

Prevalence and bidirectional association between rhinitis and urticaria: A systematic review and meta-analysis

Peng Yongjun¹, Shuying Xu¹, Siming Ni¹, and Chunli Zeng¹

¹Affiliated Hospital of Nanjing University of Chinese Medicine

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Abstract

Background: Rhinitis, allergic rhinitis in particular, and urticaria are both common atopic problems globally. However, there is controversy regarding the correlation between rhinitis and urticaria. **Objectives:** To examine the accurate association between rhinitis and urticaria. **Methods:** Three medical databases (PubMed, Embase, and Web of Science) were searched from database inception until January 11, 2022. The prevalence and association between rhinitis and urticaria were estimated by meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were followed, and quality assessment was performed using the Newcastle–Ottawa Scale. Pooled odds ratios (OR) with 95% confidence intervals (95% CI) and pooled prevalence were calculated using random-effects models. **Results:** Urticaria prevalence in patients with rhinitis was 17.6% (95% CI, 13.2%–21.9%). The pooled prevalence of rhinitis was 31.3% (95% CI, 24.2%–38.4%) in patients with urticaria, and rhinitis prevalence in patients with acute urticaria and chronic urticaria was 31.6% (95% CI, 7.4%–55.8%) and 28.7% (95% CI, 20.4%–36.9%), respectively. Rhinitis occurrence was significantly associated with urticaria (OR, 2.67; 95% CI, 2.625–2.715). **Limitations:** Urticaria and rhinitis were diagnosed based on different criteria possibly resulting in a potential misclassification of these two diseases. **Conclusion:** Rhinitis and urticaria were significantly correlated. Physicians should be cognizant regarding this relationship and address nasal or skin symptoms in patients.

Introduction

Rhinitis, allergic rhinitis (AR) in particular, and urticaria are both common global problems. Basic science and epidemiological studies have reported that AR affects more than 400 million people worldwide.¹ The estimated prevalence of rhinitis in the United States and other developed countries is from 10%–30% in adults and 40% in children,² and the incidence rate continues to increase in developing countries, including China and India.³ Although AR is not deadly, it adversely affects school performance, social life, and work productivity. Moreover, AR has a major influence on quality of life, including a duller sense of taste and smell, disturbed sleep, attention, fatigue, depression, and anxiety/mood syndromes.^{4,5} Considering that rhinitis affects the quality of life in a significant portion of the population and presents a large social and economic burden directly or indirectly, identifying risk factors for it is crucial to further enhance the prevention and control of this disease.

Urticaria is also a common but nonfatal disease. However, it has attracted increasing clinical attention in recent years as studies have reported that this disease as having a severe negative impact on patients' quality of life.⁶⁻⁸

It has been recognized that patients with rhinitis have a higher risk of developing other manifestations of atopic conditions, including asthma, atopic dermatitis (AD), and food allergy.^{9,10} Urticaria is another common condition in allergy and immunology, although its pathogenesis remains unclear.

A high correlation between rhinitis and urticaria has been reported in clinical settings. Many cross-sectional and longitudinal studies have explored the association between rhinitis and urticaria. Most clinical re-

searches have demonstrated that rhinitis was closely correlated with urticaria,¹¹⁻²⁰ while others have reported otherwise.²¹⁻²³ Therefore, whether an atopic association between rhinitis and urticaria exists should be confirmed. Thus, this systematic review and meta-analysis aimed to quantify the prevalence and investigate the association between both aforementioned diseases.

Methods

Search strategy

Since there are no guidelines for assessing the prevalence of systematic reviews studies, we followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines²⁴ to conduct and perform this meta-analysis and systematic review. Three medical databases (PubMed, Embase, and Web of Science) were independently searched by two screeners (XSY and NSM) from database inception until January 11, 2022. The details of the search strategy are listed in Supplementary Table 1. The study protocol was registered online at PROSPERO (ID CRD: 42022311156).

Inclusion and exclusion criteria

The inclusion criteria for studies were as follows: reporting the prevalence of urticaria in patients with rhinitis; reporting the prevalence of rhinitis in patients with urticaria; and reporting the association between rhinitis and urticaria. No restrictions on the study design type and type and/or definition of rhinitis and urticaria were applied. The exclusion criteria were a population size <50 patients and studies written in a language other than English.

Data extraction

Initially, at least two authors (XSY, NSM, and ZCL) independently screened the records on titles and abstracts. Any relevant studies were included for full-text assessment. Duplicates were removed if the same study population was presented in different publications, and the publication with the most comprehensive dataset was included. If there are overlaps of study population in different publications and different parts could fit into various analyses, both publications were included. The following data were collected: author, publication year, age, sex, study design, assessment of rhinitis and urticaria, number of patients in total, number of rhinitis patients, number of rhinitis patients with urticaria, number of controls, number of controls with urticaria, number of urticaria patients, number of urticaria patients with rhinitis, and number of controls with rhinitis. Detailed extracted data of all included studies are presented in Supplementary Table 2. All steps of data extraction were performed by at least two authors, and any potential disagreements were resolved by a reviewer (PYJ).

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies²⁵; studies were scored according to three variables regarding the study population representativeness, comparability, and ascertainment of exposure/outcome. As NOS was for cohort and case-control studies, an adapted version of NOS was created for cross-sectional studies. All studies were graded according to the original (maximum score, 9) and adapted version (maximum score, 10) of NOS. A detailed NOS assessment of all included studies is presented in Supplementary Table 3. We defined the NOS score of [?]7 points as good quality and <7 points as fair or poor quality.

Statistical analysis

A proportional meta-analysis was performed to calculate a pooled effect estimate in the overall population. A pooled proportion (i.e., prevalence) and pooled odds ratio (OR) with their 95% CI were computed with random effects models for the overall populations and various subgroups. The models showing significant between-study heterogeneity were presented. Moreover, the heterogeneity was assessed using Cochran's Q and I² statistics. Forest plots were constructed to present the study results visually. Statistical analysis was performed using the Stata software version 14 (Stata Corporation, College Station, TX, USA).

Results

The literature search yielded a total of 12,859 non-duplicate documents (PubMed=1719, EMBASE=6106, and WOS=5034). After evaluating titles and abstracts, 1165 articles underwent full-text review. Of these, 1111 articles were excluded due to reasons listed in the PRISMA flow diagram (Fig. 1). Finally, 56 publications were included in this analysis. A tabular summary of all analyses performed are presented in Table 1.

Prevalence of urticaria in patients with rhinitis

In total, 17 articles have reported data on the prevalence of urticaria in 14,952 patients with rhinitis, yielding a pooled prevalence of 17.6% (95% CI, 13.2%–21.9%), as presented in Fig. 2.^{15,20,21,26-39} Among reference individuals without rhinitis (5 studies^{21,26-29}; 18,698 reference individuals), the pooled prevalence of urticaria was 7.4% (95% CI 4.3%–10.4%). The overall random-effect of prevalence of urticaria was 15.2% (95% CI, 9.9%–20.4%) in adults with rhinitis (8 studies^{21,26,27,30,32,35,37,38}; 7749 adults with rhinitis) and 17.4% (95% CI, 9.2%–25.6%) in children and adolescents (5 studies^{28,29,31,34,36}; 2421 children and adolescents with rhinitis). When comparing children aged <6 years and those between the ages of 6 and 18, the pooled prevalence of having urticaria in the former (pooled prevalence, 34.8%; 95% CI, 15.3%–54.2%) than in the latter (pooled prevalence 21.3%; 95% CI, 3.3%–38.2%). Categorizing studies according to geographical region, the pooled prevalence of urticaria in patients with rhinitis was the highest among Asians (pooled prevalence, 20.9%; 95% CI, 14.7%–27.2%), followed by North Americans (pooled prevalence, 18.7%; 95% CI, 14.5%–22.9%) and Europeans (pooled prevalence, 15.3%; 95% CI, 9.6%–20.9%).

Fifteen studies had data on the occurrence of urticaria in 14,112 patients with AR; the prevalence of urticaria was 17.8% (95% CI 13.2%–22.5%).^{15,20,21,26,27,30-39} Two studies^{34,39} stratified the activity of rhinitis (persistent rhinitis and intermittent rhinitis), and a significant difference was observed between the aforementioned types. According to statistical analysis, the pooled prevalence of urticaria was 10% (95% CI, 8.0%–12.0%) and 7% (95% CI, -4.0%–17.0%) among patients with persistent rhinitis and intermittent rhinitis, respectively.

In total, 8 studies^{15,21,26-28,34,35} had a sample size of >1000 individuals, which revealed a significantly lower prevalence of urticaria (13.7%, 95% CI 7.4%–20.0%) than the remaining 10 studies,^{20,30-34,36-39} with a sample size of <1000 individuals (20.8%; 95% CI, 13.8%–27.9%). When restricting studies to articles with a clinical diagnosis of both rhinitis and urticaria, the pooled prevalence was 11.4% (95% CI, 4.7%–18.1%) (5 studies^{29,30,33,35,38}; 4061 patients with rhinitis). A total of 8 studies^{15,21,28,29,32,34,35,37} were cross-sectional, 4^{27,30,31,39} were cohort studies, and 5^{20,26,33,36,38} were clinical trials. The pooled prevalence of urticaria was the highest in clinical trials (22.4%; 95% CI, 14.7%–30.0%). Cross-sectional studies and cohort studies had a prevalence of 15.8% (95% CI, 8.7%–22.9%) and 14.9% (95% CI, 6.7%–23.2%), respectively.

Prevalence of rhinitis in patients with urticaria

From a total of 39 studies collectively comprising 6,662,860 patients with urticaria, the overall pooled prevalence of rhinitis was 31.3% (Fig. 3; 95% CI, 24.2%–38.4%).^{6,11-14,16-19,22,23,40-67} The overall pooled prevalence of rhinitis in 7,055,142 reference individuals without urticaria was 19.8% (95% CI, 17.0%–22.6%; 9 studies).^{14,16,17,23,42,45,50,56,61,66} Moreover, in patients with urticaria, the pooled prevalence of AR was 31.3% (95% CI 18.5%–44.1%; 31 studies)^{6,11-14,16-19,22,40-44,46-52,54,56,58,59,61,62,65,66}.

When comparing the prevalence of rhinitis in adult patients with urticaria (7 studies;^{6,44,46,54,58,63,64} 2354 adults with urticaria) with that in children and adolescents (14 studies;^{11-14,23,46,49,50,52,55-57,59,66} 1,305,798 children and adolescents with urticaria), the overall random-effect of prevalence of rhinitis indicated no significant difference between children and adolescents with urticaria (30.6%; 95% CI, 13.8%–47.5%) and adults with urticaria (30.0%; 95% CI, 19.3%–40.7%). Categorizing by geographical region, the prevalence of rhinitis was 26.6% (95% CI, 18.8%–33.6%) in European, 30.6% (95% CI, 20.6%–40.5%) in Asian, 35.9% (95% CI, 12.9%–58.9%) in North American, and 35.3% (95% CI, 16.2%–54.5%) in South American patients with urticaria.

In total, 13 studies had a sample size of >1000 individuals,^{14,17,40-42,47,50,52,56,57,61,62,67} indicating

a higher prevalence of rhinitis (32.5%; 95% CI, 20.8%–44.3%) than the 25 additional studies^{6,11-13,16,18,19,22,23,43,44,46,48,49,51,53-55,58-60,63-66} with a sample size of <1000 individuals (28.9%; 95% CI, 23.9%–36.8%). A total of 11 studies^{13,40,47,52,53,56,59,61,62,64,66} were cross-sectional, 10 were cohort studies,^{6,14,17,23,41-43,49,50,63} and 17^{11,12,16,18,19,22,44-46,48,51,54,55,57,58,60,65,67} were clinical trials. The pooled prevalence of urticaria was the highest among cross-sectional studies (37.9%; 95% CI, 8.5%–67.3%), followed by clinical trials (pooled prevalence, 31.2%; 95% CI, 25.3%–37.0%) and cohort studies (pooled prevalence, 25.0%; 95% CI, 15.5%–34.5%). When restricting the analysis of articles with a clinical diagnosis of both rhinitis and urticaria, the pooled prevalence was 37.4% (16 studies^{16,17,40-42,45,47,49,50,56,58,61-64,66}; 95% CI, 19.0%–55.7%). Only two studies^{6,14} defined rhinitis and urticaria using a self-reported questionnaire completed by patients, and the pooled prevalence of rhinitis was 12.2% in patients with urticaria (95% CI, -2%–26.4%). The pooled prevalence was 27.4% (95% CI, 18.4%–36.3%) in 21 studies,^{11-13,18,19,22,23,43,44,46,48,51-55,57,59,60,65,67} in which rhinitis and/or urticaria were not specifically defined.

Acute urticaria

Three studies^{6,16,67} have reported the occurrence of rhinitis in 430 patients with acute urticaria (AU), with a pooled prevalence of 31.6% (95% CI, 7.4%–55.8%). Two studies^{6,56} examined the prevalence of the parental history of AR in patients with AU, and the pooled prevalence was 39.0% (95% CI, 7.4%–85.5%).

Chronic urticaria

A total of 29 studies have reported the occurrence of rhinitis in 6,082,712 patients with chronic urticaria (CU), resulting in a pooled prevalence of 28.7% (95% CI 20.4%–36.9%).^{11-13,17,18,40,41,43,44,46-53,55,56,58-63,65} The pooled prevalence of AR was 27.7% (95% CI, 8.8%–46.7%) in patients with CU. The prevalence was 30.9% (95% CI, 11.9%–50.0%) in children and adolescents and 26.8% (95% CI 19.5%–34.2%) in adults. When stratifying CU subtypes, the prevalence of rhinitis was 33.4% (95% CI, 8.3%–58.5%) in patients with chronic spontaneous urticaria (CSU) and 34.6% (95% CI 17.3%–51.9%) in those with chronic idiopathic urticaria (CIU). Only one study reported the prevalence of rhinitis in patients with both CSU and CIU (31.7%).⁶² By geographical area, the prevalence of rhinitis was 23.7% (95% CI 13.2%–34.1%) in European, 30.4% (95% CI 16.2%–44.6%) in Asian, 33.5% (95% CI 18.1%–48.9%) in North American, and 29% (95% CI 20.6%–37.5%) in South American patients with CU.

Association between rhinitis and urticaria

The occurrence of rhinitis was significantly associated with urticaria based on the data of 11 studies (OR, 2.67; 95% CI, 2.625–2.715).^{14,17,21,22,34,42,45,47,50,61,66} When examining the association of AR in patients with CU, the corresponding pooled ORs were 3.132 (95% CI, 3.073–3.193).^{17,22,47,50,61} Moreover, the corresponding pooled ORs for AR in patients with CSU was 2.854 (95% CI, 2.665–3.055, 2 studies).^{22,50} Only one study²¹ examined the corresponding pooled OR of AU in patients with rhinitis, revealing a negative association (OR, 0.351 95% CI, 0.28–0.43).

The corresponding pooled ORs were 2.447 (95% CI, 2.326–2.573) and 1.338 (95% CI, 1.250–1.43) according to the studies reporting on the co-occurrence of rhinitis and urticaria in children and adolescents patients or adults patients separately. Only one study¹⁷ has reported on the association between rhinitis and urticaria in male and female patients, and the corresponding pooled ORs were 1.63 (95% CI, 1.52–1.76) and 1.56 (95% CI, 1.47–1.66), respectively.

Study quality and bias assessment

Concerning the prevalence of rhinitis in patients with urticaria, 8 studies were of good quality,^{15,21,26-28,37-39} yielding a pooled prevalence of 17.0% (95% CI, 10.4%–23.5%). The corresponding estimate for studies categorized as being of fair or poor quality was 17.8% (95% CI, 12.3%–23.3%) based on data from 9 studies.^{20,29-36} Regarding the prevalence of urticaria in patients with rhinitis, 23 studies^{14,17-19,22,40-42,45-47,50,52,53,55-58,61-64,66} were of good quality, with a prevalence of 38.3% (95% CI, 29.1%–47.6%), while 16 studies^{6,11-13,16,23,43,44,48,49,51,54,59,60,65,67} were considered of fair or poor quality, with a

prevalence of 19.9% (95% CI, 16.1%–23.6%).

Moreover, a large heterogeneity was observed between the included studies. The respective I^2 was 91% and 99.3% from the studies included for statistics on the prevalence of urticaria in patients with rhinitis and rhinitis in patients with urticaria. Correspondingly, according to the studies on the prevalence of urticaria in patients with rhinitis, the Egger bias test indicated a significant risk of publication bias for the aforementioned analyses ($p=0.001$). However, based on the studies on the prevalence of rhinitis in patients with urticaria, a low risk of publication bias was observed ($p=0.558$).

Discussion

Main finding

The overall prevalence of urticaria in patients with rhinitis was 17.6% (95% CI, 13.2%–21.9%). The pooled prevalence of rhinitis was 31.3% (95% CI, 24.2%–38.4%) in patients with urticaria, and the rhinitis in patients with AU and CU was 31.6 (95% CI, 7.4%–55.8%) and 28.7% (95% CI, 20.4%–36.9%), respectively. The occurrence of rhinitis was significantly associated with urticaria (OR, 2.67; 95% CI, 2.625–2.715).

Interpretation

Although rhinitis and urticaria have been traditionally studied separately, similar pathogenetic mechanisms may exist in one or more endotypes.⁶⁸ For instance, histamine and platelet activating factor (PAF) are both known as the main mediators in the pathophysiology of rhinitis and urticaria, which might explain the clinical phenomenon of their co-existence.⁶⁹ In multiple clinical trials, anaphylaxis has been reported to relieve rhinitis or urticaria with H1-antihistamines, including bilastine and rupatadine, further supporting the close association between rhinitis and urticaria.⁶⁹⁻⁷² Meanwhile, the potential monotherapy for patients with these two diseases has been investigated continuously.

We observed no significant differences in the association between urticaria and AR or non-AR. The frequency of AR symptoms has been classified as intermittent or persistent, and the severity of AR is rated as mild, moderate, or severe in the Allergic Rhinitis and its Impact on Asthma guidelines.^{73,74} This disease has been divided as either seasonal or perennial traditionally, yet this classification is no longer recommended for many limitations.^{5,73,75} According to the statistical analysis, the pooled prevalence of urticaria was 10% (95% CI, 8.0%–12.0%) and 7% (95% CI, -4.0%–17.0%) among patients with persistent rhinitis and intermittent rhinitis, respectively. Only 2 studies reported both AR severity and risk of urticaria development. One study³⁴ suggested that patients with persistent, moderate, or severe AR were more likely to present comorbidities, including asthma and atopic dermatitis, except for urticaria and food allergy. However, based on the data from 35 Italian Centers, Franco and colleagues demonstrated that patients with mild AR had a higher frequency of having no comorbidities, while patients with moderate-to-severe AR had a higher frequency of having two or more comorbidities, including urticaria.³⁵ Few studies have reported data on AR severity in patients with urticaria. More researches should evaluate the association between AR severity and risk of developing urticaria.

There is a consensus that the clinical classification of urticaria should be based on duration and causes/triggers.⁷⁶⁻⁷⁸ AU is defined as a recurrent development of wheals with/without angioedema within 6 weeks, while the recurrent period of >6 weeks is identified as chronic urticaria (CU).⁷⁸ Whether CU is classified as either CSU or chronic inducible urticaria (CIndUs) depends on the skin lesions that appear spontaneously or are induced by a specific trigger.⁷⁹ The following are the common subtypes of CindUs, which are defined as physical urticarias: cold-/heat-induced urticarias, pressure-induced delayed urticaria, solar urticaria, and symptomatic dermatographism. Contact urticaria, aquagenic urticaria, and cholinergic urticaria are non-physical CIndUs. In this meta-analysis, the occurrence of rhinitis in AU was significantly higher than that in CU. Moreover, the difference between the prevalence of rhinitis between patients with CSU (33.4%; 95% CI, 8.3%–58.5%) and those with CIU (34.6%; 95% CI, 17.3%–51.9%) was insignificant. However, the number of studies supporting our findings on the association between rhinitis and more delicate classifications of urticaria is limited.

Rhinitis and urticaria are highly similar, and both of their pathogeneses are complex. For example, the occurrence of IgE-sensitization often appears in both patients with rhinitis and those with urticaria. Clinical researches have revealed that over half of the patients with AR have a personal history of an atopic disease, including urticaria and asthma, as well as an elevated serum IgE level.^{36,39} Mast cells, which contain a myriad of preformed and pre-activated mediators, including cytokines, histamine, and chemokines, are widely known to play a key role in urticaria.^{76,80} These mediators have also been demonstrated to be critical in the mechanism of rhinitis.^{81,82} Rupatadine, as the international evidence-based guidelines recommend second generation H1-antihistamines (sgAH) owing to their dual affinity for PAF and histamine H1- receptors, has been proven to be effective in patients with AR and those with CSU.⁶⁹ Recently, more biomarkers have been identified for both rhinitis and urticaria, including (interleukin) IL-33, IL-6, brain-derived neurotrophic factor, and serum amyloid A.^{80,83-86}

This study has some limitations. First, urticaria and rhinitis were diagnosed based on different criteria between studies, varying from self-reporting to diagnosis by a physician, possibly resulting in a potential misclassification of these two diseases. Second, the scope of study populations is different between studies, varying from school- and hospital-wide to nation-wide populations. Third, our study excluded studies written in languages other than English, potentially affecting the generalization of results. Third, only two studies have reported on the activity of rhinitis and risk of developing urticaria. The linear relationship between rhinitis activity and risk of developing urticaria needs further research. Last, only two studies had data on the co-occurrence of rhinitis and AU, which could have biased our results. Further research on this matter is warranted.

Conclusion

This meta-analysis revealed that 17.6% of patients with rhinitis have urticaria, whereas the prevalence of rhinitis among patients with AU and CU was 40.7% and 29.0%, respectively. The occurrence of either rhinitis or urticaria was associated with significantly increased odds of developing other disorders as well. Further research to investigate the relationship with disorder severity is warranted.

List of abbreviations

AD, atopic dermatitis

AR, allergic rhinitis

AU, acute urticaria

CI, confidence intervals

CU, chronic urticaria

OR, odds ratios

PAF, platelet activating factor

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Figure legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for the search strategy used.

Figure 2. Risk of having rhinitis in urticaria.

Figure 3. Risk of having urticaria in rhinitis.

Table 1. Prevalence estimates and quality assessment according to different patient characteristics



