of the studies did not describe the sex distribution of patients. Two of the studies were carried out in North America,[22,24] and nine were carried out in Europe.[17,23,25-28,30-32] In some research, the majority of the patients were middle aged adults, with a mean age of 38–48 years;[28] in other investigations, the majority of the patients were teens, with a mean age of 10–15 years.[17,24,25] In the study by Myrelid et al.,[26] the two groups ranged in age from

Table 1 Basic characteristics of included studies.

						Experimental group			Control group		
Country	Type of studies	Country	Number of cases	IBD diagnostic method	AR diagnostic method	Total, n	Mean age	Gender (male/female)	Total, n	Mean Age	Gender (male/female)
Alenezy et al., 2023	Cohort study	Canada	64769	Clinical diagnosis	A prescription nasal spray was used	6346	NA	NA	58423	NA	NA
Card et al., 2016	Case-control studies	UK	336479	Clinical diagnosis	Clinical diagnosis	56097	47.20	26283/29814	280382	47.20	131352/149030
D'Arienzo, 2000	Case-control studies	Italy	100	Clinical diagnosis (histopathological)	Clinical diagnosis (skin prick test)	50	38.34	32/18	50	40.04	25/25
D'Arienzo et al., 2002	Case-control studies	Italy	77	Clinical diagnosis (endoscopic and histopathological)	Clinical diagnosis (skin prick test)	40	NA	NA	37	NA	14/23
Hammer et al., 1968	Case-control studies	UK	562	Clinical diagnosis (histological data and radiological)	Questionnaire	243	NA	NA	319	NA	NA
Jewell and Truelove, 1972	Case-control studies	UK	119	Clinical diagnosis (endoscopic and histopathological)	Clinical diagnosis (intradermal testing)	81	NA	NA	38	NA	NA
Kappelman et al., 2011	Case-control studies	America	4595	Clinical diagnosis	Clinical diagnosis	1242	15.00	683/559	3353	16.00	1811/1542
Myrelid et al., 2004	Case-control studies	Sweden	1059	Clinical diagnosis (endoscopic, histopathological, and radiological)	Questionnaire	280	NA	135/145	779	NA	360/413
Pugh et al., 1979	Case-control studies	UK	754	Clinical diagnosis (histopathological and radiological)	Questionnaire	500	NA	NA	254	NA	NA
Radon et al., 2007	Case-control studies	Germany	2229	Clinical diagnosis	Questionnaire	748	NA	430/318	1481	13.10	711/770
Wasielewska et al., 2019	Case-control studies	Poland	120	Clinical diagnosis (endoscopic, histopathological, and radiological)	Questionnaire	60	14.72	35/25	60	14.85	26/34

Experimental group: IBD with AR group; Control group: Non-IBD with AR group

18 to 50. Only the research by Card et al.[23] comprised all age categories. The specific age distribution and sex distribution of the two groups are not mentioned in the works of Hammer et al.,[32] Alenezy et al.,[22] D'Arienzo et al.,[27,31] Myrelid et al.,[26] and Pugh et al.[30] Additionally, seven of these studies had large sample sizes,[22-26,30,32] whereas the other studies had smaller samples.[17,27,28,31] We also performed a sensitivity analysis of the outcomes. We discovered that the studies with smaller samples had no significant effect on the result, and this finding was relatively robust.

Evaluation of the involved studies' quality

All investigations obtained an average score of 7.2 using the NOS quality rating technique, as shown in Table 2. The final score was between 7 and 8. Because all patients were diagnosed based on standard clinical criteria, the diagnostic results were reliable. For exposure variables, the 11 studies did not provide response rates. A quality evaluation score of 8 was provided for two of the surveys, mostly as a result of variations in the control group. In other investigations with only outpatients, the studies scored 7. The choice of control groups was different among these investigations. In the 11 investigations, hospitalized personnel (non-IBD patients with other conditions),[23,32] patients'families or companions,[27,30] clinical and paramedical workers,[28] and healthy persons[17,22,24-26,31] made up the control group, which varied.

Results of meta-analysis

Overall, AR was more prevalent in IBD patients than in patients without IBD, with high statistical heterogeneity (X^2 = 153.45, df = 10, P < 0.00001, I^2 =93%, OR = 1.48 [95% CI 1.12-1.95], Z = 2.78, P = 0.005). The random effects model was applied because the outcomes revealed P ≤ 0.1 and I^2 ≥ 50% (see Figure 2). The outcomes were statistically noteworthy.

Table 2 Quality evaluation of included studies.

	Selection					Exposure			
Study	Adequate definition of cases	Representativeness of the cases	Selection of controls	Definition of controls	Comparability Control for important factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Scores
Alenezy et al., 2023	1	1	1	1	2	0	1	0	7
Card et al., 2016	1	1	2	1	2	0	1	0	8
D'Arienzo et al., 2000	1	1	1	1	2	0	1	0	7
D'Arienzo et al., 2002	1	1	1	1	2	0	1	0	7
Hammer et al., 1968	1	1	2	1	2	0	1	0	8
Jewell and Truelove, 1972	1	1	1	1	2	0	1	0	7
Kappelman et al., 2011	1	1	1	1	2	0	1	0	7
Myrelid et al., 2004	1	1	1	1	2	0	1	0	7
Pugh et al., 1979	1	1	1	1	2	0	1	0	7
Radon et al., 2007	1	1	1	1	2	0	1	0	7
Wasielewska et al., 2019	1	1	1	1	2	0	1	0	7

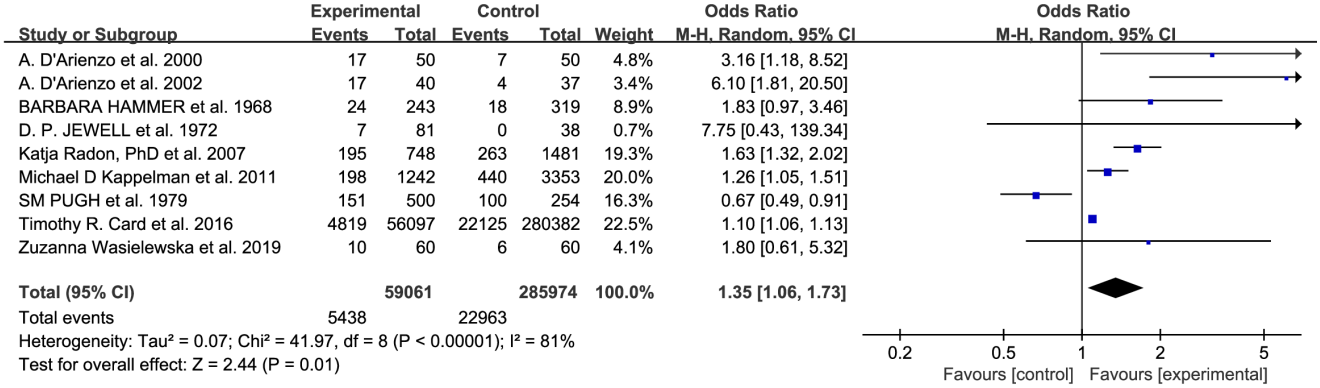

Figure 2 Eleven studies' odds ratios for the proportion of IBD patients with AR contrasted with non-IBD patients with AR are shown in a forest plot with a 95% confidence interval.

Discussion

Statement of the main conclusions

This study highlights the association between IBD and AR. AR is more likely to occur in patients with IBD. To our knowledge, this is the first meta-analysis to investigate the link between AR and IBD.

The etiology of allergy disorders and IBD has many similarities, although the precise mechanism behind their connection is yet unknown. In genetically predisposed people, an imbalance between the body's immune system and intestinal bacteria is a crucial contributing factor.[33-35] The development of immunological illnesses, particularly atopic diseases (such as AR, atopic dermatitis, and asthma), may be impacted by changes in the gut microbiota and a genetic predisposition for IBD in children.[36,37] IBD and AR have similar pathogenesis, as described below. (1) Epithelial barrier: The human body must defend itself against a variety of external stimuli, including allergies, toxins, fungi, bacteria, viruses, and other pathogens. The human body has created protective epithelial barriers, such as those in the skin, lungs, and intestines, to prevent foreign antigens from breaking the immune system barrier. The nasal epithelium barrier serves as the first line of protection against airborne allergens or harmful pathogens. It is formed by cell junctions composed of tight junctions (TJ), viscous junctions, desmosomes, and half-desmosomes.[38] Epithelial barrier dysfunction induces downward infiltration of risk factors and induces a nasal mucosal immune response.[39] The gastrointestinal mucosa acts as a semi-permeable barrier, allowing the absorption and immune sensing of nutrients while limiting the passage of potentially harmful antigens and microorganisms. The intestinal epithelial barrier maintains intestinal integrity and immune homeostasis in a dynamic manner. This is achieved through the interaction between the structural components and molecules of the intestinal mucosa: mucus, outer layer, monolayer epithelial cells, lamina propria, and immune cells (e.g., plasma cells, dendritic cells, lymphocytes, and macrophages).[40-42] There are some differences in location, structure, and partial function between nasal mucosa and intestinal mucosa, but both have similar immune functions. Airborne allergens enter principally through the passageway for the nose, and there is a situation that they may also enter the mouth and settle in the gastrointestinal tract, it is also one trigger of IBD.[43] Pollen that lingers in the stomach has some remaining allergic action, according to some research.[44] As a result, the epithelium interacts with the cellular immune system to serve as the body's initial physical defense against exogenous antigens. If these epithelial barriers are damaged, allergens, pollutants, and external toxins enter the body and cause and promote inflammation to fight them.[45] Flaws in the mucous membrane or epithelial cells might therefore result in a rise in the incidence of respiratory system illnesses. (such as AR, asthma, and COPD), as well as disorders of the digestive system (such as irritable bowel syndrome, IBD).[17,46] AR and IBD are common mucosal inflammatory diseases.[38,47] (2) Microbial alterations: The relationship between AR and IBD is explained by microbial changes. Research has demonstrated that AR patients have altered fecal flora. In addition, IBD patients' fecal microbiomes are much less diverse than those of healthy people, and their gut bacteria are different.[48] This bolsters the idea that the development of AR is influenced by the gut microbiota. In addition, IBD patients' fecal microbiomes are much less diverse than those of healthy people, and their gut bacteria are different.[49,50] Additionally, compared to healthy individuals, patients with IBD have a less stable microbiome.[51] The immune system, which includes the skin, lungs, and brain, is affected by microbiome disruption. As an outcome, the "gut-skin axis," "gut-lung axis," and "gut-brain axis" are produced. As a result, IBD and AR cases are on the rise.[29,52] (3) Immune disorders: Many researchers think that immunological abnormalities involving eosinophils, T helper cells (Th17 and Th-2), and transforming growth factor (TGF-β) might explain the complicated pathological process causing IBD and atopic illnesses (atopic dermatitis, asthma, AR, etc.).[53-56] Recent research has revealed that interleukin (IL)-17-producing Th17 cells are essential for defense. Pathogens are additionally involved in the pathogenic immune-mediated initiation and aggravation of responses, such as IBD and AR.[57] IL-6, IL-23, and IL-1β stimulate the production of Th17 cells, which then secrete IL-22, IL-17, tumor necrosis factor, and proinflammatory cytokines (TNF) to recruit neutrophils and antimicrobial peptides to eliminate external infections. However, Th17 cells have a role in lesions, particularly those of the skin and airways, and are often elevated in the peripheral blood of individuals with atopic illnesses. Th17 cells may encourage neutrophilic and eosinophilic inflammation in AR, which speeds up the progression of the condition.[58] Th17 cells boost immune-mediated responses and encourage IBD progression.[59]

Accordance and divergence from previous research

Although several studies have explored the risk of AR in patients with IBD,[17,22-28,30-32] there has not been a published meta-analysis on this subject. In addition, this meta-analysis compared IBD patients with non-IBD patients, and the rigorous comparison provided strong support for the results. A Korean study showed that AR could increase the risk of developing IBD, indicating that AR and IBD were associated; however, the study did not include a control group, nor did it further explore the relationship between the two using meta-analysis.[60]

Effects on clinical practice

There are many similarities between AR and IBD.[12-15] The findings of the meta-analysis show that individuals with IBD had a greater incidence of AR, suggesting that such people should be cautious about the risk of AR development.

Study heterogeneity

Several factors that may have contributed to the high heterogeneity of this study are as follows: (1) Among the 11 studies included, 5 used AR diagnostic questionnaires,[17,25,26,30,32] one used related drugs to diagnose AR,[22]

and the other used clinical diagnosis combined with related tests.[23,24,27,28,31] This could be one reason for the heterogeneity in the results. (2) Of the included studies, nine were in Europe[17,23,25-28,30-32] and two were in North America[22,24], and regional differences may be one of the reasons for the heterogeneity in study results. (3) There were differences in the diagnosis of IBD among the included studies. Four studies were described as clinical diagnoses only, and it was not determined whether corresponding histological, radiological, or radiological tests were present.[22-25] It is not clear whether this leads to heterogeneity. (4) The sample size of different studies is large, while the sample size of some studies is small.[17,27,28,31] This maybe lead to heterogeneity. (5) Furthermore, low-quality evidence from case-control study designs, lack of control of confounding factors in most articles. Of the included studies, five studies measured confounders such as smoking,[10,22,26] dietary differences,[28] regional differences (farm or city),[25] and survey style (written questionnaire or telephone interview).[25] None of these confounding factors changed the results. But confounders were not measured in any of the other six studies,[17,24,27,30-32] which might have an impact on the results.

Strengths and limitations

The following include a few of the research's advantages: (1) This is the first meta-analysis to research the risk of AR in IBD patients. (2) The rigorous inclusion and exclusion criteria and the elevated level of quality of research indicated by the quality evaluation of the research further supported the reliability of the findings. (3) The sample size of the literature included was large, which supports the research results. There is also a limitation of this study: there is a tight relationship between AR and IBD, we only verified the IBD increases the risk of AR, but risk of IBD in patients with AR was not explored.

Implications for future research

At present, the common pathogenesis of IBD and AR is still unclear, and further exploration of the common pathogenesis of the two is needed in the future. This may provide new ideas and new methods for the development of effective drug therapy. In addition, researchers should further investigate how to reduce the risk of AR in IBD patients and provide better treatments for those involved. It is expected that more relevant studies will be carried out in other regions in the future, with large samples and high-quality case-control studies or cohort studies to reduce sampling error. Furthermore, relevant research should be standardized to improve the level of research design and provide more reliable evidence.

Conclusion

Our findings from meta-analysis allow us to conclude that IBD and AR are connected. The occurrence of AR in people with IBD is higher than it is in individuals in general. It is possible to consider that the incidence of AR and IBD has connections and that IBD increases the risk of AR because of the associated pathologies between the two. This might serve as a foundation for estimating the risk of AR in people with IBD and further investigation into the mechanism causing their comorbidity.

Authors' contributions

Xiongbin Gui was involved in the study's idea and design. Lun Cai, Jie Liu, and Rongrong Yang wrote the first draft of the manuscript. Liping Wei, Huazheng Luo, and Xiongbin Gui critically revised the manuscript. All authors contributed to and approved the final version of the article.

Conflicts of interest

The authors claim that they have no financial conflicts of interest or close personal ties that may be thought to have affected the work shown in this study.

Ethical considerations

The study is only based on published literature, so an ethical declaration is not necessary.

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Data availability declaration

The information in this article includes all the data that were created or analyzed throughout the investigation. The corresponding author should be contacted for any more questions.

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