

Allergic asthma is associated with increased risk of infections requiring antibiotics

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ABSTRACT

Background: Viral infection and allergy have been identified as major risk factors for exacerbation in asthma, especially in the presence of both. However, whether patients with allergic asthma are more susceptible to respiratory infections requiring antibiotics remains unknown.

Objective: To investigate allergy as a risk factor for respiratory infections requiring antibiotics based on register data from a nationwide population of patients with asthma.

Methods: A register-based prospective follow-up study was performed using the Danish prescription database. In the inclusion period from 2010 through 2011, we identified patients with allergic asthma 18 to 44 years old. Patients were investigated during the follow-up period from 2012 through 2013, depending on their prescription drug use of antiallergic medication and antibiotics. Odds ratios were adjusted for age, sex, asthma severity, education, and urban vs rural residence.

Results: In a nationwide population we identified 60,415 patients with asthma. Based on prescriptions fillings for antiallergic medication, patients were subdivided into (1) nonallergic asthma (n = 35,334, 51.5%) and (2) allergic asthma (n = 25,081, 48.5%). Allergic asthma was associated with an increased risk of filling at least 2 antibiotic prescriptions per year compared with nonallergic asthma (odds ratio 1.28, 95% confidence interval 1.24–1.33, $P < .0001$). Interestingly, a subgroup analysis showed a protective effect of immunotherapy against the risk of requiring antibiotics (odds ratio 0.76, 95% confidence interval 0.66–0.87, $P = .0001$).

Conclusion: Patients with allergic asthma have an increased risk of being prescribed antibiotics for respiratory infections compared with those with nonallergic asthma. Treatment with allergen immunotherapy appears to have a protective effect against this risk.

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Introduction

Respiratory infections are common triggers of asthma exacerbations and the main cause of asthma-related hospitalizations.^{1–3} Viral infections^{2,4} and allergy^{5,6} have been identified as major risk factors for asthma exacerbations, especially in the presence of both.^{7–10} However, the association between allergic sensitization and risk of bacterial respiratory infections in patients with asthma is sparsely investigated, particularly in epidemiologic studies.¹¹ Hence, there is a need for representative population studies describing this relation.

In vivo studies of mice have shown that T-helper cell type (T_H) 2-driven airway inflammation is associated with a suppressed antimicrobial host defense.¹² In humans, evidence has suggested that

patients with asthma could have impaired innate immunity against bacteria through altered regulation of Toll-like receptors, leading to increased risk of colonization and infection in the airways.¹³ A recent systematic review has concluded that asthma is associated with an increased susceptibility to invasive pneumococcal disease.¹⁴ Furthermore, the risk of severe invasive pneumococcal disease is increased in patients with atopic conditions with or without asthma.¹⁵ Thus, pneumococcal vaccine (PPSV23) is recommended in patients 19 to 64 years old with asthma in the United States.¹⁶

Although the link between allergy and susceptibility to infection-related exacerbations is acknowledged,^{1,2,5,6} surprisingly little evidence exists on the effect of interventions targeting allergy. A potential biological mechanism for a relation between antiallergic treatment and immune defense against pathogens was described in studies of anti-immunoglobulin E (IgE) in children; treatment decreased the seasonal variation in asthma exacerbations¹⁷ and improved the antiviral interferon- α response.¹⁸ Increased interferon- α was associated with fewer exacerbations in the anti-IgE-treated children, which has been interpreted as a possible

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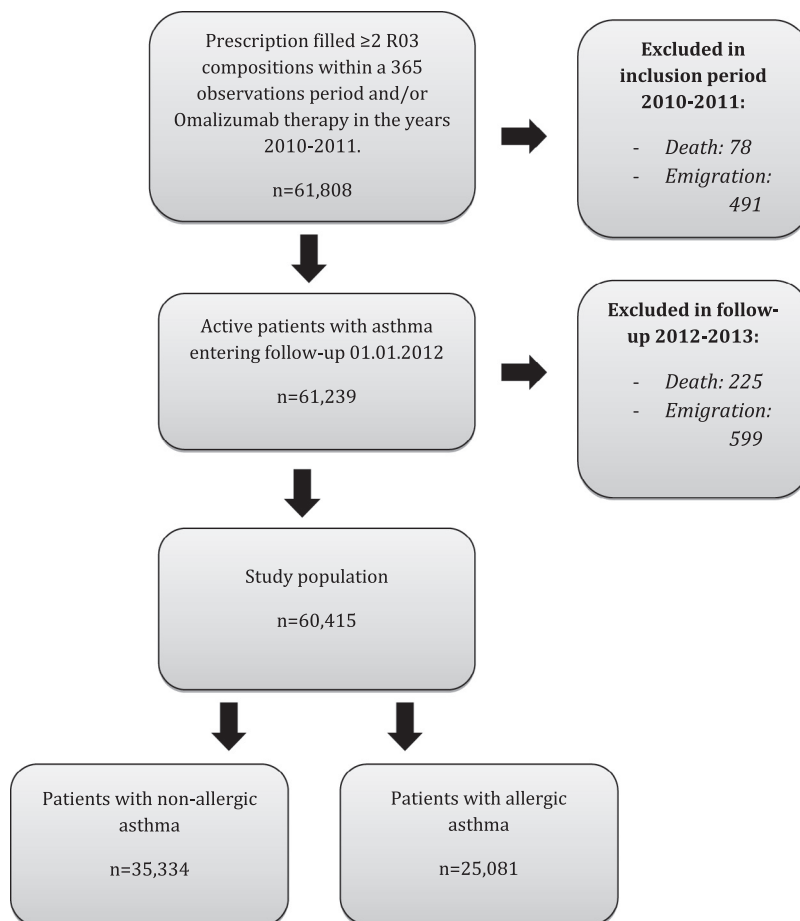


Figure 1. Patient flow.

decrease in virally induced exacerbations.¹⁹ Allergen-specific immunotherapy (AIT) lowers the risk of deterioration of asthma control,²⁰ but no studies have examined the effect on frequency of bacterial respiratory infections.

We tested the hypothesis that patients with allergic asthma would be more likely to be prescribed antibiotics (AB) targeting respiratory infections compared with patients with nonallergic asthma. Furthermore, we speculated that AIT would lower the risk of developing respiratory infections requiring AB and the risk of asthma exacerbations.

We conducted a nationwide population study of the association between allergy and the risk of being prescribed AB for respiratory infections in adults with asthma.

Methods

Study Design

This was a retrospective register-based cohort study of Danish patients with asthma using data from Statistics Denmark (www.dst.dk). All Danish residents are assigned a unique personal identification number, which enables individual linkage throughout nationwide registers. This study used the Danish prescription database and cross-referenced the data with other health and social and economic registers. It contains detailed information about every dispensed drug to an individual (eg, dose, date, pack size, etc) according to the unique Anatomical Therapeutic Chemical Classification (ATC) code. Patients were included only if they had filled prescriptions for the medicines specified below. The personal identification

number also is linked to the Danish National Patient Register, which contains detailed information about hospital admissions (eg, municipality, admission and discharge, duration, hospital, department, treatments, investigations, diagnoses, and operations) according to the *International Statistical Classification of Disease and Related Health Problems, Tenth Revision (ICD-10)*.

Study Population

Data used in this study originated from registers from 2010 through 2013 and included persons with a Danish social security number 18 to 44 years old within the inclusion period of January 1, 2010 through December 31, 2011 (24 months). All included patients entered the follow-up period of January 1, 2012 through December 31, 2013 (24 months) to avoid seasonal variation in allergen exposure, drug use, and exacerbations. [Figure 1](#) presents the patient flow.

Patients with asthma were identified and included if they fulfilled the following criteria: filled at least 2 prescriptions for a drug with an ATC code starting with R03 (medicine for obstructive airway diseases) within a 365-day observation period.²¹ If a patient redeemed an inhaled corticosteroid (ICS) combination device in 2010, then this was selected as the index date; otherwise, the date for the first redemption of an R03 drug was selected.²²

Patients who filled prescriptions for a specific medicine recommended for the treatment of chronic obstructive pulmonary disease and/or cystic fibrosis ([eTable 1](#)) or died or emigrated at any point during the observation period²² were excluded.

Table 1
Baseline Characteristics According to Asthma Phenotype

Characteristics	Study population (N = 60,415; 100%)	Nonallergic asthma (n = 35,334; 58.5%)	Allergic asthma (n = 25,081; 41.5%)	P value ^b
Age (y), mean (SD)	35.4 (7.7)	35.3 (7.8)	35.6 (7.7)	<.0001 ^c
Age group, n (%)				
18–24 y	7,697 (12.7)	4,629 (13.1)	3,068 (12.2)	—
25–34 y	16,778 (27.8)	9,945 (28.2)	6,833 (27.2)	—
35–44 y	35,940 (59.5)	20,760 (58.8)	15,180 (60.5)	—
Sex, n (%)				
Men	27,527 (45.6)	17,160 (48.6)	10,367 (41.3)	<.0001
Women	32,888 (54.4)	18,174 (51.4)	14,714 (58.7)	<.0001
Daily ICS dose (μg), median (25%–75% quartile) ^a	329 (164–585)	286 (132–526)	347 (197–657)	<.0001 ^c
Antiallergic medications, n (%)				
Oral non-sedative antihistamines	3,099 (5.13)	—	3,099 (12.4)	—
Oral sedative antihistamines	206 (0.34)	—	206 (0.82)	—
Nasal steroid spray	10,579 (17.5)	—	10,579 (42.2)	—
Intranasal antihistamine	607 (1.0)	—	607 (2.42)	—
Intraocular antihistamine	5,939 (9.83)	—	5,939 (23.7)	—
Combined (non-sedative H ₁ antagonists + vasoconstrictors)	145 (0.24)	—	145 (0.578)	—
Leukotriene receptor antagonist	5,587 (9.25)	—	5,587 (22.3)	—
Depot glucocorticoid	2,232 (3.69)	—	2,232 (8.89)	—
Immunotherapy, n (%)				
Grass (<i>Phleum pratense</i>)	842 (1.39)	—	842 (3.4)	—
House dust mite (<i>Dermatophagoides pteronyssinus</i> + <i>Dermatophagoides farinae</i>)	494 (0.82)	—	494 (1.97)	—
Birch (<i>Betula verrucosa</i>)	517 (0.86)	—	517 (2.06)	—
Insect (bee + <i>Vesparum venenum</i>)	33 (0.05)	—	33 (0.13)	—
Mugwort (<i>Artemisia vulgaris</i>)	62 (0.1)	—	62 (0.25)	—
Animals (horse, dog, cat)	157 (0.26)	—	157 (0.63)	—

Abbreviation: ICS, inhaled corticosteroid.

^aBudesonide equivalents.^bBy χ^2 test unless indicated otherwise.^cBy unpaired *t* test.

Allergy was defined by the prescription of medicine recommended in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines for treatment of allergic rhinitis and conjunctivitis (see eTable 1 in the Online Repository for full drug list).

Definition of Subpopulation

Patients with asthma were divided into subgroups based on their prescriptions for antiallergic medicine or AIT (Tables 1 and 2).

1. Patients with nonallergic asthma: No prescriptions for antiallergic medicine or AIT or a procedure code for anti-IgE therapy during the inclusion period.
2. Patients with allergic asthma: At least 1 prescription for antiallergic medicine or AIT or a procedure code for anti-IgE therapy during the inclusion period. Subjects defined as having allergy were further sub-grouped according to receipt of AIT during the inclusion period:
 - a. AIT: Patients being treated with AIT.
 - b. Non-AIT: Patients not being treated with AIT.

Table 2
Overview of ICD-10 and ATC of Drugs Used to Identify Diseases and Outcomes

Group	Group definitions	ICD-10	ATC code prefix	Description
Nonallergic asthma	Asthma	J45	R03-	Inhalant steroids, β_2 -agonist, anticholinergic, leukotriene antagonists, xanthines
Allergic asthma	Asthma	J45	R03-	Inhalant steroids, β_2 -agonist, anticholinergic, leukotriene antagonists, xanthines
Non-AIT	Allergic rhinitis	J30	R06AX-, R01AC-, R01AD-, R01AX-, R01BA-, R03DC-	Oral and intranasal antihistamines, intranasal corticosteroids, LRTA
		J30	H02AB-,	Depot injection (glucocorticoid)
	Allergic conjunctivitis	H10	R06AE-, R06AX-, R06AA-, R06AD-, S01GX-, S01GA-	Oral antihistamine and intraocular antihistamine
AIT	Allergic rhinitis	J30	V01AA-	AIT
Outcomes	SKS codes in DNPR (ICD-10)		ATC code prefix	Description
Antibiotics	—		J01-	Penicillins, cefuroxime, macrolides, quinolones, cephalosporins
Exacerbation	—		H02AB06	Oral prednisolone
	DJ45-		—	Hospitalization or emergency department visit with associated diagnosis of asthma
	DJ46, DJ469		—	Hospitalization or emergency department visit with associated diagnosis of asthma
Respiratory tract infection	DJ12-18		—	Hospitalization or emergency department visit with associated diagnosis of pneumonia
Exacerbation related to infection	—		J01-	Antibiotics
	—		H02AB06	Oral prednisolone

Abbreviations: AIT, allergen-specific immunotherapy; ATC, Anatomical Therapeutic Chemical Classification; DNPR, Danish National Patient Register; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; LRTA, leukotriene receptor antagonist; SKS, the Danish healthcare classification system (ICD-10).

Definition of Outcomes

1. Respiratory infection: Defined as at least 1 prescription for AB for respiratory infection during the follow-up period.
2. Exacerbation: Defined as at least 1 prescription for oral corticosteroids (OCSs) and/or emergency department (ED) visit or hospitalization with an associated ICD-10 code for asthma and/or status asthmaticus during the follow-up period.²³
3. Exacerbation related to infection: Defined as at least 1 prescription for OCS and AB within the same 4-week period during the follow-up period.
4. Hospital attendance with pneumonia: Defined as at least 1 ED visit or hospitalization with an associated ICD-10 code for pneumonia.

Selection of Antibiotics

Types of AB used to investigate the primary outcome were selected in accordance with national recommendations²⁴ and international guidelines²⁵ for the treatment of lower respiratory tract infections. In Denmark, first line of treatment is with narrow-spectrum β -lactam AB (eg, amoxicillin plus clavulanate, ampicillin or phenoxymethylpenicillin, etc), accounting for approximately 50%, and macrolides, accounting for 36%, of prescriptions for lower respiratory tract infections issued by general practitioners.²⁴

Definition of Severity of Allergy

We defined severity of allergy by the number of different types of antiallergic medicine prescribed. This sub-analysis was performed to explore the effect of an increasing severity of allergy.

1. Prescription for 1 type of antiallergic drug (eg, oral antihistamines)
2. Prescriptions for 2 different types of antiallergic medicine (eg, oral antihistamines and nasal corticosteroids)
3. Prescriptions for at least 3 different types of antiallergic medicine (eg, oral antihistamines, nasal steroids, and intraocular antihistamine)

Data Analysis and Statistics

All data were extracted and analyzed using the SAS 9.4 for Windows (SAS Institute, Cary, North Carolina). Odds ratios (ORs) were adjusted for age, sex, asthma severity, education, and urban vs rural area. Nonparametric data were reported with median and 25% to 75% quartiles. The Mann-Whitney *U* test was used to test differences between groups. Numeric parametric variables were analyzed using independent *t* tests. Categorical variables were analyzed using χ^2 tests. All *P* values were extracted from the regressions analysis to minimize the effect of mass significance. Statistical significance was defined as a *P* value less than .05.

Adjustment for Asthma Severity

The regression analyses were adjusted according to asthma severity. Severe asthma was defined as requiring high-dose ICS ($\geq 1,600$ μ g of budesonide equivalent) in accord with the European Respiratory Society and the American Thoracic Society.²⁶ Calculation of daily ICS consumption was performed according to the method described by von Bülow et al.²²

Ethics

This study was approved by the Research Service at Statistics Denmark with project ID 704119-2 and access to the prescription

database was specifically approved by the State Serum Institute. Register studies do not require ethical approval in Denmark.

Results

Study Population

In this nationwide population, we identified 60,415 patients with asthma in the 2-year inclusion period from 2010 through 2011 based on the prescription of at least 2 antiasthmatic medicines during a 12-month period (Table 1). We also identified 58.5% of patients as having nonallergic asthma and 41.5% as having allergic asthma (Table 1). The mean age was 34.5 ± 7.6 years and 52.7% were women. Daily median ICS (budesonide equivalent) dose was 395 μ g (interquartile range 219–708). Of patients with allergic asthma, 1,247 (4.9%) received treatment with AIT during the inclusion period.

Prescription of Antiallergic Medications and Risk of Infections

During the 24-month follow-up period (2012–2013), patients with allergic asthma were more likely to be prescribed AB than patients with nonallergic asthma (OR 1.20, 95% confidence interval [CI] 1.17–1.25; Figure 2). Furthermore, patients with allergic asthma were more likely to have repeated prescriptions for AB (Fig 2).

Patients undergoing AIT had a lower risk of being prescribed AB than patients with non-AIT (Fig 3A) and a similar risk compared with patients with nonallergic asthma (Fig 3B).

The risk of repeatedly being prescribed AB increased with the number of antiallergic medications prescribed. Patients treated with at least 3 different types of antiallergic medications had a 47% increased risk of having AB prescribed at least twice during the follow-up period (≥ 2 AB; OR 1.47, 95% CI 1.32–1.64) compared with patients with nonallergic asthma (Fig 4).

However, patients with allergic asthma did not have an increased risk of ED visit or hospital admission with a pneumonia diagnosis. Forty-four patients with allergic asthma (0.2%) had at least 1 ED visit compared with 76 patients with nonallergic asthma (0.2%; OR 0.76, 95% CI 0.56–1.12). Two hundred eight patients with allergic asthma (0.8%) had at least 1 hospitalization vs 318 patients with nonallergic asthma (0.9%; OR 0.95, 95% CI 0.79–1.13).

Prescription of Antiallergic Medications and Risk of Asthma Exacerbations

Patients with allergic asthma had more prescriptions for OCS compared with patients with nonallergic asthma (Fig 5A). In addition, patients with allergic asthma had an increased OR of ED visits and hospitalizations with an exacerbation compared with patients with nonallergic asthma with at least 1 ED visit (OR 1.23, 95% CI 1.08–1.41; Fig 5A) and at least 1 hospitalization (OR 1.20, 95% CI 1.07–1.36; Fig 5A). Patients with allergic asthma had increased risk of exacerbation related to infection (OR 1.27, 95% CI 1.18–1.37; Fig 5A).

Patients with allergic asthma undergoing AIT also demonstrated an increased risk of being prescribed an OCS (≥ 1 ; OR 1.62, 95% CI 1.35–1.95) compared with patients with nonallergic asthma (Fig 5C). However, the risk of ED visits and hospital admission with an exacerbation was not increased compared with patients with nonallergic asthma (Fig 5C). In addition, patients treated with AIT did not have an increased risk of exacerbations related to infection compared with patients with nonallergic asthma (OR 0.90, 95% CI 0.65–1.24; Fig 5C). Compared with patients with non-AIT-treated allergy, patients with AIT-treated allergy tended to have a lower risk of ED visits and hospital admissions, although this was not statistically significant (Fig 5B).

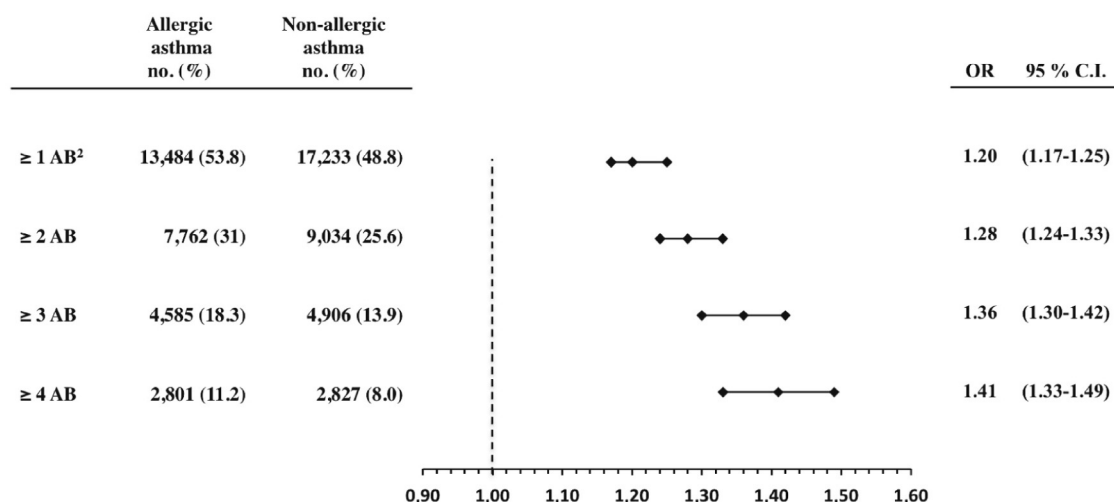


Figure 2. Risk of filling at least 2 prescriptions for antibiotics (AB) targeting respiratory tract infections in patients with allergic asthma vs patients with nonallergic asthma (reference). Odds ratio (OR) was adjusted for age, sex, asthma severity, education, and urban vs rural area. CI, confidence interval; PF, prescription filling.

Discussion

To our knowledge, this is among the first epidemiologic studies investigating the association between allergic asthma and risk of respiratory infection requiring AB. Our results demonstrate that patients with allergic asthma have a higher frequency of AB-requiring infections compared with patients with nonallergic asthma and more exacerbations related to infections. Furthermore, the likelihood of prescribing AB increases with the severity of allergy. In addition, our results indicate that AIT could have a protective effect against the need for AB and exacerbations caused by infections. Overall, these findings suggest that allergic sensitization in asthma is a potentially modifiable risk factor for respiratory infections and related asthma exacerbations.

The association we report between allergy and risk of infection in asthma is supported by several previous studies,^{11,15}

demonstrating that patients with allergic asthma exhibit a diminished innate immune response to airway infection.^{27–29} Impairment of the epithelial T_H2 response in the airways can lead to a cascade of events,^{12,13,30–32} resulting in increased susceptibility to respiratory infections. This negative spiral can induce a further suppression of the immune defense³³ against airway pathogens and could explain why patients with allergic asthma have an increased risk of respiratory infections and exacerbations. Green et al⁷ reported this in 2002 and described a synergistic effect between allergic sensitization to aeroallergens and viral infection leading to an increased risk of hospital admission in patients with asthma. This aligns closely with our results demonstrating an increased risk for hospitalization and ED visits in patients with allergic asthma (Fig 5A).

It is well described that AIT decreases the risk of “loss of symptom control” and the need for up-titration of treatment in asthma.²⁰ Gern³⁰ suggested that controlling allergic inflammation might be

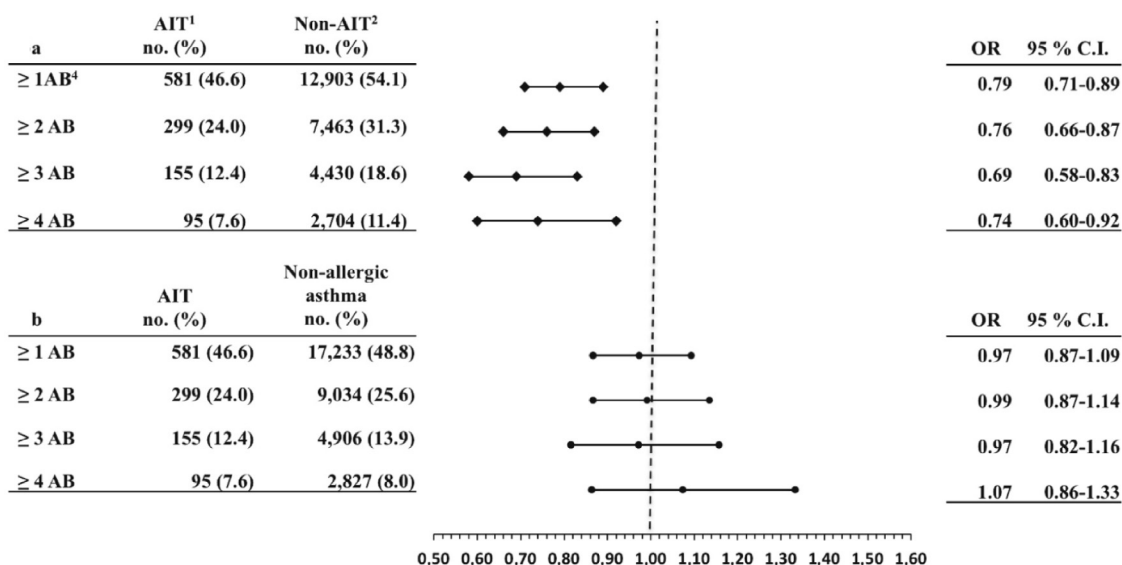


Figure 3. Effect of allergen-specific immunotherapy (AIT) on the risk of filling at least 1 prescription for antibiotics (AB) targeting respiratory tract infections. (A) Comparison of patients with allergic asthma receiving AIT vs patients with allergic asthma patients not receiving AIT (non-AIT; reference). (B) Comparison of patients with allergic asthma receiving AIT vs patients with nonallergic asthma (reference). Odds ratio (OR) was adjusted for age, sex, asthma severity, education, and urban vs rural area. CI, confidence interval; PF, prescription filling.

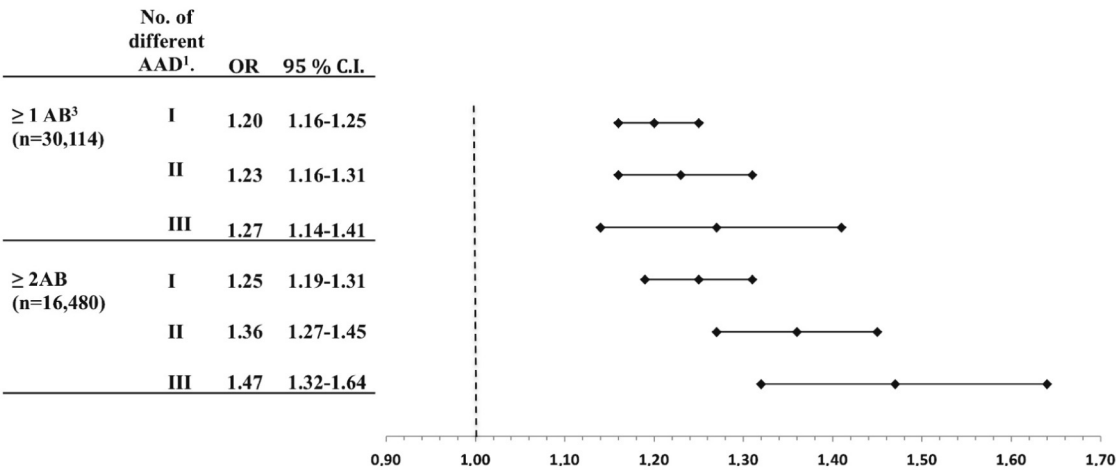


Figure 4. Impact of using 1, 2, or at least 3 different types of antiallergic medication (no allergen-specific immunotherapy) on the risk of filling prescriptions for antibiotics (AB) targeting respiratory infections. Patients with nonallergic asthma were used as reference. Odds ratio (OR) was adjusted for age, sex, asthma severity, education, and urban vs rural area. AAD, antiallergic drugs; CI, confidence interval; PF, prescription filling.

an effective approach to decrease the frequency and severity of asthma exacerbation as shown in inner-city children treated with anti-IgE.¹⁷ Our findings indicate that treatment with AIT could have a protective effect against the development of AB-requiring respiratory infections. AIT weakens the allergic response through a number of mechanisms. Most importantly, AIT stimulates a T_H2-to-T_H1 switch.³⁴ Furthermore, AIT induces IgG4, which blocks

the interaction between IgE and high- and low-affinity IgE receptors on antigen-presenting cells, effector cells, and B cells.³⁴ Accordingly, a decreased activation of IgE receptors could improve the innate immune defense against pathogens in patients with allergy, including the production of interferon- α . Interestingly, the absence of effect of AIT on exacerbations per se indicates that drivers other than IgE are important. This could

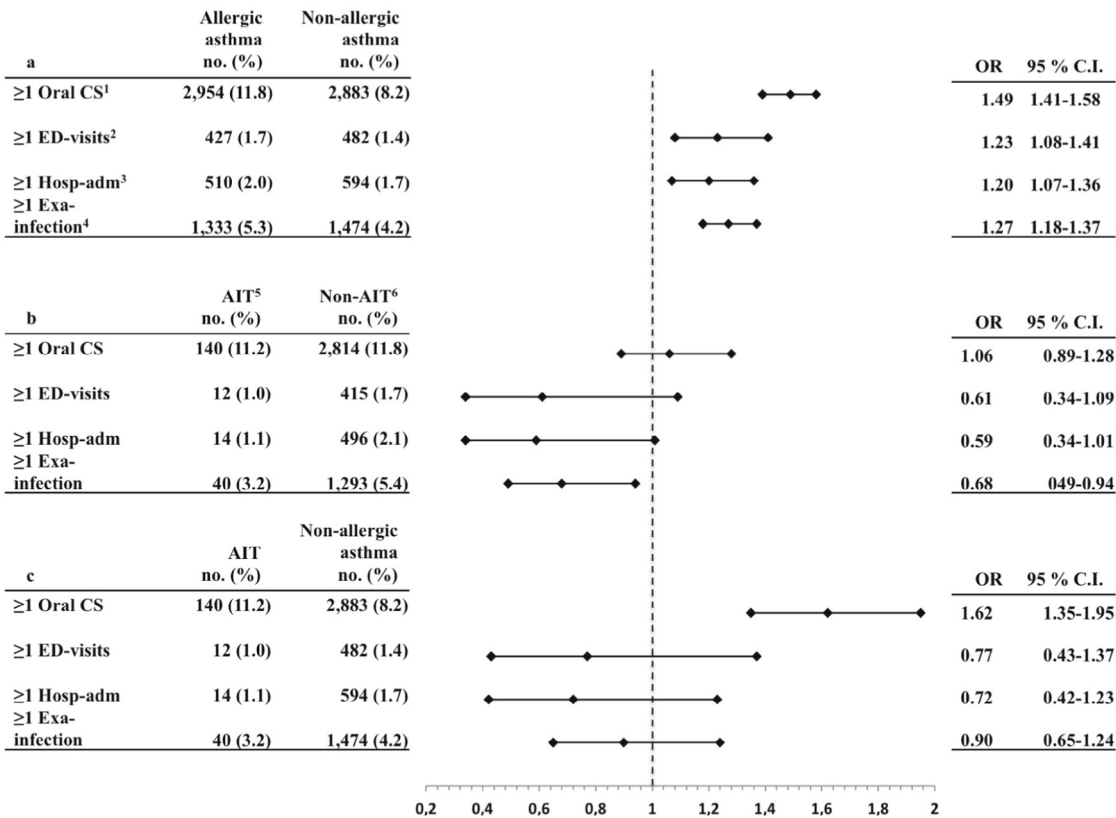


Figure 5. Risk of exacerbations specified by at least 1 prescription filling of oral corticosteroids (CS) and/or 1 emergency department visit (ED-visit) and/or 1 hospital admission (Hosp-adm) and the risk of exacerbation related to infections between subgroups. (A) Comparison of patients with allergic asthma vs nonallergic asthma (reference). (B) Comparison of patients with allergic asthma treated with allergen-specific immunotherapy (AIT) vs patients not treated with AIT (non-AIT; reference). Patients with non-hyposensitized allergic asthma are used as reference. (C) Comparison of patients with allergic asthma treated with AIT vs patients with nonallergic asthma (reference). Odds ratio (OR) was adjusted for age, sex, asthma severity, education, and urban vs rural area. CI, confidence interval; Exa-infection, exacerbation related to infection.

include the interleukin-5 pathway, which promotes eosinophilia, as opposed to the interleukin-4 and -13 pathway, which drives IgE production. Another explanation for the equal use of OCS between patients treated with AIT and non-AIT could be that those with allergic asthma receiving AIT received more OCSs to treat severe allergy, because the indication for the prescription of OCS was not available in the prescription database. In addition, OCSs could be more easily accessible to the AIT group because of close contact with a specialist. However, because of the study design, it was not possible to determine the answer to this question.

By using nationwide public register databases, we ensured high completeness and external validity^{35–37} through the elimination of selection bias and recall bias. We acknowledge there are several limitations in our study, particularly in the classification of patients as allergic or nonallergic. In this study, prescriptions were used as surrogate markers of disease because ICD-10 diagnoses are available only for patients being admitted to hospital. Patients are usually managed in primary care, where we have no access to anamnestic information such as general conditions, comorbidities, severity of allergy and asthma symptoms, smoking history, clinical information regarding symptoms, IgE levels or skin prick test reactions, or the specific action diagnoses. We recognize the lack of confirmation of a diagnosis of bacterial infection in this study population and AB could have been prescribed for conditions mimicking bacterial infection. However, Cooke et al³⁸ found that practitioners in Denmark are among the most restrictive in Europe in prescribing AB for respiratory tract infections. They acknowledged the wide use of the point-of-care biomarker (eg, C-reactive protein),³⁸ which has been shown to significantly lower the initial rate of prescriptions in primary care. Furthermore, we could not investigate patients with allergic disease receiving no antiallergic treatment owing to poor adherence, underdiagnosis of allergy, or milder degree of symptoms.

A large number of antiallergic medicines are available “over the counter” and therefore are not registered in the Danish National Prescription Registry. Therefore, these patients would have been falsely identified as having nonallergic asthma, resulting in a lowered prevalence of allergic asthma. However, because of the availability of partial state funding of prescription medicine in Denmark, there is a financial incentive to obtain a prescription rather than use over-the-counter medicine. Thus, we determined that patients with mild or few allergic periods were using over-the-counter drugs instead of obtaining a prescription. Therefore, we assess this to be a minor problem.

Pont et al²¹ demonstrated that prescription filling of at least 2 drugs against obstructive lung diseases (ATC R03) predicts asthma with a sensitivity of 0.71, specificity of 0.99, and a positive predictive value of 0.79 in patients 18 to 49 years old. The strict age definition argues against the major representation of chronic obstructive pulmonary disease, chronic bronchitis, and emphysema. In addition, patients in treatment with specific medicines for these diseases were excluded. However, we recognize that some patients could be prescribed monotherapy with ICS for other diseases than asthma and that absolute exclusion of a non-asthma diagnosis as listed earlier is not certain. Considering the population size, we believe this to be a limitation of minor importance because the impact of these would be diluted among patients with asthma.

Patients in the AIT group might not have experienced the full efficacy of the therapy during the study because they had not yet completed their course. The likelihood of an AB prescription for a respiratory infection might have been further lowered if a 3- to 5-year course of AIT had been completed.³⁹ Furthermore, patients who completed their course of AIT before the inclusion period could have been found in either of the 2 primary groups (nonallergic asthma or allergic asthma). If anything, this contributes to our results with an underestimate of the effect size.

There also could be a small number of patients with allergic rhinosinusitis who were not treated in accordance with current guidelines for AB use in respiratory infections.⁴⁰ Bacterial infection occurs in 0.5% to 2% of episodes with allergic rhinosinusitis.⁴¹ In a recent review by Rosenfeld,⁴² approximately 85% of patients with a history of acute rhinosinusitis have a decrease or resolution of symptoms without AB. However, 84% to 91% of patients diagnosed with rhinosinusitis in the ED or outpatient clinic are prescribed AB. Furthermore, some patients with rhinitis might have been incorrectly identified as having allergy. The prescription data used in this study do not enable us to differentiate between allergic and nonallergic rhinitis, and a proportion of patients classified as having allergy could in fact have nonallergic rhinitis. Nasal corticosteroid, intranasal antihistamines, and/or oral antihistamines also can be used in the treatment of nonallergic rhinitis, which could overestimate the prevalence of allergy within our study population. The prevalence of nonallergic rhinitis is described to vary from 10% to 25%.^{43–45}

Overall we consider our results to be conservative estimates owing to likely under-identification of allergy, with a likely even higher risk of respiratory infection in patients with allergy, and greater protective effect with AIT than reported in this study.

Patients with allergic asthma have an increased risk of respiratory infections requiring AB compared with patients with nonallergic asthma. Conversely, patients with allergic asthma who are treated with AIT have a risk of respiratory infection requiring AB comparable to that of patients with nonallergic asthma. These findings suggest that allergic sensitization in asthma is a potentially modifiable risk factor for respiratory infections and infection-driven asthma exacerbations. Furthermore, this study supports the relevance of future studies investigating immunologic mechanisms involved in infections and associated exacerbations in patients with allergic asthma.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jana.2017.11.015>.

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Supplementary Data

eTable 1

Specific Medication Related to ATC Codes

Specific medication	ATC codes
Asthma (inclusion)	
ICS	R03BA01, R03BA02, R03BA05, R03BA07, R03BA08
ICS + LABA	R03AK06, R03AK07
SABA	R03AC02, R03AC03
LABA	R03AC12, R03AC13, R03AC18
LTRA	R03DC03
Xanthines	R03DA04
SAMA	R03BB01
LAMA	R03BB04
Oral SABA	R03CC02, R03CC03
Oral LABA	R03CC12
Asthma exacerbation	
Oral corticosteroid (prednisolone)	H02AB06
Chronic obstructive pulmonary disease (exclusion)	
Daxas (Takeda Pharma, Roskilde, Denmark)	R03DX07
Cystic fibrosis (exclusion)	
Pulmozyme (Roche, Hvidovre, Denmark)	R05CB13
Promixin (Swedish Orphan Biovitrum A/S, Lyngby, Denmark)	J01XB01
Tobi (Novartis Healthcare A/S, Copenhagen, Denmark)	J01GB01
Cayston (Gilead Sciences Sweden A/S, Solna, Sweden)	J01DF01
Antiallergic	
Oral non-sedative	R06AX26, R06AX28, R06AE07, R06AE09, R06AX13, R06AX18, R06AX27, R06AX22, R06AX29
Oral sedative antihistamine	R06AA04, R06AD02, R06AE05
Oral non-sedative antihistamine + vasoconstrictor	R01BA52
Intranasal antihistamine	R01AC01, R01AC02, R01AC03
Intranasal corticosteroid	R01AD01, R01AD05, R01AD08, R01AD09, R01AD11, R01AD12, R01AD58
Intranasal ipratropium	R01AX03
LTRA	R03DC03
Intraocular antihistamine	S01GX01, S01GX02, S01GX04, S01GX05, S01GX06, S01GX07, S01GX08, S01GX09, S01GA51
Depot injection (glucocorticoid)	H02AB01, H02AB04, H02AB08
Allergen-specific immunotherapy	
SCIT (Alutard, Aquagen)	V01AA02, V01AA03 V01AA05, V01AA07, V01AA10, V01AA11, V04CL
SLIT	V01AA02
Antibiotics	
Penicillin	J01CE02, J01CA02, J01CA04, J01CA01
Penicillin + β -lactamase inhibitor	J01CR02
Cefuroxime	J01DC02
Macrolide	J01FA10, J01FA06, J01FA09, J01FA01
Quinolones (moxifloxacin, ciprofloxacin):	J01MA14, J01MA02
Cephalosporin	J01DB01

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2 -agonist; SAMA, short-acting muscarinic antagonist; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.