

Allergic Status is Associated with Increased Number of Asthma Exacerbations

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RATIONALE

- Allergic asthma, predominant among asthma phenotypes, coexists with atopic (allergic) symptoms such as sinusitis, rhinitis, conjunctivitis, and nasal polyps. It is unclear to what extent these symptoms may be linked to asthma-related complications.
- We aimed to investigate the following research question: is allergic status associated with increased number of asthma exacerbations?

METHODS

Study Design

- Cross-sectional analysis used data from administrative healthcare claims linked with electronic medical records (EMR).
- We identified severe asthma patients having ≥ 2 asthma claims with an ICD-9 code of 493.xx in the identification period of 7/1/2008 - 3/31/2013, 12 years of age or older, and who had evidence of step V or VI asthma therapies: high-dose inhaled corticosteroid (ICS), omalizumab, or oral corticosteroid (OCS).¹
- Patients not continuously enrolled for 6 months before the index date (baseline) and 1 year after (follow-up) were excluded. Subjects were followed for ≥ 1 year, until the end of study period (median follow-up time was 2.2 years).

Measures

- We defined an asthma exacerbation as an OCS burst (≤ 15 days supply), or an asthma-related (primary diagnosis of asthma) hospitalization or ED visit. Exacerbations were measured during the baseline and follow-up periods.
- Demographic characteristics were measured at index (age) and during follow-up (sex, race, and region) periods.
- Selected comorbidities were measured during follow-up, including the Charlson Comorbidity Index (CCI), chronic obstructive pulmonary disease (COPD; 491.x, 492.x, 496.x), gastroesophageal reflux disease (GERD; 530.10, 530.11, 530.12, 530.19, 530.81), and allergy-related comorbidities.
 - Allergy-related comorbidities were defined via ICD-9 codes and included sinusitis (461.x, 473.x), rhinitis (472.0, 477.0, 477.8, 477.9), conjunctivitis (372.0x, 372.1x, 372.2x, 372.3x), and nasal polyps (471.x).

Statistical Analysis

- We used negative binomial regression to model the number of exacerbations (dependent variable) based on the presence of allergy-related comorbidities (combined and independently), controlling for patient's age, sex, region, selected comorbidities, baseline exacerbations, and medication use.

METHODS (continued)

Statistical Analysis (continued)

- The main predictor in Model 1 was the count of allergy-related comorbidities that were present, while in Model 2 the main predictors were the individual allergy-related comorbidities.
- We ran sensitivity analyses of Models 1 and 2 by removing patients with nasal polyps, who may be treated with OCS.
- Results were annualized to account for variable follow-up.
- Data transformations and statistical analyses were performed using SAS® version 9.4. Statistical significance was pre-established at $P=0.05$.

RESULTS

Demographic Characteristics

- Study included 6,784 asthma patients, 68.4% were female, and mean age was 52.3 years (standard deviation [SD]=18.1) (**Table 1**).
- Patients were primarily Caucasian (81.4%) or African American (7.9%) and resided predominately in the Midwest and South regions in the US (**Table 1**).

Age, year, mean (SD)	52.3 (18.1)
12-17, n (%)	347 (5.1)
18-50	2,568 (37.9)
51-64	1,983 (29.2)
65+	1,886 (27.8)
Female, n (%)	4,642 (68.4)
Race, n (%)	
African American	538 (7.9)
Asian	70 (1.0)
Caucasian	5,524 (81.4)
Other/Unknown	652 (9.6)
Region, n (%)	
Midwest	2,944 (43.4)
Northeast	338 (5.0)
South	3,021 (44.5)
West	481 (7.1)

^a Demographic indicators were measured at index (age) and during follow-up (sex, race, and region).

Selected Comorbidities and Asthma Exacerbations during Follow-up

- Patients had a mean CCI of 2.8 (SD=2.7), while 30.8% had COPD, and 36.8% had GERD (**Table 2**).
- Rhinitis (45.7%) and sinusitis (43.0%) were most common among patients, followed by conjunctivitis (11.2%), and nasal polyps (2.9%), shown in **Figure 1**.
 - An average patient experienced a mean of 1.0 (SD=0.9) of these symptoms in the follow-up period.

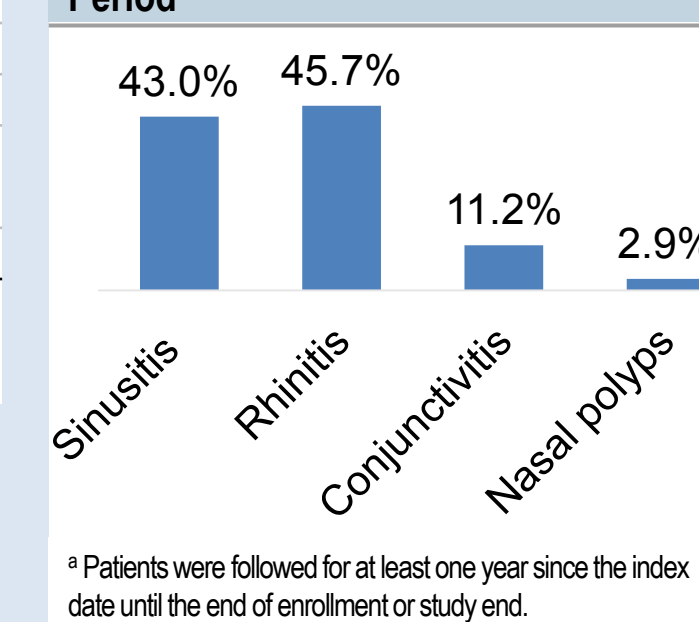
RESULTS (continued)

Selected Comorbidities and Asthma Exacerbations during Follow-up (continued)

Charlson Comorbidity Index, mean (SD)	2.8 (2.7)
COPD, n (%)	2,087 (30.8)
Gastroesophageal reflux disease, n (%)	2,495 (36.8)
No. of allergy-related comorbidities, mean (SD)	1.0 (0.9)
No. of asthma exacerbations^b, PPY (SD)	0.90 (2.01)

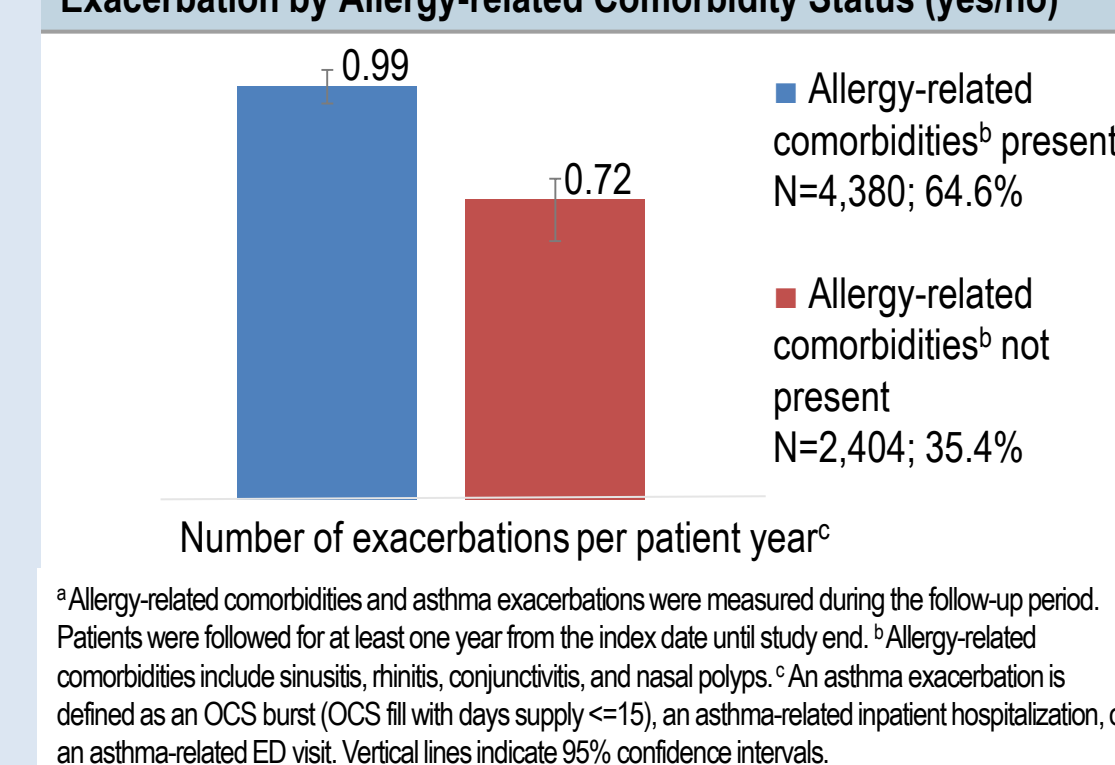
^a Patients were followed for at least one year since the index date until the end of enrollment or study end. ^b An asthma exacerbation is defined as an OCS burst (OCS fill with days supply ≤ 15), an asthma-related inpatient hospitalization, or an asthma-related ED visit.

Figure 1. Comorbidities in Follow-up Period^a



- Asthma exacerbations occurred at a rate of 0.90 exacerbations per patient year (PPY) (SD=2.01), with a higher number of exacerbations PPY among patients with an allergy-related comorbidity (0.99, SD=2.06) than in those without it (0.72, SD=1.87), $P<0.001$ (**Figure 2**).

Figure 2. Unadjusted Annualized Number of Asthma Exacerbation by Allergy-related Comorbidity Status (yes/no)^a



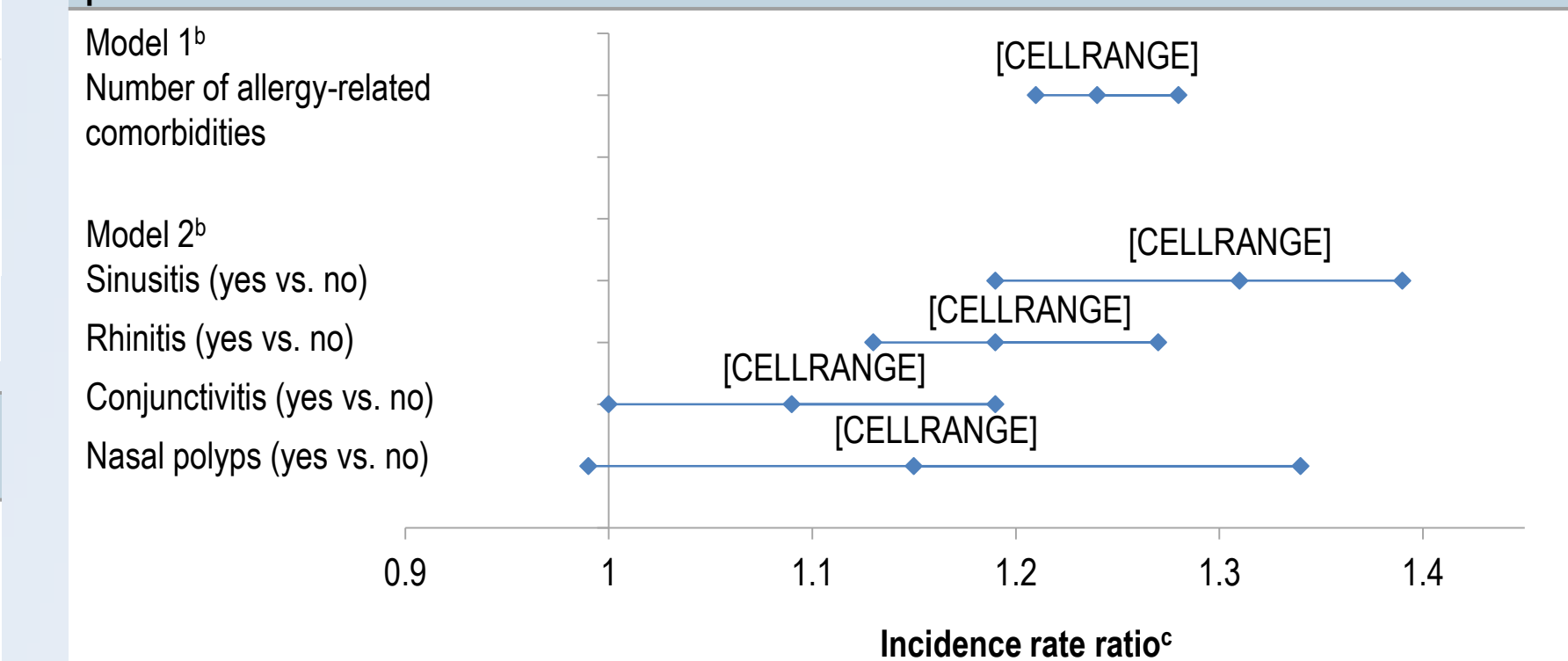
Association between Allergy-related Comorbidities and Asthma Exacerbations

- Model 1: The adjusted incidence rate ratio (IRR) for the association between the number of allergy-related comorbidities and asthma exacerbations was 1.24 ($P<0.001$), meaning the presence of each additional allergic comorbidity is associated with about a 24% increase in the number of exacerbations per year (**Figure 3**).
- Model 2: Results showed a similar direction when the presence of each comorbidity was examined independently (**Figure 3**): sinusitis (IRR=1.39, $P<0.001$), rhinitis (1.19, $P<0.001$), conjunctivitis (1.09, $P=0.039$), and, although not statistically significant, nasal polyps (1.15, $P=0.071$).
 - In the case of sinusitis, the presence of the allergy symptom was associated with a 39% increase in the number of exacerbations per year compared to patients without the symptom.

Association between Allergy-related Comorbidities and Asthma Exacerbations (continued)

- The sensitivity analyses revealed no change in the results when nasal polyps were excluded from the models.

Figure 3. Adjusted Association between Allergy-related Comorbidities and Number of Exacerbations per Year^a



LIMITATIONS

- Results may not be fully generalizable to uninsured individuals or to those with other types of insurance not included in this database.
- As with all claims studies, miscoding may affect accuracy.

CONCLUSIONS

- Real-world data demonstrate that allergic comorbidities such as sinusitis, rhinitis, and conjunctivitis are associated with an increase rate of asthma exacerbations (controlling for relevant confounders).
- An allergic phenotype in asthma patients may confer additional exacerbation risk. Prospective clinical or disease registry studies may help confirm these findings.

REFERENCES

- Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. 2007.