

ENVIRONMENTAL DETERMINANTS

Association between Episodes of Upper Respiratory Infection and Exacerbations in Adult Patients with Asthma

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Background. Asthma has several phenotypical features, including recurrent exacerbations and recurrent episodes of upper respiratory infection (URI). **Purpose.** A retrospective study was performed to identify the characteristics of adult patients with recurrent exacerbations of asthma, especially in association with recurrent episodes of URI. **Methods.** Information was collected using a self-administered questionnaire given to 7070 patients in autumn–winter 2006, 4859 patients in spring–summer 2007, and 4452 patients in autumn–winter 2007. The patients reported the degree of symptoms and the frequency of febrile episodes of URI and exacerbations. Severe exacerbations were defined as a self-report of asthma-related hospitalization, an emergency department visit, or a requirement for systemic corticosteroids. Recurrent febrile URI and exacerbations were defined as two or more episodes within the previous 6 months. A Poisson regression model was used to identify the factors that were predictors of a risk for exacerbations. **Results.** Of the 6266 patients who completed the questionnaire, the frequencies of febrile URI and episodes of severe exacerbations were 1.54 and 0.54 per subject per year, respectively. Logistic regression analysis showed that an older age [odds ratio (OR): 1.57; 95% confidence interval (CI): 1.15–2.13], female sex (OR: 1.58; 95% CI: 1.20–2.08), recurrent febrile episodes of URI (OR: 2.68; 95% CI: 1.47–4.91), a history of previous exacerbation within 1 year (OR: 1.74; 95% CI: 1.28–2.34), disuse of inhaled corticosteroids (ICSs) (OR: 2.63; 95% CI: 1.68–4.12), and disuse of add-on leukotriene receptor antagonists (LTRAs) (OR: 1.42; 95% CI: 1.06–1.74) were independently associated with moderate to severe symptom-severity. Poisson regression analysis showed that the independent factors that contributed to the frequency of recurrent severe exacerbations were female sex (regression coefficient $\beta = 0.62$, $p < .01$), an episode of sputum with coughing ($\beta = 1.23$, $p < .01$), nocturnal awakening ($\beta = 1.22$, $p < .01$), and severe exacerbation ($\beta = 0.78$, $p < .01$) within the previous 6 months. **Conclusion.** Symptom-severity of asthma and the frequency of severe exacerbations were associated with previous exacerbations and susceptibility to URI.

Keywords asthma, exacerbation, upper respiratory infection

INTRODUCTION

Asthma is a syndrome with heterogeneous phenotypes, including the recently proposed entity of “exacerbation-prone” asthma, which involves frequently occurring exacerbations (1). The characteristic features of exacerbation-prone patients include irreversible airflow limitation, a history of cigarette smoking, psychosocial dysfunction, medication noncompliance, and comorbidities including rhinosinusitis, obesity, gastroesophageal reflux, and intolerance to nonsteroidal anti-inflammatory medications (2, 3). Recent asthma exacerbations are a predictor of future exacerbations (4), but not all exacerbations are associated with severe disease.

Periodic exacerbations are generally thought of as a worsening of asthma symptoms in response to a variety of triggers. Upper respiratory infection (URI) due to viral infection is recognized as a major trigger of acute exacerbation of asthma in children and adults and results in frequent outpatient visits and hospitalization (5–7). The frequency of URI is suspected to contribute to exacerbation-prone asthma, but the factors underlying the exacerbation-prone phenotype are incompletely understood.

Asthma guidelines recommend achieving and maintaining current control, as well as reducing the future risk of exacerbations (8, 9). We examined the prevalence of URI and exacerbations in patients with adult asthma using a self-administered questionnaire to determine the risk factors for severe exacerbations. We focused on the association between the episodes of URI and a deteriorated asthma status, such as that in patients with moderate to severe symptom-severity and severe exacerbations.

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METHODS

Subjects and Study Design

The study was designed as a questionnaire-based retrospective study to capture all febrile episodes of URI, symptom-severity, and severe exacerbations that occurred in adult patients over a 6-month period. Adult patients with asthma that had been diagnosed by physicians were consecutively recruited during their regular visits to 446 centers, including the outpatient departments of 7 university hospitals, 24 general hospitals, and 315 clinics. The questionnaires were handed to the subjects in autumn–winter in 2006, spring–summer in 2007, and autumn–winter in 2007. Male and female asthma patients aged above 18 years were eligible for inclusion in the study if they had a diagnosis of moderate or severe persistent asthma confirmed by a chest physician, and the diagnosis had occurred at least 6 months before the beginning of the study. Each center's Institutional Review Board approved the protocol and all subjects gave signed informed consent.

Questionnaire

Questions to each patient concerning febrile episodes of URI, symptoms associated with asthma, and exacerbations were based on symptom-severity scores (10) and were modified to fit the design of this study (see Appendix). Another questionnaire was concurrently given to the physicians regarding the events of asthma-related hospitalization and treatment, based on chart review.

Definition of Symptom-Severity and Severe Exacerbations

The definition of moderate to severe symptom-severity was based on symptom-severity scores (10), as having at least one symptom of cough, sputum with coughing, and nocturnal awakening per week. Among the cold-severity indicators validated in the Wisconsin Upper Respiratory Symptom Survey (WURSS) (11), fever was one of the symptoms associated with acute exacerbations of asthma requiring hospitalization (12). To avoid inclusion of data for rhinitis and milder common colds, URIs were defined as self-reported episodes of nasal stuffiness and discharge, combined with sneezing, sore throat, or cough with fever. The American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force on Asthma Control and Exacerbations defined exacerbations as events characterized by a change from the patient's previous status that prompts a need for a change in treatment (13). In this study, severe exacerbations were defined as self-reported episodes requiring systemic glucocorticosteroids, an emergency room (ER) visit, or asthma-related hospitalization. Recurrent events of exacerbations and URI were defined as two or more episodes within the previous 6 months. The primary outcomes were the rates of URI and severe exacerbations of asthma per patient per 6 months.

Statistical Analysis

SPSS version 18.0 (SPSS, Chicago, IL, USA) was used for all calculations. Factors associated with poor asthma control were evaluated by logistic regression analysis. The

results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The frequency of exacerbations was analyzed using a simple model assuming a Poisson distribution. The associations between recurrent severe exacerbations and clinical variables were initially explored by univariate regression. Multivariate regression models were then used to evaluate the relationship between recurrent severe exacerbations and variables found to be significant in univariate analysis, while adjusting for potential confounding factors that were also significant in univariate analysis.

RESULTS

Patient Characteristics

The self-administered questionnaire survey was given to a total of 16,381 adult patients with asthma in three separate periods (Table 1): 7070 subjects in autumn–winter 2006, 4859 subjects in spring–summer 2006, and 4452 subjects in autumn–winter 2007. A total of 11,573 completed questionnaires (70.6%) were received from 6266 patients (some patients completed questionnaires in two or all three of the periods). Of these patients, 42.7% were male. There were no significant differences in response rates among patients of different sex or age.

Incidence of URI

A total of 8876 URI episodes were documented in the 11,573 patients over 6 months, giving a rate of 1.54 episodes per patient per year. Recurrent febrile URI, which was defined as two or more episodes per 6 months, occurred in 17.4% of the patients. The incidence of febrile URI in autumn–winter was more frequent than that in spring–summer ($p < .05$) (Figure 1).

Independent Factors Associated with Asthma Symptom-Severity

A nested case–control study was performed to identify the characteristics of adult patients with poor asthma control, especially in those with a previous history of severe exacerbations. The nested study included the 1012 patients who answered the questionnaire in all three periods. Of these patients, 66% showed moderate to severe symptom-severity, which was defined as having at least one symptom of cough, sputum, and nocturnal awakening per week. The results of logistic regression analysis of covariate factors for symptom-severity are shown in Table 2. An older age (OR: 3.42; 95% CI: [1.75–8.06]; $p < .01$), female sex (OR [CI] = 1.59 [1.22–2.07]; $p < .01$), ≥ 3 episodes of febrile URI in the previous 6 months or an episode of sputum with coughing (OR = 3.83 [2.29–6.40], $p < .01$), previous exacerbations within 1 year (OR = 4.96 [1.75–14.0], $p < .01$), disuse of inhaled corticosteroids (ICSs) (OR = 2.70 [1.82–4.00], $p < .01$), and disuse of add-on leukotriene receptor antagonists (LTRAs) (OR = 1.58 [1.21–2.07], $p < .01$) contributed significantly to symptom-severity. In contrast, disuse of add-on long-acting β -agonists (LABAs) and add-on theophylline did not contribute to symptom-severity.

TABLE 1.—Characteristics of the patients.

	First questionnaire	Second questionnaire	Third questionnaire
Number of responses	7084	4858	4451
Responses with complete answers	4038 (57%)	3090 (64%)	2798 (63%)
Age (year)	54.5 (54.0–55.0)	56.2 (55.6–56.8)	56.8 (56.2–57.4)
Sex (male/female)	1784/2254	1331/1759	1272/1526
Frequency of URI per 6 months	0.79 (0.76–0.83)	0.80 (0.73–0.86)	0.60 (0.56–0.64)
Frequency of events using SABA per 6 months	10.0 (9.04–11.0)	9.50 (8.33–10.7)	11.9 (10.5–13.3)
Frequency of events using oral CS	1.64 (1.38–1.91)	1.90 (1.58–2.22)	1.83 (1.47–2.18)
Frequency of events of visiting ER	0.72 (0.56–0.90)	0.72 (0.60–0.84)	0.54 (0.47–0.62)
Coughing lasted over 1 week	2907 (72%)	2232 (72%)	2159 (77%)
None	0.90 (0.80–1.00)	0.74 (0.67–0.81)	0.65 (0.55–0.74)
Frequency per 6 months			
Sputum with coughing			
None	2027 (50%)	1621 (52%)	1584 (57%)
1–2 events per 6 months	928 (23%)	687 (22%)	622 (22%)
1–2 events per 1 month	500 (12%)	370 (12%)	291 (10%)
1–2 events per 1 week	339 (9%)	235 (8%)	183 (7%)
Almost every day	224 (6%)	177 (6%)	118 (4%)
Nocturnal awakening			
None	2549 (63%)	2135 (69%)	1965 (70%)
1–2 events per 6 months	864 (21%)	554 (18%)	523 (19%)
1–2 events per 1 month	366 (9%)	258 (8%)	209 (7%)
1–2 events per 1 week	189 (5%)	118 (4%)	75 (3%)
Almost every day	70 (2%)	25 (1%)	26 (1%)
Rhinitis symptoms			
None	1671 (41%)	1250 (40%)	1314 (47%)
Nasal obstruction	1394 (35%)	1077 (35%)	852 (30%)
Runny nose	1581 (39%)	1233 (40%)	973 (35%)
Sneeze	1187 (29%)	935 (30%)	703 (25%)
Treatment			
ICS ^a	5869 (83%)	4064 (84%)	3655 (82%)
Add-on LABA	2258 (32%)	1789 (36%)	1760 (38%)
Add-on LTRA	3061 (43%)	2246 (45%)	2059 (46%)
Add-on theophylline	2664 (38%)	1804 (37%)	1698 (38%)

Notes: Data are expressed as number (%) or mean (95% CIs) unless otherwise indicated.

CS, corticosteroid; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2 agonist, URI, upper respiratory infection; CI, confidence interval.

^aIncluding ICS therapy alone and additional therapy with LABAs, LTRAs, and/or theophylline.

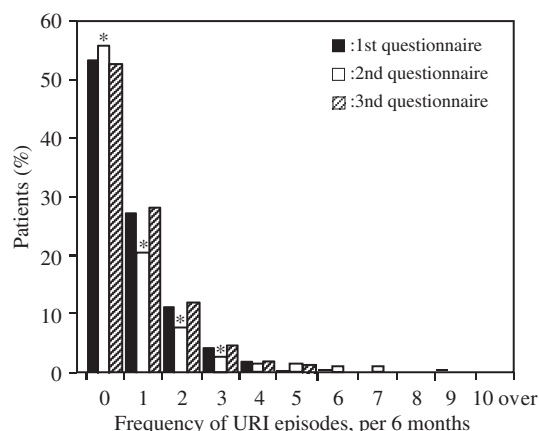


FIGURE 1.—Frequency of febrile URI episodes in adult patients with asthma in three periods. A self-administered questionnaire was given to 7070 patients in autumn–winter 2006 (1st questionnaire), 4859 patients in spring–summer 2007 (2nd questionnaire), and 4452 patients in autumn–winter 2007 (3rd questionnaire).

Note: * $p < .05$, compared with the first questionnaire.

Multivariate logistic regression analysis showed that recurrent febrile episodes of URI (OR = 2.68 [1.47–4.91]), disuse of ICS (OR = 2.63 [1.68–4.12]), a previous

exacerbation within 1 year (OR = 1.74 [1.28–2.34]), female sex (OR = 1.58 [1.20–2.08]), older age (OR = 1.57 [1.15–2.13]), and disuse of add-on LTRAs (OR = 1.42 [1.06–1.74]) were independently associated with symptom-severity.

Independent Factors Associated with Frequency of Severe Exacerbations

To analyze previous episodes of severe exacerbations, we examined the responses of the 1012 patients who answered the questionnaire 3 times. In these patients, the frequency of severe exacerbations was 0.27 per subject per 6 months and 5.5% had ≥ 2 severe exacerbations. The results of univariate Poisson regression analysis are shown in Table 3. In a multivariate Poisson regression model, the independent factors that contributed to the frequency of severe exacerbations were a history of previous exacerbations within 1 year ($\beta = 0.99$, $p < .01$), an episode of sputum with coughing ($\beta = 0.97$, $p < .01$), an episode of nocturnal awakening ($\beta = 0.72$, $p < .01$), and female sex ($\beta = 0.59$, $p < .01$) (Table 4). The contributions of age ($\beta = 0.34$, $p = .26$), episodes of rhinitis symptoms ($\beta = -0.52$, $p = .88$), and any treatment were not significant. The

TABLE 2.—Univariate and multivariate logistic analysis of factors associated with moderate to severe symptom-severity.

	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Age		
< 65 years old	1	1
≥ 65 years old	3.42* (1.75–8.06)	1.57* (1.15–2.13)
Sex		
Male	1	1
Female	1.59* (1.22–2.07)	1.58* (1.20–2.08)
URI		
< 3 episodes in the past 6 months	1	1
≥ 3 episodes in the past 6 months	3.83* (2.29–6.40)	2.68* (1.47–4.91)
Previous exacerbation		
None	1	1
≥ One episode in the past year	4.96* (1.75–14.04)	1.74* (1.28–2.34)
ICS ^a		
Use	1	1
Disuse	2.70* (1.82–4.02)	2.63* (1.68–4.12)
Add-on LABA		
Use	1	1
Disuse	0.78 (0.60–1.02)	0.98 (0.73–1.30)
Add-on LTRA		
Use	1	1
Disuse	1.58* (1.21–2.07)	1.42* (1.06–1.74)
Add-on theophylline		
Use	1	1
Disuse	1.25 (0.96–1.62)	1.24 (0.82–1.90)

Notes: Poor asthma control is defined as having one or more symptom of cough, sputum with coughing and nocturnal waking per week. ORs and 95% CIs of analyses using logistic regression models for associations between older age, female sex, recurrent URI, and a previous exacerbation are shown.

OR, odds ratio; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; URI, upper respiratory infection.

^aICS therapy alone and additional therapy with LABA and/or LTRA and/or theophylline were included.

* $p < .01$.

Poisson regression model predicting the frequency of severe exacerbations from the four independent significant factors was statistically significant with a chi-square likelihood ratio = 171.503, $df = 3$ ($p < .0001$).

Analysis of the expected frequency of severe exacerbations showed that one or more previous exacerbations within 6 months had an expected log count of 0.99, indicating about 0.20 more events of severe exacerbations in patients with previous exacerbations, compared to those without exacerbations, with other factors held constant (Table 4).

DISCUSSION

To our knowledge, this study is the largest retrospective study of URI and exacerbations in adult patients with asthma performed to date. The results indicate that the “exacerbation-prone” and “URI-prone” asthma phenotypes are common, with rates of 5.5% and 17.4%, respectively, and frequencies of severe exacerbations and febrile URI of 1.54 and 0.54 per subject per year, respectively. Recurrent URI and frequency of URI were associated with moderate to severe symptom-severity and severe

TABLE 3.—Univariate Poisson analysis of factors associated with the frequency of severe exacerbations.

	β (95% CI)	
Age		$p = .26$
<65 years old		
≥65 years old	0.34 (−0.26 to 0.94)	
Sex		$p < .01$
Male		
Female	0.62 (0.17–1.07)	
Episodes of URI		$p = .06$
<3 episodes in the past 6 months	−0.43 (−0.88 to 0.02)	
≥3 episodes in the past 6 months		
Episodes of rhinitis symptom		$p = .88$
None	−0.52 (−0.74 to 0.64)	
≥One episode in the past 6 months		
Episodes of sputum with coughing		$p < .01$
None	1.23 (0.77–1.68)	
≥One episode in the past 6 months		
Episodes of nocturnal awakening		$p < .01$
None	1.22 (0.61–1.82)	
≥One episode in the past 6 months		
Previous exacerbation		$p < .01$
none	0.78 (0.6–1.02)	
≥one episode in the past 6 months		
ICS ^a		$p = .08$
Disuse	0.16 (−0.08 to 0.52)	
Use		
Add-on LABA		$p = .12$
Disuse	0.24 (−0.14 to 0.52)	
Use		
Add-on LTRA		$p = .23$
Disuse	0.21 (−0.11 to 0.46)	
Use		
Add-on theophylline		$p = .66$
Disuse	−0.32 (−0.72 to 0.08)	
Use		

Notes: Severe exacerbations are defined as a self-report of an asthma-related hospitalization, an emergency department visit, or a requirement for systemic corticosteroids. CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; URI, upper respiratory infection.

^aIncluding ICS therapy alone and additional therapy with LABAs, LTRAs, and/or theophylline.

β = regression coefficient.

exacerbation, respectively, and therefore our results support the hypothesis of an association between episodes of URI and a deteriorated asthma status.

The overall incidence of URI per subject per year of follow-up was 1.54, which is similar to the results of previous prospective reports (range 1.2–6.7) (14–19). To avoid overreporting of URI episodes, the subjects were specifically instructed not to report a URI if they were experiencing URI without fever. Severe exacerbations were defined as those requiring hospitalization or a course of antibiotics or oral corticosteroids, and this definition gave an overall rate of 0.54 exacerbations per patient per year. This frequency is in agreement with the previous reports showing that asthma leads to severe exacerbations with a frequency of 0.12–0.77 per patient per year (20–22).

Exacerbations are defined as events characterized by a change from the patient’s previous status that prompts a need for a change in treatment (13). The ATS/ERS Task Force considered that episodes of “mild” exacerbations were only just outside the normal range of variation for

TABLE 4.—Multivariate Poisson analysis of factors associated with the frequency of severe exacerbations.

	β (95% CI)	Adjusted mean (95%CI)
Sex		
Male		0.11 (0.08–0.13)
Female	0.59* (0.16–1.01)	0.19 (0.13–0.26)
Episodes of sputum with coughing		
None		0.10 (0.08–0.12)
≥One episode in the past 6 months	0.97* (0.48–1.47)	0.26 (0.15–0.38)
Episodes of nocturnal awakening		
None		0.09 (0.05–0.12)
≥One episode in the past 6 months	0.72* (0.26–1.19)	0.18 (0.13–0.23)
Previous exacerbation		
None		0.12 (0.08–0.16)
≥One episode in the past 6 months	0.99* (0.34–1.65)	0.32 (0.20–0.42)

Notes: Severe exacerbations are defined as a self-report of an asthma-related hospitalization, an emergency department visit, or a requirement for systemic corticosteroids. Results are shown for an analysis using a Poisson regression model adjusted with covariates that were significant factors in univariate analysis. The adjusted mean is estimated as the arithmetic mean of the sample and the confidence interval is estimated using the relationship between the chi-square and Poisson distributions. CI, confidence interval.

β = regression coefficient; * p < .01.

an individual patient and that current methods of analysis could not distinguish such exacerbations from a transient loss of asthma control. In the current study, we analyzed patients' experiences of a deteriorated status of asthma to identify "moderate to severe symptom-severity" and "severe exacerbations". The prevalence of moderate to severe symptom-severity is in concordance with that in a report by Soriano et al. (23), in which it was shown that 65% of adult asthma patients had moderate to severe symptom-severity. We assessed factors that contributed to poor asthma control, which was considered as a "mild" exacerbation by the ATS/ERS Task Force (10). Our findings were an agreement with those in Temprano et al. (24) showing that women were more likely to have poor asthma control, despite higher rates of ICS use, compared with men. Previous severe exacerbations and recurrent episodes of URI were also covariates for moderate to severe symptom-severity. Hermosa et al. (25) also found that the number of exacerbations during the previous year is the variable with the greatest effect on control in patients with severe asthma. Symptom-severity is also significantly affected by adherence to treatment, patient knowledge of the disease, body mass index (BMI), and the number of visits to a physician in the previous 6 months (25). Viral infection also contributes to deteriorated asthma control, and cold-severity within the first 2 days can be used to predict subsequent changes in asthma control in adult patients (11).

Many studies have demonstrated that URI is a trigger of acute exacerbations of asthma (5–7), but there is little information on the association of the frequency of exacerbations and the episodes of URI. The hypothesis of our study was that recurrent episodes of URI might contribute to loss of control, but not to severe exacerbations. The rates of severe exacerbations were analyzed using a Poisson regression model. In agreement with a previous study

(26), our results showed that asthma exacerbations are more common in females than in males. Exacerbations also occurred most frequently in individuals with severe disease (27). Previous reports have also identified other risk factors, including a history of a recent exacerbation, comorbidities such as an increased BMI and psychological problems, as well as current smoking and lower socioeconomic status. A recent exacerbation within the last 3 months is associated with a markedly increased risk of a future exacerbation (2). The host response to viral infection is also likely to influence susceptibility to asthma exacerbation, and the association of a previous exacerbation with a risk for recurrent exacerbations suggests the presence of an "exacerbation-prone" subset of patients with asthma (1).

In the current study, we showed that drug intervention with ICSs and add-on LTRAs might improve symptoms, but severe exacerbations still occurred in some patients despite the use of these drugs. Many studies have described pharmacologic interventions in asthma exacerbations (28–30), and the exacerbations have been associated with poor asthma control (31). The Formoterol and Corticosteroids Establishing Therapy (FACET) study (32) revealed that a higher ICS dose had a marked beneficial effect on exacerbation frequency, but relatively less effect on symptoms and peak expiratory flow, whereas the opposite was true with the addition of LABAs (32, 33). Rosi et al. (34) also found that the asthma exacerbation frequency is not closely related to symptoms and measures of disrupted airway function. These reports and our results demonstrate that different strategies might be needed to reduce asthma exacerbations, as well as to optimize asthma control.

Leukotrienes produced in the airway in response to infection play important roles in the mechanism of exacerbation of asthma following viral infection (35). In a few studies, LTRAs have been shown to reduce asthma symptoms or exacerbations in children with colds (36–38). However, it has also been reported that LTRAs did not improve asthma control or cold symptom scores caused by experimental rhinovirus infection (39). Our results showing that add-on LTRAs with ICSs might lessen the symptoms of asthma in adults are consistent with the previous reports that add-on LTRAs are equivalent to add-on LABAs for control of asthma symptoms (40, 41). In the current study, discontinuing add-on LABAs was not associated with developing asthma symptoms, which might be due to low drug adherence.

The limitations of the study include the selection criteria, study design, and availability of data. Because we did not require evidence of bronchodilator reversibility, the enrolled patients may have had a combination of chronic obstructive pulmonary disease (COPD) and asthma. Therefore, the results cannot be generalized to all patients with asthma with the conditions described above. The questionnaire was incomplete due to missing data and distribution of the questionnaire to some patients after cold episodes. Second, microbiological specimens were not collected during the cold episodes and this prevented

determination of the role of viral or bacterial respiratory tract infections. However, because URI is self-limiting, a viral diagnosis is not clinically indicated. In children, viral URI has been associated with >80% of asthma exacerbations (42), but a recent study showed that the virus detection rate was only 36.7% in all unscheduled hospital visits in children (43). Third, we did not assess comorbidities and airway obstruction. Several comorbidities including severe nasal sinus disease, gastroesophageal reflux, recurrent respiratory infection, and obstructive sleep apnea (44), as well as current smokers (45) and increased BMI (2, 46), are associated with an increased risk for future exacerbations. Airway obstruction is also an important risk factor for multiple asthma exacerbations requiring hospital care or systemic corticosteroids (3, 47). Finally, the survey in the study was based on recall, and recall bias can distort the description of events. However, often a person recalls positive events more than negative events, and therefore it seems reasonable to assume that this recall bias did not skew our results.

In conclusion, our data suggest an association between episodes of URI and a deteriorated asthma status. These findings require confirmation in further studies in a larger number of affected individuals.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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APPENDIX

Questionnaire

Answer these questions and select the first answer that you think of.

1. During the past 6 months, have you had a bout of coughing that lasted over 1 week? If yes, how many events?
☐ No ☐ Yes (event(s))
2. During the past 6 months, have you had any sputum with coughing? If yes, how many events?
☐ No ☐ 1–2 events/6 months ☐ 1–2 events/a month
☐ 1–2 events/a week ☐ Almost every day
3. During the past 6 months, have you been woken up at night by an attack of asthma? If yes, how many events?
☐ No ☐ 1–2 events/6 months ☐ 1–2 events/a month
☐ 1–2 events/a week ☐ Almost every day
4. During the past 6 months, have you had any of these rhinitis symptoms?
☐ None ☐ Nasal obstruction ☐ Runny nose ☐ Sneeze
 If yes, what was the grade of the symptoms?
☐ Mild ☐ Intermittent ☐ Severe ☐ Extreme
5. During the past 6 months, have you had any episodes of common cold with fever (temperature >37.0°C)? If yes, how many episodes?
☐ No ☐ Yes (event(s))
6. During the past 6 months, how many times have you experienced the following events during an asthma attack?
 During these episodes, how many times did you use a reliever inhaler?
 (event(s))
 During these episodes, how many times did you use an oral steroid?
 (event(s))
 During these episodes, how many times did you visit an emergency room?
 (event(s))

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