

Comorbid allergy and rhinitis and patient-related outcomes in asthma and COPD: a cross-sectional study

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ABSTRACT

Introduction: The study aimed to compare prevalence of comorbid allergic manifestations and rhinitis, allergy testing and associations with patient-related outcomes in patients with asthma and COPD.

Methods: Cross-sectional study of randomly selected Swedish patients with a doctor's diagnosis of asthma ($n = 1291$) or COPD ($n = 1329$). Self-completion questionnaires from 2014 provided data on demographics, rhinitis, allergic symptoms at exposure to pollen or furry pets, exacerbations, self-assessed severity of disease and scores from the Asthma Control Test (ACT) and the COPD Assessment Test (CAT), and records were reviewed for allergy tests.

Results: Allergic manifestations were more common in asthma (75%) compared with COPD (38%). Rhinitis was reported in 70% of asthma and 58% of COPD patients. Allergy tests had been performed during the previous decade in 28% of patients with asthma and in 8% of patients with COPD.

In patients with asthma; comorbid allergy and rhinitis were both independently associated with increased risk for poor asthma symptom control (ACT < 20) (OR [95% CI] 1.41 [1.05 to 1.87] and 2.13 [1.60 to 2.83]), exacerbations (1.58 [1.15 to 2.17] and 1.38 [1.02 to 1.86]), and self-assessed moderate/severe disease (1.64 [1.22 to 2.18] and 1.75 [1.33 to 2.30]). In patients with COPD, comorbid allergy and rhinitis were both independently associated with increased risk for low health status (CAT ≥ 10) (OR [95% CI] 1.46 [1.20 to 1.95] and 2.59 [1.97 to 3.41]) respectively, with exacerbations during the previous six months (1.91 [1.49 to 2.45] and 1.57 [1.23 to 2.01]), and with self-assessed moderate/severe disease (1.70 [1.31 to 2.22] and 2.13 [1.66 to 2.74]).

Conclusion: Allergic manifestations and rhinitis are more common in asthma than COPD but associated with worse outcomes in both diseases. This highlights the importance of examining and treating comorbid allergy and rhinitis, not only in asthma but also in COPD.

ARTICLE HISTORY

Received 11 May 2024

Accepted 22 August 2024



KEYWORDS

Asthma; chronic obstructive pulmonary disease; allergy; rhinitis; exacerbations; self-assessed severity of disease; asthma control test; assessment test

Introduction

Asthma and COPD are common respiratory diseases, affecting 8–10% of the population worldwide [1,2]. Both conditions are characterised by chronic airway inflammation and airflow obstruction, which can potentially lead to structural remodeling [1,2]. Rhinitis is a common condition of the upper airways, and includes both allergic and non-allergic forms [3]. The observational study BREATHE, conducted in Denmark and Sweden, found that allergic rhinitis was present in 55% of patients with

asthma, 35% of patients with COPD and 42% of those with a double diagnosis [4]. In a French observational cross-sectional study involving 17 000 asthma patients, the frequency of allergic rhinitis was reported to be 55% [5]. Other studies have described an allergic phenotype in asthma in 50% of asthma patients [6] and in 25–30% of COPD patients [7]. However, assessment of allergic sensitization and environmental exposures is recommended in international guidelines of asthma [1] but is not included in guidelines of COPD management [2].

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In asthma, rhinitis has been reported to increase the risk of hospitalisations and emergency visits, as well as adverse effects on asthma control, health-related quality of life and lung function [8–14]. In COPD, studies are more scarce but allergic rhinitis has been shown to be associated with an increased risk for COPD exacerbations [7,15]. However, studies exploring both rhinitis and allergic manifestations and their associations with other patient-related manifestations in patients with COPD are still lacking. In addition, studies investigating and comparing both prevalences and associations with important outcomes in asthma and COPD are missing. As other patient characteristics may differ between investigated populations and contribute to differences in prevalence and associations with outcomes, studies comparing randomly selected populations of patients with asthma and COPD obtained from the same centres are needed.

We hypothesised that comorbid allergy and rhinitis is common not only in asthma but also in COPD, that allergy tests are underused, and that comorbid allergy and rhinitis are associated with poor patient-related outcomes in both asthma and COPD. Consequently, the primary aim of our study was to determine the prevalence of allergy and rhinitis in patients with asthma and COPD from both primary and secondary care in the same area in central Sweden. The secondary aims were to determine to what extent allergy tests had been performed, both in the entire populations and in the subpopulations of patients diagnosed with their obstructive disease during the present study period; and to determine the associations of reported allergy and rhinitis with patient-related outcomes, in these patients. The outcome variables were Asthma Control Test (ACT) [16] for patients with asthma, COPD Assessment Test (CAT) [17] for patients with COPD,

and exacerbations during previous six months and subjective moderate/severe disease among patients with asthma and COPD.

Methods

Study design and data collection

This was a cross-sectional study using questionnaire data collected during 2014 and 2015. In addition, medical record review from the period of 1 January 2004 to 31 December 2014 was used to address the secondary aim of examining allergy testing.

The study included randomly selected patients from primary and secondary care with a doctor's diagnosis of asthma or COPD. Data were obtained from 13 hospitals and 54 primary health care centers in central Sweden (Figure 1). At each site, lists of all patients with the inclusion criteria of age 18–75 years and a doctor's diagnosis of asthma (International Classifications of Diseases (ICD) J45) and COPD (ICD J44), respectively, were collected. There were no exclusion criteria other than the need of cognitive and linguistic ability to understand and complete the questionnaire. From all lists, a centralised random selection using the web page <http://www.random.org> was performed, to achieve a number of 2804 patients with asthma and 2310 patients with COPD to which letters with questionnaires were sent together with an invitation letter, a consent form and a pre-stamped envelope for returning the completed questionnaires. The number of invited patients was based on a power analysis including adjustment for expected attrition. The numbers of patients receiving, returning and having completed the questionnaires is summarised in Figure 1 and in the result section. Self-reported data from questionnaires were collected in 2014–2015, including patient demographics, allergy, rhinitis, exacerbations and self-assessed severity

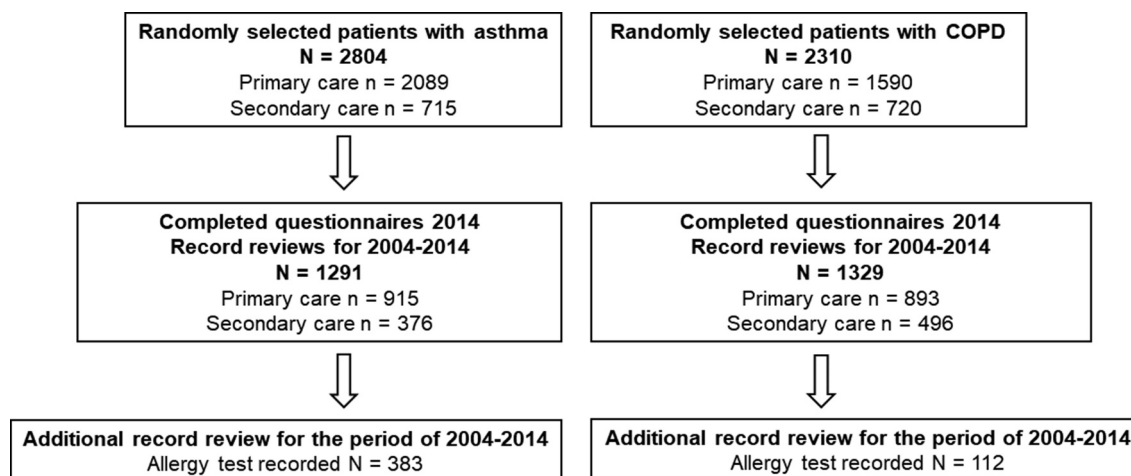


Figure 1. Flow chart.

of disease. The asthma questionnaires also included the Swedish version of ACT [16] and the COPD questionnaires included the Swedish version of the CAT [17].

Allergy was defined as self-reported allergic symptoms with exposure to pollen or furry pets any time and rhinitis as self-reported symptoms of rhinitis within the previous 12 months.

ACT measures asthma symptom control using five items on a 5-point score from 1 to 5 referring to the previous four weeks, where the main outcome is the total score. An ACT score of 25 denotes excellent asthma control, and poor asthma control is defined as ACT score <20 [16]. CAT assesses COPD-related health status and includes eight items on a 6-point score from 0 to 5 referring to the present status, where the main outcome measure is the total score. A CAT score ≥ 10 indicates low COPD-related health status [17].

In this study, an exacerbation of asthma or COPD was defined as a worsening of respiratory symptoms requiring an emergency visit or an oral steroid course during the previous six months, with or without concomitant antibiotics. Self-assessed severity of disease was reported as very mild, mild, moderate, severe or very severe. The answers were dichotomised into the categories 'mild' (very mild and mild) and 'moderate/severe' (moderate, severe and very severe) asthma or COPD.

Smoking was categorised as current daily smoking, occasional smoking, ex-smoking or non-smoking. Body mass index (BMI, kg/m²) was divided into four groups; underweight (<20), normal weight (20–24.9), overweight (25–29.9) and obesity (≥ 30). The education variable was dichotomised as continued full-time education for at least two years beyond the Swedish compulsory school period of nine years or not. Age was categorised into three groups, <60 years, 60–69, and ≥ 70 years.

Information on allergy testing with blood or skin prick tests during the study period was obtained from reviews of medical records from the period of 1 January 2004 to 31 December 2014.

Statistics

The primary outcomes, prevalences of allergy against pollen or furry pets and rhinitis during the previous 12 months were calculated in patients with asthma, COPD and concomitant asthma and COPD, respectively. The secondary outcome of prevalence of performed allergy tests were calculated in the entire population, as well as in subpopulation where the asthma or COPD was diagnosed during the study period.

Unadjusted and adjusted logistic regression was used to examine the secondary outcomes of associations with allergy and rhinitis, respectively, with exacerbations,

disease severity, and asthma symptom control or COPD-related health status. Multivariable analysis adjusted for sex, age (three groups), smoking habits (four groups), body mass index (four groups) and educational level. The outcome variables were at least one exacerbation during the previous 6 months, subjective moderate/severe disease, poor asthma control (ACT <20) and low COPD-related health status (CAT ≥ 10). All statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA). *p* values <0.05 were considered statistically significant.

Ethics

The study was approved by the regional ethical board in Uppsala, Sweden, Dnr 2011/318. All patients gave written informed consent.

Results

Patient characteristics

In total, 1291 patients with asthma and 1329 patients with COPD were included. The characteristics of the study populations are presented in Table 1. In summary, the asthma population was younger and had a higher proportion of women, never smokers and patients with higher level of education. Having had exacerbations during the previous six months and subjectively assessing one's disease as moderate or severe as opposed to mild disease, were more common in patients with COPD than in those with asthma.

Prevalence of allergy and rhinitis

Allergic manifestations due to pollen and furry pets were reported in 75% (*n* = 968) of patients with asthma and in 38% (*n* = 505) of patients with COPD (Figure 2). Rhinitis during the previous 12 months was reported in 70% (*n* = 904) of the patients with asthma and 58% (*n* = 771) of the patients with COPD (Figure 2).

Prevalence of allergy tests

During the study period, 30% (*n* = 503) of patients with asthma and 8% (*n* = 106) of those with COPD were tested for allergy. Among patients with asthma and an allergy test, 54% were reported as testing positive. The corresponding number for COPD was 28%.

In patients who were diagnosed with asthma (*n* = 336) or COPD (*n* = 615) during the present study period, allergy testing was performed in 41% and 11%, respectively.

Table 1. Patient characteristics.

	Asthma N = 1291 n (%)	COPD N = 1329 n (%)
Sex		
Female	793 (61)	745 (56)
Male	498 (39)	584 (44)
Age		
<60	708 (55)	167 (12)
60-69	336 (26)	553 (42)
70-79	247 (19)	609 (46)
Smoking		
Never	723 (57)	57 (4)
Ex	416 (32)	829 (64)
Occasional	62 (5)	75 (6)
Current	74 (6)	345 (26)
BMI		
<20	13 (1)	82 (6)
20-24.9	311 (24)	349 (27)
25-29.9	497 (38)	488 (38)
≥30	494 (37)	371 (29)
Educational level		
Low	808 (63)	1135 (87)
High	466 (37)	164 (13)
Exacerbations during the previous six months	335 (26)	452 (34)
ACT <20	509 (39)	
CAT ≥10		959 (72)
Moderate/severe disease	581 (45)	796 (66)
Performed allergy tests during the study period	383 (30)	111 (8)
Concomitant asthma and COPD	119 (9)	119 (9)

Patient characteristics by obstructive disease. Abbreviations: ACT = Asthma Control Test, BMI = body mass index, CAT = COPD Assessment Test, COPD = chronic obstructive pulmonary disease, N = numbers.

Comorbid allergy and rhinitis and patient-related outcomes

The results from logistic regression analyses of associations allergy and rhinitis with patient-related outcomes are shown in Table 2 and Figure 3.

Having comorbid allergic manifestations due to pollen and furry pets was independently associated with

poor asthma symptom control defined as ACT score < 20, with low COPD health status defined as CAT score ≥ 10, with having had exacerbations during the previous six months, and with self-assessed severe or moderate disease as compared with mild disease (Table 2, Figure 3).

Rhinitis during the previous 12 months was independently associated with poor asthma symptom control defined as ACT score < 20, with low COPD health status defined as CAT score ≥ 10, with having had exacerbations during the previous six months, and with self-assessed moderate/severe disease (Table 2, Figure 3).

Discussion

The first main finding and primary outcome of our study in central Sweden was that allergic manifestations due to pollen or furry pets and rhinitis during the previous 12 months was common in both asthma and COPD. The second main finding and secondary outcome was that, in spite of this, allergy testing with skin or blood test had only been recorded in a minority of these patients. The third main finding and further secondary outcome was that allergy due to pollen or furry pets and rhinitis were independently associated with several adverse patient-related outcomes.

The primary outcome, prevalence of reported allergy, is consistent with the previous findings of the BREATHE study, where concomitant allergic rhinitis was more common in patients with asthma than in COPD [4]. However, although we found that both allergy and rhinitis were more common in asthma

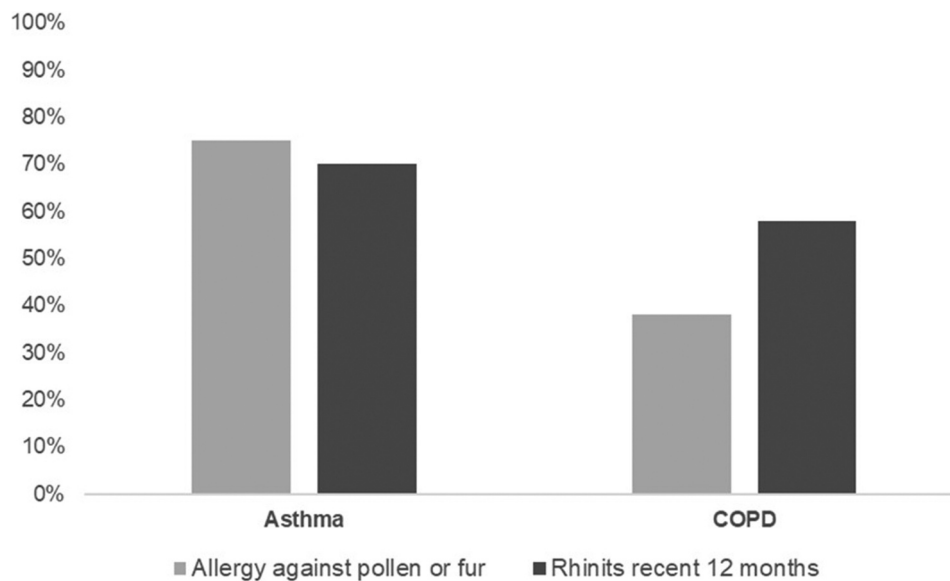
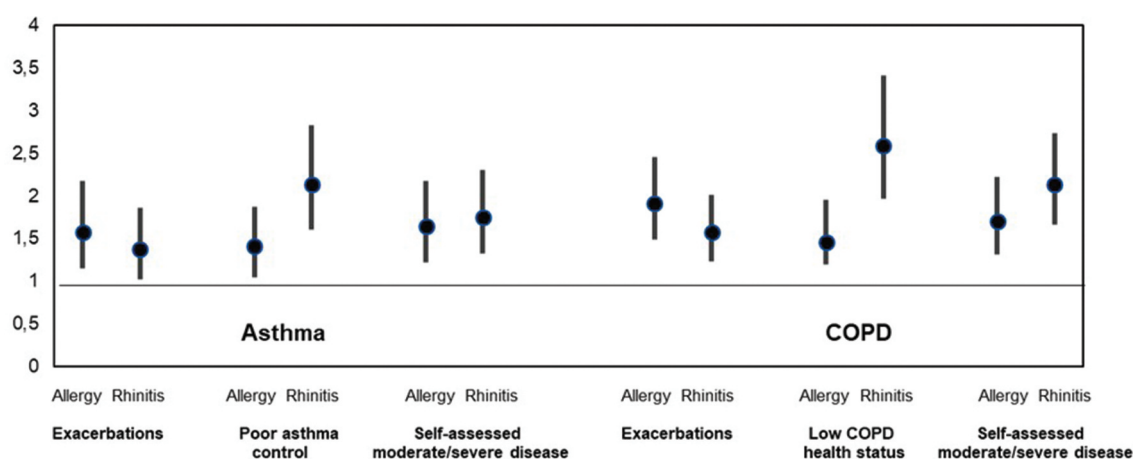


Figure 2. Prevalence of allergy and rhinitis in asthma and COPD.

Table 2. Associations of allergy and rhinitis with patient-related outcomes.

	Asthma		COPD	
	Exacerbation >1 in the previous 6 months			
	OR (95% CI)	p-value	OR (95% CI)	p-value
Allergy due to pollen or furry pets	1.58 (1.15 to 2.17)	0.005	1.91 (1.49 to 2.45)	<0.001
Rhinitis during the previous twelve months	1.38 (1.02 to 1.86)	0.036	1.57 (1.23 to 2.01)	<0.001
	ACT <20			
Allergy due to pollen or furry pets	1.41 (1.05 to 1.87)	0.020		
Rhinitis during the previous twelve months	2.13 (1.60 to 2.83)	<0.001		
	CAT ≥10			
Allergy due to pollen or furry pets			1.46 (1.20 to 1.95)	0.010
Rhinitis during the previous twelve months			2.59 (1.97 to 3.41)	<0.001
	Moderate/severe disease			
Allergy due to pollen or furry pets	1.64 (1.22 to 2.18)	<0.001	1.70 (1.31 to 2.22)	<0.001
Rhinitis during the previous twelve months	1.75 (1.33 to 2.30)	<0.001	2.13 (1.66 to 2.74)	<0.001

Results from multivariate logistic regression with ≥ 1 exacerbation recent 6 months, ACT <20, CAT ≥ 10 and self-assessed moderate/severe disease as dependent variables. Adjustment for sex, age, smoking habits, body mass index and educational level. Abbreviations; CI = confidence interval, COPD = chronic obstructive pulmonary disease, OR = odds ratio.

**Figure 3.** Associations of allergy and rhinitis with patient-related outcomes.

than in COPD in our study, the prevalence of allergy in COPD was higher than what has been reported in the Swedish general population. In the Swedish sub studies from the European population-based GA²LEN study on symptoms of asthma and rhinitis, the reported prevalence of allergic rhinitis was 31% and the prevalence of chronic rhinosinusitis 11% [13,18]. Consequently, allergy and rhinitis are important conditions to consider not only in asthma but also in COPD. As for the secondary outcome of allergy testing, allergy tests were performed in only a small proportion of patients who reported allergy. This proportion was higher in the subgroup of patients whose obstructive disease was diagnosed during the study period, but even in this group the majority of patients was not tested for allergy. In the present study, rhinitis was associated with important patient-related outcomes and an underlying allergy may indicate the need for altering the medical treatment. Interestingly, a positive result from the allergy tests were recorded in 54% with asthma and 28% with COPD. In our opinion, allergy testing could

be performed to a larger extent than presently as a basis for correct treatment.

Further secondary outcome in our study were associations of allergy and rhinitis with several important patient-reported outcomes. Our findings that allergy and rhinitis are associated with exacerbations and poor asthma control in patients with asthma is in line with several previous asthma studies reporting an increased risk for exacerbations [8–10] and poor asthma control as measured by Asthma Control Questionnaire ACQ [12,13]. Our study adds the information on increased risks for poor asthma control assessed by ACT and for self-assessed disease severity in patients with asthma. The association of allergy and rhinitis with exacerbations has been reported in COPD patients from tertiary centres and from population-based studies [7,15], but to the best of our knowledge, our reported associations with CAT score and self-assessed disease severity in patients with COPD in both primary and secondary care are novel findings. Another unique aspect of our study is

that all patients were from the same geographic area and centres, which facilitated the comparison of allergy and rhinitis in patients with asthma and COPD.

The biological explanation for our findings could be the underlying, shared inflammation in the upper and lower airways; the united airways disease hypothesis [19–22]. This hypothesis is supported by previous findings about nasal symptoms in patients with asthma and COPD being associated with several different inflammatory parameters [19], that rhinitis is associated with chronic bronchitis [20], and that similar epithelial and basal membrane features are found in asthma and chronic rhinosinusitis [23,24]. Allergen-induced inflammation, postnasal drip, naso-bronchial reflex, and systemic immune response may also contribute to the association between the lower and upper airway [21].

Strengths and limitations

The major strength of our study is that the population includes randomly selected patients from both primary and secondary care, which should result in a high generalisability and external validity. Other strengths are the investigation and comparison of allergy and rhinitis in both asthma and COPD, and that associations with several clinically important patient-related outcome measures were investigated.

A major limitation in our study is that the doctor's diagnoses of the study were not verified objectively, which could mean both under- and over diagnoses of asthma and COPD. However, as they were based on electronic medical records they represented real world data. We also believe that clear associations with patient-related associations indicate that most patients had true obstructive disease. Other limitations are that the outcome data were self-reported which may cause recall bias, and that data on allergy tests were confirmed by medical records but for a limited time period, potentially resulting in false low numbers. Finally, the cross-sectional design of the study does not allow for conclusions of causal relationships between allergy/rhinitis and patient outcomes, and there may be other confounding variables such as environmental factors, genetic predisposition or adherence to treatment regimens which could influence the results.

Clinical implications and generalisibility

An important clinical implication of our study is to consider and treat allergy and rhinitis in both asthma

and COPD, with the aim of improving several patient-related outcomes. As prevalence of allergy and rhinitis has been reported to increase during the recent years [13,18], this makes the result even more relevant. Our results are consistent with several studies in different countries [4,7–10,12,13,15], and as the pathophysiological impact of allergy and rhinitis on patient-related outcomes should reasonably be the same regardless of where the patients live. Subsequently, we believe that our findings have high external validity and generalisability outside Sweden as well.

Conclusion

Allergic manifestations due to pollen and furry pets, and rhinitis are more common in asthma than COPD but associated with worse outcomes in both diseases. This highlights the importance of examining and treating comorbid allergy and rhinitis not only in asthma but also in COPD.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

No specific funding related to this study.

Data availability statement

Data cannot be made freely available as they are subject to secrecy in accordance with the Swedish Public Access to Information and Secrecy Act, but can be made available to researchers upon request, after approval from the Swedish Ethical Review Authority has been obtained.

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