



Aspirin-intolerant asthma in the Korean population: Prevalence and characteristics based on a questionnaire survey

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Summary

Background: Aspirin-intolerant asthma is a unique clinical syndrome characterized by acute bronchoconstriction following the administration of aspirin and/or non-steroidal anti-inflammatory drugs.

Objective: We assessed the prevalence and investigated the demographic and clinical characteristics of adult patients with aspirin-intolerant asthma in Korea.

Methods: Using an adult asthma cohort (COREA) from 11 university hospitals in Korea, we analyzed the prevalence of aspirin-intolerant asthma, defined as a positive response to the question: "Have you ever experienced dyspnea and cough after taking an aspirin or any NSAID (cold medicine)?" Demographic and clinical characteristics were compared between patients with aspirin-intolerant asthma and aspirin-tolerant asthma.

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Results: Aspirin-intolerant asthma was reported in 68 (5.8%) of 1173 adult asthmatics (age 15–84). Patients with aspirin-intolerant asthma had a lower mean age (43.9 ± 13.4 vs. 49.0 ± 15.6 , $P = 0.003$) and a higher prevalence of rhinosinusitis (77.9% vs. 61.7%, $P = 0.012$) and atopic dermatitis (16.2% vs. 5.7%, $P = 0.001$) than aspirin-tolerant asthma patients. There were no significant differences in lung function, asthma severity or the use of asthma controllers. However, aspirin-intolerant asthma was associated with greater use of healthcare services over a lifetime and over the past 12 months. Aspirin-intolerant asthma was significantly associated with emergency room visits over the past 12 months ($P = 0.029$, OR 2.19, 95% CI 1.08–4.42).

Conclusion: Based on histories, the prevalence of aspirin-intolerant asthma is 5.8% among adult asthma patients in Korea. Aspirin-intolerant asthma is associated with lower age, higher prevalence of rhinosinusitis and atopic dermatitis, and more frequent exacerbations.

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Introduction

Asthma is a chronic inflammatory disease of the airways characterized by recurrent attacks of breathlessness, chest tightness, and wheezing. Some patients with asthma experience acute reactions to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs).^{1–4} Aspirin-intolerant asthma (AIA) is a distinct syndrome associated with more severe asthma, severe rhinosinusitis with recurrent nasal polyposis, and precipitation of asthma and rhinitis attacks by ingestion of aspirin.^{1,3–8} This syndrome is increasingly being termed aspirin-exacerbated respiratory disease (AERD), emphasizing the underlying inflammation of the respiratory tract as the fundamental disease and aspirin/NSAIDs as an intensifying.^{7–11} This indicates that, despite appropriate avoidance of aspirin and NSAIDs, AIA does not resolve and runs a protracted course.^{3,12,13} AIA-associated acute exacerbations of asthma are clinically important and costly. Accordingly, identifying aspirin sensitivity is essential for the treatment of patients with asthma in order to prevent and manage frequent acute exacerbations that could be related to aspirin sensitivity.

To date, several studies have used questionnaire surveys to assess the prevalence of aspirin-intolerance in the general population and in patients with asthma. The reported prevalence of AIA ranges from 4.3% to 14% in asthmatics^{14–18} and from 0.6% to 2.5% in the general population.^{15–17} Estimates of the prevalence of AIA vary according to the methodological approach, which has included aspirin challenge tests, postal questionnaire surveys, and face-to-face interviews.¹⁹ In a meta-analysis of 15 studies, the prevalence rates were 21% based on oral aspirin challenge and 2.7% based on patient histories.¹⁹ In addition, the variation in measured prevalence of AIA depends considerably on the population assessed. Most studies of the prevalence and clinical characteristics of AIA have been on Western populations, and there are no clinical data from large cohort studies involving East Asian patients. Since ethnic disparities have been observed in the prevalence and characteristics of asthma,^{20–23} research on Asian patients suffering from AIA would be useful. Moreover, the reported demographic and clinical features of AIA, including female predominance and atopic traits, have been inconsistently observed. Therefore, the aims of the present study were to investigate the prevalence,

demographics, and clinical characteristics of aspirin-intolerance in Korean adult cohorts with asthma.

Materials and methods

Subjects

The COhort for Reality and Evolution of Adult Asthma in Korea (COREA) is a 9-year (2005–2013), multicenter, prospective cohort study of patients aged 19 years or older suffering from asthma. The design and methods of the COREA study have been described previously.²⁴ Briefly, the patients were enrolled from 11 clinical centers in various regions of South Korea. Asthma was diagnosed by allergy or pulmonology professionals based on symptoms, clinical course and positive responses to the methacholine bronchial provocation test or short-acting bronchodilator test. Patients with obvious chronic obstructive pulmonary disease (COPD) and acute exacerbation within the previous month were excluded. The enrolled patients underwent radiologic studies, spirometry, skin prick tests, and laboratory tests including sputum examination. The methods used and criteria for a positive response have been described in a previous study.²⁵ Briefly, skin prick tests were performed for common aeroallergens including house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), tree pollen mixture, grass pollen mixture, ragweed, mugwort, cockroach, alternaria, aspergillus, cat and dog. A positive control with histamine (1 mg/mL) and a negative diluent control were included in all tests. A wheal size of 3 mm or more was considered positive, and atopy was defined as one or more positive responses to allergens. Patients were interviewed at enrollment via a questionnaire assessing frequency and duration of symptoms, patterns of hospital use, and smoking status. They were reevaluated and treated by allergy or pulmonology physicians based on the Global Initiative for Asthma (GINA) guidelines²⁶ every 3 months (± 30 days) during the follow-up period. The presence of rhinosinusitis in a given subject was determined by the physicians in charge of that patient. Subjects with atopic dermatitis were those who answered 'yes' to the question 'Have you ever been diagnosed with atopic dermatitis by a doctor?'. Starting with the second visit in the third month,

Asthma Control Test (ACT) scores were determined at each visit. Of the 1,965 subjects enrolled in COREA, 1,173, who reported either presence or absence of asthma exacerbation following the intake of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), were analyzed. All subjects were ethnic Koreans and provided written informed consent. The research protocol for this cohort study was approved by the institutional review board of each center.

Definition of aspirin-intolerant asthma

Patients with AIA were distinguished from patients with aspirin-tolerant asthma (ATA) by the question: "Have you ever experienced dyspnea and cough after taking an aspirin or any NSAID (cold medicine)?" The patients were also asked if they had experienced urticaria/edema after taking an aspirin or any NSAID (cold medicine). Subjects who experienced cough or dyspnea after taking drugs such as fever remedies, analgesics, and aspirin were classified as having AIA.

Characteristics and severity of asthma

At study entry we examined the clinical features of all the patients. Atopy was defined by one or more positive reaction in the skin prick tests; airway hyperresponsiveness in the methacholine challenge test was used to diagnose asthma; and the severity of allergic rhinosinusitis was diagnosed by physicians. The severity of asthma was also assessed by physicians and by the use of controller medication, based on the GINA guidelines and the number and types of controllers, respectively.

Acute exacerbation and the control of asthma

Levels of asthma control were based on frequencies of acute exacerbation in the previous year and the ACT scores in the third month. Severity and frequency of asthma exacerbation were assessed by using the following questions: "Have you ever visited or been admitted to a hospital due to an acute exacerbation of cough, dyspnea, or wheezing?"; "If you have, how many times have you visited or been admitted?"; "If you have, how many times were you visited or admitted in the past year?" Subjects counted the number of times each of these events had occurred including any unscheduled outpatient clinic (OPD) visits, emergency room (ER) visits, and admissions to a general hospital ward or to an intensive care unit (ICU).

Statistical analyses

Data from the subjects with AIA and ATA were compared. The Kolmogorov–Smirnov test was used to analyze the distribution of variables. According to the distribution, Student's *t*-test or the Mann–Whitney *U* test was used to analyze continuous outcomes including age at baseline (years), BMI (in kilograms per square meter), duration of symptoms, duration of treatment, serum total IgE, percentage of eosinophils among peripheral blood leukocytes and PC₂₀ in the bronchial challenge test. The χ^2 test was used for categorical variables including gender,

presence of rhinosinusitis, aspirin-induced urticaria, history of atopic dermatitis, and positive skin test. Due to differences in the demographic characteristics of the two groups, models were developed to adjust for covariates including age at baseline, gender, BMI, positive skin test, presence of allergic rhinitis, and smoking status; multivariate regression analysis was used for spirometry (FEV₁, FVC and the FEV₁/FVC ratio before and after administration of a β -agonist), healthcare use, and ACT scores; multivariate logistic regression analysis was used for asthma severity assessed by physician, and medication data. *P*-values below 0.05 were considered statistically significant. Data were analyzed using SPSS software (version 17.0, Chicago, USA).

Results

Prevalence and demographic characteristics of patients with AIA

Of the 1,173 adult subjects with asthma enrolled in the study, 68 (5.8%) were identified as AIA from the questionnaire. The demographic and clinical characteristics of these patients and those with ATA are presented in Table 1. Sixteen patients under the age of 19 were ineligible for inclusion in this cohort but were enrolled and included in all the analyses. Patients with AIA were younger than those with ATA (43.9 ± 13.4 vs. 49.0 ± 15.6 years, $P = 0.003$). Patients in the two groups had similar body mass index and durations of symptoms and treatment. The patients with AIA were more likely to have rhinosinusitis (77.9% vs. 61.7%, $P = 0.012$) and atopic dermatitis (16.2% vs. 5.7%, $P = 0.001$). Similar frequencies of positive test results were reported among the patients who had undergone the bronchial challenge test and the allergy skin test. There were no significant differences in total IgE levels and eosinophil percentages in peripheral blood. Aspirin-induced urticaria was more common in the patients with AIA (49.2% vs. 2.7%, $P < 0.001$).

Lung function

Spirometric data are summarized in Table 2. There were no significant difference of pre- or post-bronchodilator spirometric indices between the patients with AIA and those with ATA. These findings were not affected by adjustment for confounding factors such as age, gender, BMI, positive skin test, smoking status, and presence of allergic rhinitis.

Asthma severity

Asthma severity was determined by a physician based on the GINA classification and compared in patients with AIA and ATA (Table 3). Among the patients with AIA, 27.9% were considered to have severe asthma, almost the same as the 26.4% among the ATA patients. There were no significant differences in the ratios of different levels of asthma severity in the two groups. We also analyzed current use of asthma controllers to assess asthma severity in the AIA and ATA patients. The proportions of subjects using three or more controllers were similar in the AIA (32.4%) and ATA

Table 1 Demographic and clinical characteristics of patients with aspirin-intolerant asthma (AIA) and aspirin-tolerant asthma (ATA).

	AIA (n = 68)	ATA (n = 1105)	P-value*
Female	41 (60.3%)	597 (54.0%)	NS
Age, years	43.9 ± 13.0	49.0 ± 15.6	0.003
BMI, kg/m ²	23.1 ± 3.3	23.9 ± 3.3	NS
Duration of symptoms, years	10.1 ± 9.9	8.0 ± 10.3	NS
Duration of treatment, years	5.4 ± 5.8	4.2 ± 5.4	NS
Smoking (current/past/never)	11 (16.4)/30 (44.8)/26 (38.8)	175 (16.1)/442 (40.6)/473 (43.4)	NS
PC ₂₀ , mg/ml	3.7 ± 4.4	4.0 ± 3.9	NS
Rhinosinusitis	53 (77.9)	682 (61.7)	0.012
Aspirin induced urticaria	33 (49.2)	30 (2.7)	<0.001
Atopic dermatitis	11 (16.2)	63 (5.7)	0.001
Positive skin test	36 (52.4)	488 (44.2)	NS
Serum total IgE, IU/mL	410.2 ± 932.3	392.9 ± 611.1	NS
Peripheral blood eosinophil, %	5.5 ± 4.5	6.5 ± 46.2	NS

Continuous values are presented as mean ± SD, and categorical variables as numbers (%). AIA, aspirin-intolerant asthma; ATA, aspirin-tolerant asthma; NS, not significant; BMI, body mass index. *P-values less than 0.05 were considered significant.

(23.8%) patients and there was no difference in the proportion of subjects using asthma controllers. Although the guidelines recommend leukotriene receptor antagonists (LTRA) for the treatment of AIA, there was no difference between the use of LTRA in the two groups (26.5% vs. 23.2%). The severity of AIA based on physician assessment and controller use was comparable to that of ATA even after adjusting for potential confounding variables such as age, gender, BMI, and allergic conditions.

Healthcare utilization and current control status

As the frequency of acute exacerbations is a key determinant of asthma control, we examined whether aspirin sensitivity was associated with an increased risk of acute exacerbations. Our data indicated that significantly more patients with AIA used healthcare services for asthma both over their lifetime and over the previous 12 months (Table 4). In particular, visits to the ER were more common in AIA patients than in ATA patients (11.8% vs. 6.4%, $P = 0.029$). The number of unscheduled OPD visits and hospitalizations was also higher in AIA patients, but the difference was not statistically significant.

We also compared overall asthma control status using the ACT scores. The mean total ACT score in AIA patients was not significantly different from that in ATA patients (20.8 ± 3.3 vs. 20.6 ± 3.2 , $P = 0.352$). This suggests that the overall asthma-control status in AIA is comparable to that in ATA. Nonetheless, frequent exacerbation of asthma is an important feature of AIA.

Discussion

This is the first report on the prevalence of AIA in Asian asthmatic patients based on a large number of subjects. In this observational study of an adult asthma cohort in Korea we found that the prevalence of AIA was 5.8%, based on a questionnaire survey. AIA was associated with lower age

and a higher prevalence of rhinosinusitis and atopic dermatitis. While no significant differences were seen in lung function, asthma severity, medication use, and control status, exacerbations were more common in the AIA patients than in the ATA patients.

The prevalence of AIA of 5.8% in our study population appears to be relatively low. Although there have been a number of publications on AIA, controversy remains over its prevalence, as this has been reported to range from 4% to 44% according to the nationality of the subjects and the evaluation method.^{14–19,27} Since the late 1990s, the reported prevalence of AIA based on questionnaires completed by randomly selected patients with asthma was 5.4% in Poland,¹⁶ 8.8% in Finland,¹⁷ and 10–11% in Australia.¹⁵ In Saudi Arabia,¹⁸ a review of medical records

Table 2 Lung functions based on pre- and post-bronchodilator spirometry.

	AIA (n = 68)	ATA (n = 1105)	P-value
Prebronchodilator			
FEV ₁ , L	2.4 ± 0.8	2.3 ± 0.9	NS
FEV ₁ % predicted	82.9 ± 21.8	82.7 ± 21.5	NS
FVC, L	3.3 ± 0.8	3.1 ± 1.0	NS
FVC % predicted	92.0 ± 19.5	88.4 ± 17.3	NS
FEV ₁ /FVC	73.4 ± 12.2	73.6 ± 12.8	NS
Post-bronchodilator spirometry			
FEV ₁ , L	2.5 ± 0.7	2.4 ± 0.9	NS
FEV ₁ % predicted	86.6 ± 20.6	85.3 ± 22.1	NS
FVC, L	3.4 ± 0.7	3.2 ± 0.9	NS
FVC % predicted	91.1 ± 14.6	88.3 ± 16.7	NS
FEV ₁ /FVC	75.8 ± 13.4	74.9 ± 12.9	NS

Values are presented as mean ± SD. AIA, aspirin-intolerant asthma; ATA, aspirin-tolerant asthma; NS, not significant.

Table 3 Severity classified by physicians and medication status.

	AIA (n = 68)	ATA (n = 1105)	P-value
Severity assessed by the physicians			NS
Mild intermittent	4 (6.9)	55 (5.8)	
Mild persistent	15 (25.9)	268 (28.4)	
Moderate persistent	23 (39.7)	371 (39.3)	
Severe persistent	16 (27.6)	249 (26.4)	
Current use of controllers			
Use of three or more controllers	22 (32.4)	263 (23.8)	NS
Oral corticosteroid	6 (8.8)	55 (5.0)	NS
Theophylline	9 (13.2)	81 (7.3)	NS
Leukotriene modifier	18 (26.5)	256 (23.2)	NS

Values are presented as numbers (%). AIA, aspirin-intolerant asthma; ATA, aspirin-tolerant asthma; NS, not significant.

at one center yielded a prevalence of 12.6% in patients with asthma. Previous studies did not include any cohort of East Asian asthmatics, and the Australian study, the last study with a large number of subjects, was published almost a decade ago. Thus, our figure of 5.8% could be of interest as it is the most recently reported prevalence of AIA in a large sample of East Asian asthmatic subjects. In our study we used the questionnaire method to diagnose AIA, and the prevalence was similar to that obtained in the Polish study. The Australian and Polish studies gave different results, even though they used similar methods, and the Polish study also had a larger sample size (12,971 subjects).^{15–18} It has been suggested that differences in the prevalence of AIA are caused by differences in study design or surveyed population (general inhabitants vs. asthmatics). In addition, the tools used for diagnosis and the severity of asthma could make substantial contributions to the variability in the measured prevalence of AIA.

There are some limitations associated with the use of questionnaire methods for diagnosing AIA. In this study, as in most others, AIA was diagnosed by a prior history of

intolerance for 'aspirin or NSAIDs (cold medicine)', based entirely on the subjects' memory. For that reason, some provoking drugs might have been forgotten or misclassified. In addition, we added the word 'cold medicine' for explanation, because most over-the-counter cold medicines have NSAIDs as their effective ingredient. Therefore, the possibility cannot be denied that some patients experienced asthma-like adverse reactions to other drugs than aspirin or NSAIDs. Moreover, the basic problem with questionnaire studies is the absence of any gold standard for diagnosis of the disease of interest. Although a definitive diagnosis of AIA can only be established using oral or inhalation challenge tests with increasing doses of aspirin, these are time-consuming procedures and may cause serious complications. Accordingly, it would have been very difficult to assess all participants using provocation tests in the present cohort study. Chang et al.²⁸ recently reported that a history of aspirin hypersensitivity was the most reliable clinical parameter for forecasting the outcome of the positive aspirin challenge test, with an overall accuracy of 88.2%. Nevertheless, due to the low sensitivity of aspirin hypersensitivity for diagnosing AIA, the prevalence of AIA would be higher if it was determined by an aspirin provocation test rather than by using patient history.¹⁹

The TENOR study, which involved patients from the USA and addressed severe or difficult-to-treat asthma, reported a high prevalence of AIA (14%).¹⁴ Because patients with AIA usually have a severe and prolonged clinical course, the higher prevalence of AIA in patients with severe or difficult-to-treat asthma compared with patients with mild-to-moderate asthma is understandable. In this regard, the differences in asthma severity and medication status between the two groups were substantial in the TENOR study. However, in the present study the prevalence of AIA in the patients with moderate-to-severe asthma was 6.2% (data not shown). Hence, it may not be the severity of the subjects' asthma, but differences between the assessed populations, that are responsible for the variation in the reported prevalence of AIA.

With regard to the relationship between the presence of atopy and AIA, our data showed that AIA was associated with atopic dermatitis and rhinosinusitis. Although uncertainty remains, some previous studies have reported that patients with AIA exhibit more clinical and immunological

Table 4 Healthcare utilization due to acute exacerbations, and level of asthma control.

	AIA (n = 68)	ATA (n = 1105)	P-value	OR (95% CI)
Healthcare utilization ever	46 (67.6)	392 (35.5)	<0.001	3.12 (1.85–5.56)
Healthcare utilization in the previous 12 months				
Any	21 (30.9)	183 (16.6)	0.007	2.14 (1.23–3.75)
Unscheduled OPD visit	8 (11.8)	71 (6.4)	0.052	2.23 (1.00–4.98)
ER visit	11 (16.2)	83 (7.5)	0.029	2.19 (1.08–4.42)
Asthma related hospitalization	6 (8.8)	75 (6.8)	0.887	1.07 (0.44–2.60)
ACT total score, mean $\pm$ SD	20.8 $\pm$ 3.3	21.6 $\pm$ 3.2	0.350	—

Continuous values are presented as mean $\pm$ SD, and categorical variables as numbers (%). AIA, aspirin-intolerant asthma; ATA, aspirin-tolerant asthma; ACT, Asthma Control Test[®] (total score 25) Multivariate regression analysis adjusted for age, gender, BMI, positive skin test, presence of allergic rhinitis, and smoking status.

markers of atopy, including the presence of chronic urticaria, positive skin tests, and high levels of total IgE and eosinophilia in peripheral blood than those with ATA.^{12,29–31} The incidence of rhinitis is strikingly high in patients with AIA; previous surveys showed that approximately 80% of them had rhinitis.^{12,14} These findings are in accord with those of the present study. However, there is also a clinical study claiming the opposite effect.³²

In the present survey, we found no significant differences in lung function and asthma severity between the two groups. A very limited number of workers have compared lung function in patients with AIA and those with ATA. Chang et al. noted lower FEV₁ in patients with AERD.²⁸ However, after logistic regression, this difference was not significant. By contrast, the TENOR study demonstrated that AIA was associated with decreased lung function and increased asthma severity in patients with severe or difficult-to-treat asthma. We enrolled patients with mild-to-moderate as well as severe asthma, and this might be the reason that we observed a lower prevalence of AIA and no difference between asthma severity and lung function between the two groups. However, although pulmonary function data were not presented, the Australian¹⁵ and Saudi Arabian¹⁸ patients with AIA suffered from more severe asthma than those with ATA. In both of the previous studies that enrolled patients suffering from asthma of all levels of severity, the differences in asthma severity between the two groups were significant. However, those studies also reported a higher prevalence of AIA than we found. In fact, it is possible that the underdiagnosis of AIA among asthmatics in the present study was due to a low sensitivity of the questionnaire for diagnosing AIA, and this may also have contributed to the absence of significant differences in lung function and asthma severity according to presence of aspirin sensitivity.

It is notable that there was no significant difference in gender bias between the two groups. A number of previous studies reported a preponderance of women among those with AIA.^{12,14,18,33,34} In contrast, an American study found no difference according to gender.¹¹ It has also been reported that females tend to have higher rates of severe asthma.^{34,35} The studies reporting these results also identified other characteristics that differed from the findings of the present study, including a higher prevalence of AIA among asthmatics and more severe asthma in patients with AIA.^{14,15,18} Taken together, these observations suggest that the differences in gender seen in the previous studies could be due to the characteristics of the subjects with severe asthma that were enrolled.

Interestingly, despite the absence of differences in lung function and severity of asthma between the two groups in the present study, a difference with respect to acute exacerbation of asthma was observed according to clinical criteria. Thus the patients with AIA visited the ER almost twice as often as did those with ATA, as also seen in the studies conducted in Australia and the USA.^{14,15} However, the Australian study found increased asthma severity in the patients with AIA, and the USA study reported not only increased asthma severity but also decreased lung function in those patients. Similarly, a study conducted in Japan showed that patients who suffered multiple exacerbations of asthma per year were much more likely to have NSAID

hypersensitivity and decreased lung function than those who had one or less exacerbations in the previous year.³⁶ Furthermore, the European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA) study,³⁴ a cross-sectional observational study comparing patients with severe asthma and those with mild-to-moderate asthma, and the Severe Asthma Research Program (SARP),³⁷ a multicenter asthma research group funded by the National Heart, Lung, and Blood Institute, both demonstrated that aspirin sensitivity was more common in subjects with severe asthma.

The definition of asthma control has two components: current clinical asthma control and future risk.^{38,39} Clinical parameters including symptoms, the degree to which asthma impairs the patient's usual activities, and lung function are major indicators of the level of current clinical asthma control.⁵ The future risk of exacerbation or disease progression is also reflected in asthma control. In that sense, this study reveals that aspirin hypersensitivity may be a risk factor for acute exacerbation of asthma independent of current clinical asthma control. Consistent with this finding, in a comparison between a near-fatal asthma group and a control asthma group based on a questionnaire survey, AIA was strongly associated with near-fatal asthma, whereas asthma severity did not differ significantly in the two groups.²⁷

In conclusion, in this first report of AIA in a large cohort of Asian asthmatics, we found that the current prevalence of AIA based on a questionnaire was 5.8% in Korea. Patients with AIA were younger and had a higher prevalence of rhinosinusitis and atopic dermatitis than those with ATA. Multivariate analysis, adjusting for potential demographic and clinical confounders, revealed no differences in lung function and asthma severity between the two groups, but AIA was associated with more frequent exacerbations. These findings suggest that AIA is a distinct phenotype of asthma, associated with a high likelihood of acute exacerbations.

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Conflicts of interest statement

The authors do not have any conflicts of interest.

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