Original Article

Smoking Cessation as a Possible Risk Factor for the Development of Aspirin-Exacerbated Respiratory Disease in Smokers

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What is already known about this topic? Aspirin-exacerbated respiratory disease (AERD) is characterized by low cyclooxygenase-2 (COX-2) expression and decreased production of prostaglandin E_2 from airway epithelia. Conversely, cigarette smoking stimulates COX-2 expression in airway epithelia.

What does this article add to our knowledge? Continuation of smoking may suppress the development of AERD and its cessation may increase susceptibility to AERD, which is thought to be due to smoking-related changes in prostaglandin E_2 levels.

How does this study impact current management guidelines? Although the results of this study are not intended to have any influence on public policies regarding smoking, physicians should be aware that smoking cessation may be followed by the development of AERD.

BACKGROUND: The pathogenesis of aspirin-exacerbated respiratory disease (AERD) is characterized by the low expression of cyclooxygenase-2 (COX-2) in airway epithelia, which decreases the production of prostaglandin E_2 (PGE_2). Conversely, cigarette smoke stimulates COX-2 expression in airway epithelia. Therefore, it was hypothesized that the development of AERD would be suppressed by elevated PGE_2 levels in smokers, and smoking cessation might increase susceptibility to AERD.

OBJECTIVE: The objective of this study was to evaluate the relationship between smoking and the risk of AERD development.

METHODS: The smoking status of patients with AERD (n = 114) was compared with 2 control groups with aspirin-tolerant asthma (ATA), patients diagnosed by a systemic aspirin provocation test (ATA-1, n = 83) and outpatients randomly selected from a large-scale dataset (ATA-2, n = 914), as well as a healthy control group (HC, n = 2313).

RESULTS: At the age of asthma onset, there was a low frequency of current smokers (9.7%), but a high frequency of past smokers (20.2%) in the AERD group compared with the ATA-1 (20.5% and 12.0% for current and past smokers, respectively), ATA-2 (24.5% and 10.3%, respectively), and HC group (26.2% and 12.6%, respectively). After adjustment for confounding variables, AERD was positively associated with smoking cessation between 1 and 4 years before disease onset compared with the ATA-2 group (adjusted odds ratio [aOR] 4.63, 95% confidence interval [CI]: 2.16-9.93) and the HC group (aOR 4.09, 95% CI: 2.07-8.05), implying that smoking cessation was followed by the development of AERD.

CONCLUSION: Smoking cessation may be a risk factor for the development of AERD. **© 2017 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).** **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Aspirin-exacerbated respiratory disease; Cyclooxygenase-2; Prostaglandin E_2; Smoking; Smoking cessation*

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Abbreviations used
AERD- Aspirin-exacerbated respiratory disease
aOR- Adjusted odds ratio
ATA- Aspirin-tolerant asthma
CI- Confidence interval
COX- Cyclooxygenase
EP- E-prostanoid
FEV_1- Forced expiratory volume in 1 second
GINA- Global Initiative for Asthma
HC- Healthy control
L-ASA- Lysine aspirin
NSAID- Nonsteroidal anti-inflammatory drug
PGE_2- Prostaglandin E_2
SD- Standard deviation

Aspirin-exacerbated respiratory disease (AERD) is an acquired, nonallergic disorder characterized by selective hypersensitivity to cyclooxygenase (COX)-1 inhibitors such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).[1-3] The majority of patients with AERD have severe asthma and symptoms tend to develop after 20 years of age.[4-7] AERD causes rhinosinusitis, nasal polyps, and elevated levels of cysteinyl leukotrienes[8-10] in the airways and throughout the body.[11] Its pathogenesis is associated with reduced COX-2 expression, which stimulates the production of prostaglandin E_2 (PGE_2) from airway epithelia.[12-15] PGE_2 acts as a smooth muscle relaxant in the airways, and it has bronchoprotective and anti-inflammatory effects in patients with asthma.[16] In previous studies, inhaled PGE_2 completely prevented aspirin-induced bronchoconstriction in patients with AERD.[17,18]

Smoking is a well-established risk factor for the development and worsening of asthma.[19-22] Cigarette smoke increases the expression of COX-2 and PGE_2 in airway epithelia[23-25] and throughout the body[26,27] in healthy individuals and asthmatic patients. In contrast, smoking cessation decreases COX-2 and PGE_2 levels.[26] Therefore, it may be speculated that the inhalation of cigarette smoke, a natural COX-2 inducer, suppresses the development of AERD.

The association between smoking history and aspirin sensitivity was investigated, and smoking was found to promote the development of AERD.[28-30] However, the interpretation of these studies is limited because the diagnosis of aspirin hypersensitivity was based on a single question[29,30] or the controls were patients' asymptomatic spouses.[28] Furthermore, the temporal relationship between smoking status and the development of asthma symptoms in AERD was not determined. The hypothesis of the present study was that AERD would be suppressed by smoking continuation and induced by smoking cessation, and the causal relationship between smoking cessation and the onset of AERD was evaluated.

METHODS

Study design

This case-control study was designed to elucidate the association between smoking status and the risk of AERD development, by comparing the case group (patients with AERD) with 3 control groups: 2 groups of patients with aspirin-tolerant asthma (ATA), and a healthy control (HC) group. The study protocol was approved by the Ethics Committee of Sagamihara National Hospital (Sagamihara, Japan). All patients provided written informed consent.

Case group and asthma control groups

Between January 2002 and December 2012, consecutive patients aged from 20 to 79 years were assigned to the AERD case group or the ATA-1 control group, according to positive or negative results of a systemic aspirin provocation test. The second control group, ATA-2, comprised a large sample of gender- and age-matched patients with ATA who were randomly selected from the outpatient database at Sagamihara National Hospital between January 2000 and December 2009. The ATA-2 group included asthmatic patients with a history of aspirin and/or NSAID use, without adverse effects, even if they had not undergone the systemic aspirin provocation test. Asthma was diagnosed by pulmonologists and allergists according to the American Thoracic Society criteria.[31] Asthma severity was evaluated according to the Global Initiative for Asthma (GINA) guidelines 2006.[32]

A total of 126 AERD cases and 1338 controls (99 and 1239 in the ATA-1 and ATA-2 groups, respectively) were identified. However, considering that the aim of this study was to explore a causal relationship between smoking and risk of asthma development in AERD, the final dataset was restricted to patients with an age of asthma onset from 20 to 69 years, which resulted in 114, 83, and 914 patients in the AERD, ATA-1, and ATA-2 groups, respectively (Figure 1). The reasons for this restriction were that the minimum age to legally purchase cigarettes in Japan is 20 years, and none of the patients in the AERD group had an age of onset of 70 years or older.

HC group

The HC group ($n = 2685$) included residents of Sagamihara City who had participated in a population-based postal survey in 2006.[33] Using the Japanese version of the first stage of the European Community Respiratory Health Survey questionnaire,[34] none of the HC group had asthma-related symptoms (wheeze, chest tightness, dyspnea, and cough) in the last 12 months or an asthma diagnosis by questionnaire. Consistent with the case group and the 2 ATA control groups, the dataset was restricted to individuals aged 20 to 69 years, with a final population of 2313 individuals (Figure 1).

Smoking status classification

Smoking status and pack-year were evaluated by the self-reported European Community Respiratory Health Survey questionnaire,[34] which includes questions about the age of asthma onset, the age of initiation/cessation of smoking, and the number of cigarettes consumed per day. Because smoking can influence the pathogenesis of asthma, in the case and ATA control groups, smoking status at the age of asthma onset was estimated from the age of smoking initiation/cessation and the age of asthma onset, and was used for smoking status classification. In the HC group, smoking status was determined by responses to the postal survey questionnaire. At registration, smoking status was defined as "never smoked," "past smoker," or "current smoker."

Smoking status at the age of asthma onset was sequentially categorized using a 3-level classification system. For smoking classification 1, in "past smokers" at registration, the age at asthma onset was subtracted from the age at smoking cessation, and values of <0, 0, and >0 were defined as "past smoker," "concomitant smoker" (smoking cessation and asthma onset were concurrent, or the time interval was very close or unknown), and "current smoker," respectively. Subsequently, the entire cohort was classified into 4 categories: "never smoked," "cessation before asthma onset," "concomitant cessation/asthma onset," and "current smoker" at the

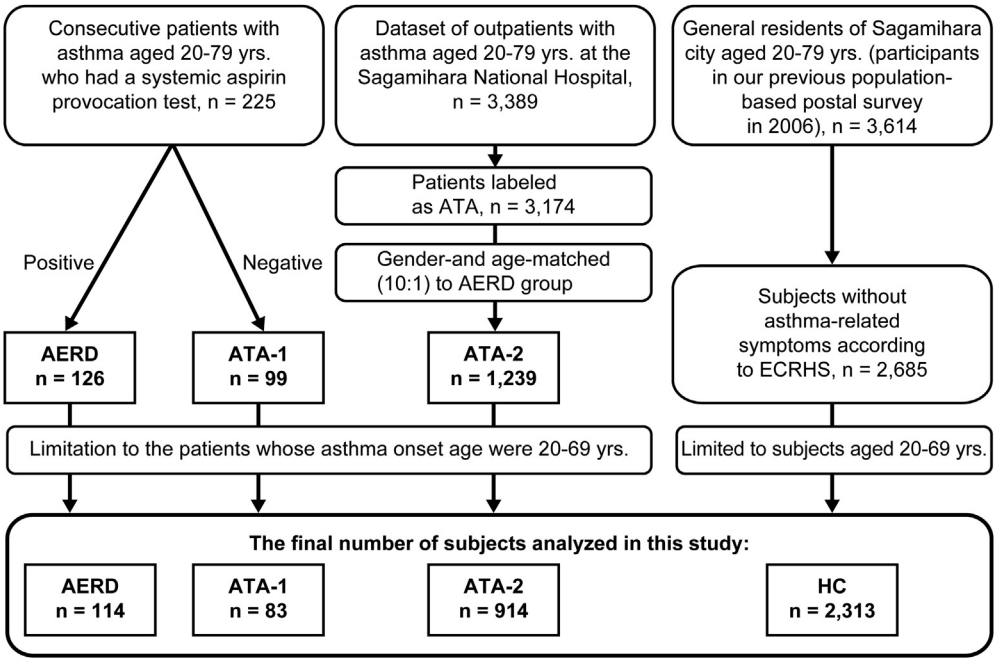


FIGURE 1. Flow chart of patient enrollment. *AERD*, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *ECRHS*, European Community Respiratory Health Survey; *HC*, healthy control.

age of asthma onset. For smoking status classification 2, the "cessation before onset" category was divided into 2 groups, according to smoking cessation for at least 5 years before asthma onset and smoking cessation within 1 to 4 years of asthma onset.

The temporal relationship between smoking cessation and the risk of AERD was further characterized by using smoking classification 3. The "cessation before onset" category was further divided according to smoking cessation for at least 6 years before asthma onset and smoking cessation within 1, 2, 3, 4, and 5 years of onset. Schematic examples of smoking status classification in specific cases are shown in Figure 2.

Aspirin provocation tests

Single-blind aspirin provocation tests were performed by the modified oral challenge protocol,[35] or by intravenous administration of double doses of lysine aspirin (L-ASA), as described previously.[36] All patients were in a clinically stable condition at the time of testing. All medications, except for daily oral corticosteroids, were stopped for at least 24 hours before the test. Forced expiratory volume in 1 second (FEV_1) was assessed by spirometry, 3 times at each time point, and the highest value was used. A decrease in FEV_1 by 20% or greater as compared with the baseline or a decrease in FEV_1 by 10% to 20% with the presence of nasal (rhinorrhea and congestion) and/or ocular (watery or red eyes) symptoms was defined as a positive reaction. Provocation was stopped after a positive reaction occurred or when the highest dose of aspirin had been administered.

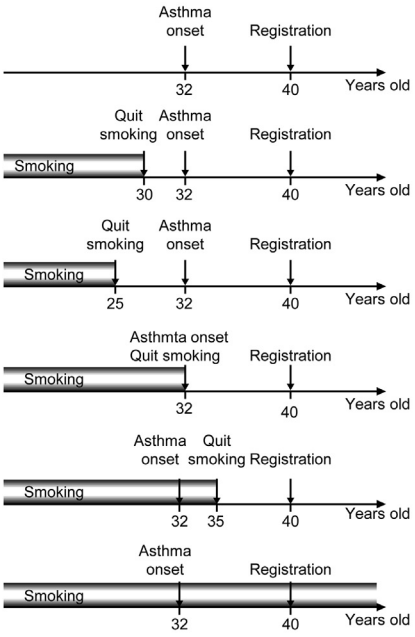
Intravenous L-ASA provocation test: after the intravenous injection of 1 mL saline, if FEV_1 did not change by more than 10% from the prechallenge baseline, doubling doses (25, 50, 100, and 200 mg equivalent to aspirin; equivalent total dose = 375 mg) of L-ASA were intravenously administered. FEV_1 was recorded every 10 minutes after administration, and the interval between doses was 30 minutes until a positive reaction occurred. The mean ± standard deviation (SD) provoking L-ASA dose was 93.8 ± 72.8 mg and the mean cumulative provoking L-ASA dose was 134.2 ± 121.0 mg. None of the patients exhibited a positive reaction after saline injection.

Oral aspirin provocation test: the dosage of ASA was started at 30 mg, and the dose was doubled (30, 60, 120, 240, and 480 mg; total dose = 930 mg) at 3-hour intervals until a positive reaction occurred. The mean provoking ASA dose was 90.0 ± 32.1 mg and the mean cumulative provoking ASA dose was 123.8 ± 60.9 mg.

Before the provocation test, urine samples were obtained for leukotriene E_4 assays. After purification with high-performance liquid chromatography, urinary leukotriene E_4 was quantified by enzyme immunoassay, as previously described.[37]

Statistical analysis

Data on clinical characteristics of cases and controls are expressed as the mean ± SD for continuous variables, and as the frequency (%) for categorical variables. Comparisons between 2 groups (case vs control) were performed with χ^2 tests for categorical variables and *t*-tests for continuous variables. To assess the differences in frequency of current smokers, past smokers, and all smokers (including current, past, and concomitant smokers) at the age of asthma onset in each group, the age- and gender-adjusted frequency of each group was calculated with the HC group as the standard population. To examine the association of smoking status classification and pack-year with the risk of AERD, the crude and adjusted odds ratio (aOR), and corresponding 95% confidence intervals (CI) were calculated using a multivariate logistic regression model. The aOR for the association between each smoking category and the risk of AERD was estimated using "never smoked" as the reference category, after adjustment for gender, age of asthma onset, and body mass index. P values $<.05$ were considered to denote statistical significance. All statistical analyses were performed using SAS version 9.3 (Cary, NC).



Smoking status at registration	Smoking status at the age of asthma onset		
	Smoking status classification 1	Smoking status classification 2	Smoking status classification 3
Never smoked	Never smoked	Never smoked	Never smoked
Past smoker	Cessation before onset	Cessation 1 to 4 years before onset	Cessation 2 years before onset
Past smoker	Cessation before onset	Cessation ≥5 years before onset	Cessation ≥6 years before onset
Past smoker	Concomitant cessation/onset	Concomitant cessation/onset	Concomitant cessation/onset
Past smoker	Current smoker	Current smoker	Current smoker
Current smoker	Current smoker	Current smoker	Current smoker

FIGURE 2. Schematic examples of smoking status classification.

RESULTS

Clinical characteristics and smoking status in the case group vs control groups

The characteristics and smoking status at the age of asthma onset in the AERD case group, and the ATA-1, ATA-2, and HC groups are shown in Table I. The age of asthma onset was lower in the AERD group (39.5 ± 12.6 years) than the ATA-2 group (43.1 ± 12.9 years, $P = .005$). The frequency of current smokers at the age of asthma onset was lower in the AERD group (12.1%) compared with the ATA-1 (23.1%, $P = .042$), ATA-2 (27.6%, $P < .001$), and HC groups (26.2%, $P = .001$) (Figure 3, *A*). In contrast, there was a higher frequency of past smokers at the age of asthma onset in the AERD group (30.2%) than the ATA-1 (13.3%, $P = .006$), ATA-2 (14.6%, $P < .001$), and HC groups (12.6%, $P < .001$) (Figure 3, *B*). When pooling data on all smokers (current, past, and concomitant smokers), there were no differences in smoking status at the age of asthma onset between the AERD group and either the ATA-1 group ($P = .792$) or the ATA-2 group ($P = .194$) (Figure 3, *C*). However, the frequency of all smokers was higher in the AERD (52.9%) than the HC group (39.8%) ($P = .005$). The distribution of pack-year categories at the age of asthma onset was not different between the AERD group and the 2 ATA control groups (ATA-1, $P = .695$ and ATA-2, $P = .326$, respectively) (Table I).

Smoking status at the age of asthma onset and risk of AERD development

The association between smoking status (smoking status classification 1 and pack-year) at the age of asthma onset and risk of AERD is shown in Table II. The odds of "cessation before onset" compared with "never smoked" was higher in the AERD group compared with the ATA-2 group (aOR 2.55, 95% CI: 1.42-4.59) and the HC group (aOR 3.40, 95% CI: 1.97-5.90; smoking status classification 1 in Table II). Conversely, the odds of "current smoker" compared with "never smoked" was lower in the AERD group than the ATA-2 group (aOR 0.42, 95% CI: 0.21-0.84), but not different from the HC group (aOR 0.53, 95% CI: 0.27-1.05). There was no correlation between pack-year and risk of AERD (Table II).

To exclude the potential effect of asthma severity on the relationship between smoking status and the risk of AERD, sensitivity analysis was performed by adjusting for asthma severity (GINA treatment step and asthma control). Because the severity of asthma at the time of onset was unclear, adjustments were made according to asthma severity at registration. The distribution of asthma severity is shown in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). Sensitivity analysis produced similar results to those shown in Table II (Table E2 and Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

Temporal relationship between smoking cessation and AERD onset

The temporal relationship between smoking cessation and AERD development is shown in Table III and Figure 4. In smoking status classification 2, the odds for "cessation within 1 to 4 years before onset" in the AERD group were higher than in the ATA-2 (aOR 4.63, 95% CI 2.16-9.93) and the HC group (aOR 4.09, 95% CI: 2.07-8.05). However, the likelihood of "cessation for at least 5 years before onset" was higher in the AERD group than the HC group (aOR 2.79, 95% CI: 1.33-5.85), but not the ATA-2 group (aOR 1.60, 95% CI: 0.74-3.45). These results indicated an association between smoking cessation within 1 to 4 years before asthma onset and

TABLE I. Comparison of characteristics and smoking status at asthma onset age between AERD and controls (ATA-1, ATA-2, and HC)

	Cases	Controls					
		AERD vs ATA-1		AERD vs ATA-2		AERD vs HC*	
	AERD	ATA-1		ATA-2		HC	
Variable at asthma onset age	n = 114	n = 83	*P* value	n = 914	*P* value	n = 2313	*P* value
Gender, n (%)							
Male	32 (28.1)	26 (31.3)	.638	268 (29.3)	.828	1123 (48.6)	<.001
Female	82 (71.9)	57 (68.7)		646 (70.7)		1190 (51.4)	
Age (y)							
Mean ± SD	39.5 ± 12.6	43.0 ± 13.8	.067	43.1 ± 12.9	.005	47.9 ± 14.5	<.001
Age (y)							
20-29	30 (26.3)	14 (16.9)	.332	171 (18.7)	.054	307 (13.3)	<.001
30-39	32 (28.1)	24 (28.9)		188 (20.6)		457 (19.8)	
40-49	22 (19.3)	13 (15.7)		233 (25.5)		372 (16.1)	
50-59	20 (17.5)	21 (25.3)		212 (23.2)		521 (22.5)	
60-69	10 (8.8)	11 (13.3)		110 (12.0)		656 (28.3)	
Body mass index† (kg/m^2)							
Mean ± SD	21.9 ± 3.5	23.3 ± 3.5	.007	22.9 ± 3.4	.005	22.8 ± 4.3	.013
Smoking status classification 1‡							
Never smoked (never smoked)	68 (59.6)	46 (55.5)	.106	569 (62.3)	<.001	1392 (60.2)	<.001
Cessation before onset (past smoker)	23 (20.2)	10 (12.0)		94 (10.3)		291 (12.6)	
Concomitant cessation/onset	12 (10.5)	10 (12.0)		27 (2.9)		24 (1.0)	
Current smoker (current smoker)	11 (9.7)	17 (20.5)		224 (24.5)		606 (26.2)	
Smoking status classification 2§							
Never smoked	68 (59.6)	46 (55.4)	.154	569 (62.3)	<.001	1392 (60.2)	<.001
Cessation ≥5 y before onset	10 (8.8)	6 (7.2)		67 (7.3)		180 (7.9)	
Cessation 1-4 y before onset	13 (11.4)	4 (4.8)		27 (3.0)		111 (4.8)	
Concomitant cessation/onset	12 (10.5)	10 (12.0)		27 (3.0)		24 (1.0)	
Current smoker	11 (9.6)	17 (20.5)		224 (24.5)		606 (26.1)	
Pack-year‖							
0	68 (59.6)	46 (55.4)	.695	569 (62.3)	.326	1392 (60.2)	.002
>0-5	16 (14.0)	12 (14.5)		99 (10.8)		153 (6.6)	
>5-10	11 (9.6)	6 (7.2)		59 (6.5)		141 (6.1)	
>10	19 (16.7)	19 (22.9)		187 (20.5)		627 (27.1)	

AERD, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *HC*, healthy control; *SD*, standard deviation.
*Age when participating in our previous survey.
†Data on initial visit.
‡Smoking status at the age of asthma onset estimated from the age of asthma onset and age of smoking initiation/cessation.
§"Cessation before onset" group according to "smoking status classification 1" was classified into 2 subcategories.
‖Pack-year at the age of asthma onset.

the risk of AERD. Moreover, in smoking status classification 3 (Table III), the association with AERD appeared to be relatively strong for smoking cessation within 2 to 3 years before asthma onset.

Dose-response relationship between cigarette consumption and risk of AERD

To investigate the dose-response relationship between cigarette consumption and risk of AERD, the same analysis was performed using only data from the "never smoked," "cessation before onset," and "current smoker" categories, and the latter 2 of the 3 categories were each divided into 2 groups (>0 to 10 or >10 cigarettes per day) based on the reported number of cigarettes smoked per day (Tables E3 and E4, available in this article's Online Repository at www.jaci-inpractice.org). A dose-response relationship between increased cigarette consumption before the cessation of smoking for "cessation before onset" and increased risk of AERD was observed when comparing the AERD and ATA-2/HC groups, but not when comparing the AERD and ATA-1 groups (Table E3). A dose-response relationship between increased cigarette consumption at the age of asthma onset for "current smoker" and decreased risk of AERD was observed when comparing the AERD and ATA-2 groups, but not when comparing the AERD and ATA-1/HC groups (Table E4).

Smoking cessation after asthma onset in current smokers

There were no significant differences between smokers in the AERD and ATA-1 groups in the frequency of "cessation after asthma onset" (Table E5, available in this article's Online Repository at www.jaci-inpractice.org). In contrast, the frequency of "cessation after asthma onset" was higher in the AERD group (72.7%) than the ATA-2 group (36.6%, $P = .024$), suggesting

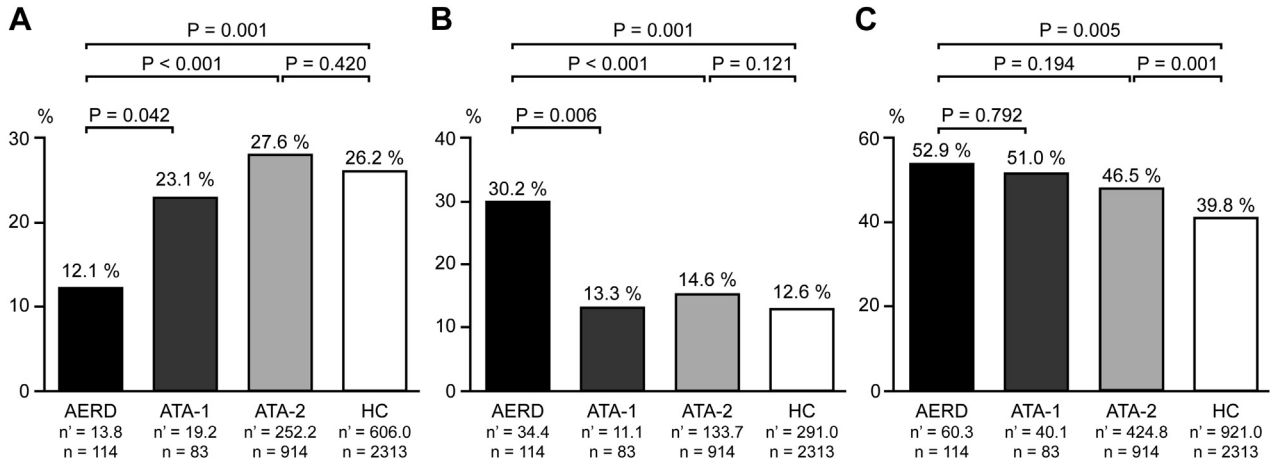


FIGURE 3. Frequency of current smokers (**A**), past smokers (**B**), and all smokers (**C**) at the age of asthma onset. The age- and gender-adjusted frequency of each group was calculated with the HC group as the standard population. *AERD*, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *HC*, healthy control, *n*, total number of subjects; *n′*, number of subjects adjusted for age and gender distribution of healthy controls.

TABLE II. Association between smoking status at age of asthma onset and risk of AERD

	AERD vs ATA-1		AERD vs ATA-2		AERD vs HC	
	Crude OR	Adjusted OR*	Crude OR	Adjusted OR*	Crude OR	Adjusted OR†
Variable at asthma onset age	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Smoking status classification 1‡						
Never smoked (never smoked)	1.00	1.00	1.00	1.00	1.00	1.00
Cessation before onset (past smoker)	1.56 (0.68-3.57)	1.99 (0.77-5.18)	**2.08 (1.22-3.45)**	**2.55 (1.42-4.59)**	1.62 (0.99-2.64)	**3.40 (1.97-5.90)**
Concomitant cessation/onset	0.81 (0.32-2.04)	0.91 (0.34-2.49)	**3.72 (1.80-7.68)**	**4.28 (1.96-9.36)**	**10.24 (4.91-21.33)**	**15.34 (6.75-34.85)**
Current smoker (current smoker)	0.44 (0.19-1.02)	0.44 (0.18-1.11)	**0.41 (0.21-0.79)**	**0.42 (0.21-0.84)**	**0.37 (0.20-0.71)**	0.53 (0.27-1.05)
Pack-year§						
0	1.00	1.00	1.00	1.00	1.00	1.00
>0-5	0.9 (0.39-2.08)	0.85 (0.35-2.08)	1.35 (0.75-2.43)	1.13 (0.61-2.08)	**2.14 (1.21-3.78)**	1.79 (0.97-3.28)
>5-10	1.24 (0.43-3.59)	1.19 (0.39-3.70)	1.56 (0.78-3.11)	1.51 (0.74-3.07)	1.60 (0.83-3.09)	1.88 (0.94-3.76)
>10	0.68 (0.32-1.41)	0.83 (0.34-2.06)	0.85 (0.50-1.45)	1.01 (0.54-1.90)	0.62 (0.37-1.04)	1.45 (0.80-2.62)

AERD, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *CI*, confidence interval; *HC*, healthy control; *OR*, odds ratio.
Values in bold are statistically significant ($P < .05$).
Multivariate logistic regression analysis.
*After adjustment for gender, body mass index, and asthma onset age.
†After adjustment for gender, body mass index, and age when participating in our previous survey.
‡Smoking status at the age of asthma onset, which was estimated from the age of asthma onset and age of smoking initiation/cessation.
§Pack-year at the age of asthma onset.

that smoking cessation was more likely in patients with AERD, possibly due to the severity of asthma symptoms.

Case series of patients with AERD who stopped smoking before asthma onset

To further characterize the clinical relationship between smoking cessation and the onset of AERD, detailed case histories on the time of smoking cessation and the onset of symptoms were examined for patients with AERD with asthma onset after smoking cessation. Among 9 patients who developed asthma within 2 to 4 years after smoking cessation, 5 remained on treatment as outpatients at Sagamihara National Hospital. Four of these patients provided consent for detailed case histories in relation to smoking cessation and the onset of respiratory symptoms (Figure 5). After smoking cessation, all 4 patients developed nasal and lower respiratory symptoms, indicating that smoking cessation was followed by the onset of sinusitis in such patients as well as asthma. None of the patients reported the development of any respiratory symptoms before stopping smoking, and the reason for quitting was not the presence of asthmatic or nasal symptoms.

DISCUSSION

To the best of the authors' knowledge, this is the first study to report the possibility that smoking cessation is a risk factor for the development of AERD. The results demonstrate that AERD was positively associated with smoking cessation between 1 and 4 years before disease onset compared with the patients with ATA.

TABLE III. Temporal relationship between smoking cessation preceding asthma onset and risk of AERD

	Cases	Controls			AERD vs ATA-1		AERD vs ATA-2		AERD vs HC	
	AERD	ATA-1	ATA-2	HC	Crude OR*	Adjusted OR†	Crude OR*	Adjusted OR†	Crude OR*	Adjusted OR†
Variable at asthma onset age	n = 114	n = 83	n = 914	n = 2313	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Smoking status classification 2‡										
Never smoked	68 (59.6)	46 (55.4)	569 (62.3)	1392 (60.2)	1.00	1.00	1.00	1.00	1.00	1.00
Cessation ≥5 y before onset	10 (8.8)	6 (7.2)	67 (7.3)	180 (7.9)	1.13 (0.38-3.32)	1.63 (0.51-5.25)	1.25 (0.61-2.54)	1.60 (0.74-3.45)	1.14 (0.58-2.25)	**2.79 (1.33-5.85)**
Cessation 1-4 y before onset	13 (11.4)	4 (4.8)	27 (3.0)	111 (4.8)	2.20 (0.68-7.17)	2.56 (0.69-9.45)	**4.03 (1.99-8.18)**	**4.63 (2.16-9.93)**	**2.40 (1.29-4.47)**	**4.09 (2.07-8.05)**
Concomitant cessation/onset	12 (10.5)	10 (12.0)	27 (3.0)	24 (1.0)	0.81 (0.32-2.03)	0.92 (0.34-2.52)	**3.72 (1.80-7.68)**	**4.24 (1.94-9.27)**	**10.24 (4.91-21.33)**	**15.26 (6.72-34.62)**
Current smoker	11 (9.6)	17 (20.5)	224 (24.5)	606 (26.1)	0.44 (0.19-1.02)	0.45 (0.18-1.12)	**0.41 (0.21-0.79)**	**0.42 (0.21-0.84)**	**0.37 (0.20-0.71)**	0.53 (0.27-1.05)
Smoking status classification 3§										
Never smoked	68 (59.6)	46 (55.4)	569 (62.3)	1392 (60.2)	NA	NA	1.00	1.00	1.00	1.00
Cessation ≥6 y before onset	8 (7.0)	6 (7.2)	60 (6.6)	167 (7.2)	NA	NA	1.12 (0.51-2.43)	1.49 (0.64-3.46)	0.98 (0.46-2.08)	**2.49 (1.11-5.58)**
Cessation 5 y before onset	2 (1.8)	0 (0)	7 (0.8)	13 (0.6)	NA	NA	2.39 (0.49-11.74)	2.46 (0.49-12.35)	3.15 (0.70-14.23)	**5.33 (1.07-26.54)**
Cessation 4 y before onset	2 (1.8)	0 (0)	3 (0.3)	33 (1.4)	NA	NA	5.58 (0.92-33.98)	5.98 (0.94-28.18)	1.24 (0.29-5.28)	2.05 (0.47-9.06)
Cessation 3 y before onset	3 (2.6)	1 (1.2)	8 (0.9)	27 (1.2)	NA	NA	3.14 (0.81-12.11)	**4.34 (1.03-18.28)**	2.28 (0.67-7.68)	**5.13 (1.41-18.73)**
Cessation 2 y before onset	4 (3.5)	2 (2.4)	6 (0.7)	29 (1.3)	NA	NA	**5.58 (1.54-20.26)**	**7.20 (1.85-28.02)**	2.82 (0.97-8.26)	**5.20 (1.64-16.47)**
Cessation 1 y before onset	4 (3.5)	1 (1.2)	10 (1.1)	22 (1.0)	NA	NA	**3.35 (1.02-10.96)**	3.25 (0.97-10.88)	**3.72 (1.25-11.10)**	**4.74 (1.46-15.41)**
Concomitant cessation/onset	12 (10.5)	10 (12.0)	27 (3.0)	24 (1.0)	NA	NA	**3.72 (1.80-7.68)**	**4.28 (1.96-9.38)**	**10.24 (4.91-21.33)**	**15.21 (6.70-34.50)**
Current smoker	11 (9.6)	17 (20.5)	224 (24.5)	606 (26.2)	NA	NA	**0.41 (0.21-0.79)**	**0.43 (0.22-0.84)**	**0.37 (0.20-0.71)**	0.53 (0.27-1.05)

AERD, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *CI*, confidence interval; *HC*, healthy control; *NA*, not available; *OR*, odds ratio.
Values in bold are statistically significant ($P < .05$).
Multivariate logistic regression analysis.
*After adjustment for gender, body mass index, and asthma onset age.
†After adjustment for gender, body mass index, and age when participating in our previous survey.
‡"Cessation before onset" group of "smoking status classification 1" in Table I was classified into 2 subcategories.
§The number of patients in the ATA-1 group was too small to permit statistically meaningful analysis.

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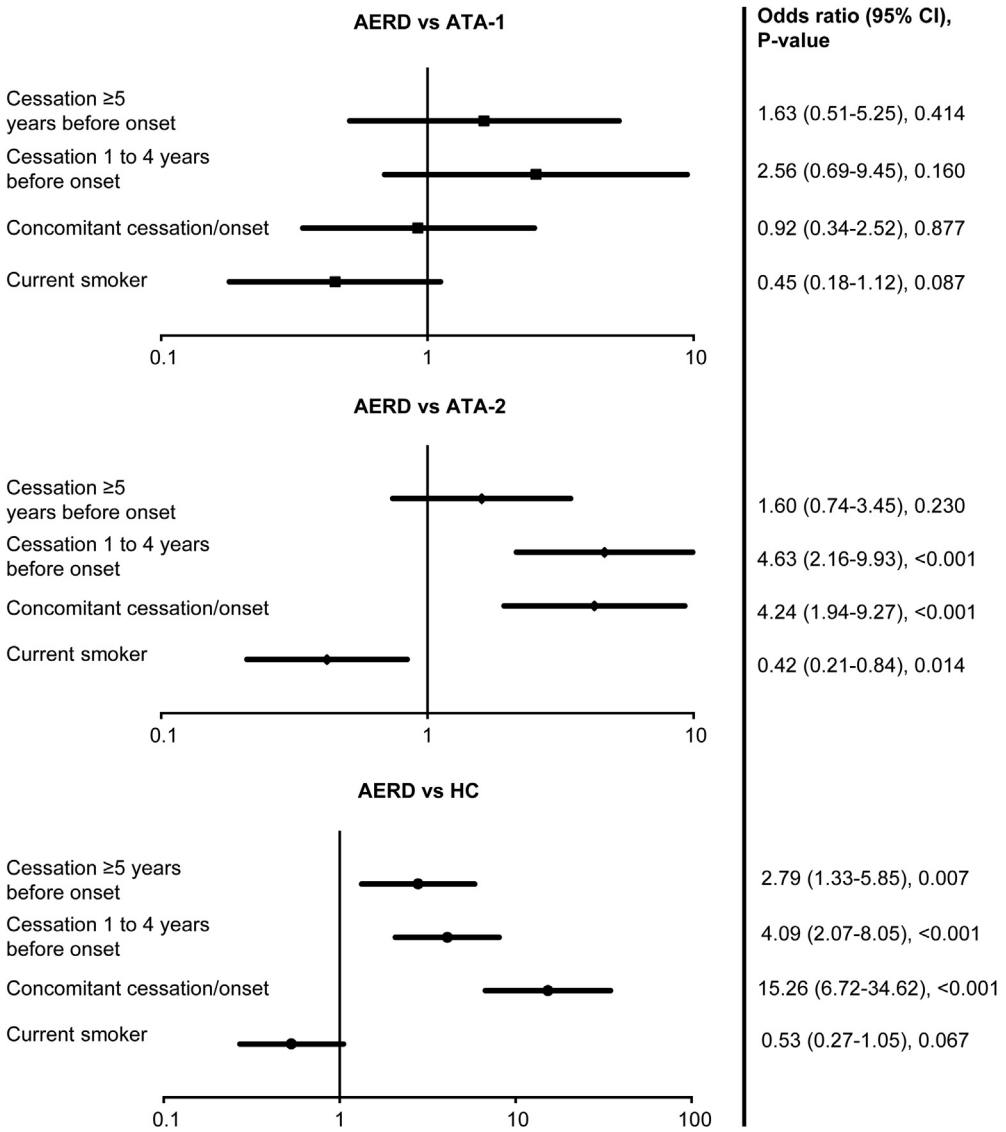

FIGURE 4. Adjusted odds ratios for the association between smoking cessation preceding asthma onset and the risk of AERD (smoking classification 2). The reference group was "never smoked." *AERD*, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *CI*, confidence interval; *HC*, healthy control.

This supports the hypothesis that smoking cessation may lead to AERD onset.

Epidemiological studies have confirmed that smoking is an important risk factor for the development of general asthma.[38-40] In this study, the frequency of past and current smokers at the age of asthma onset in the ATA-2 group was higher than in the HC group, which is compatible with previous reports.[38-40] However, there were fewer current smokers in the AERD group than the ATA-2 group, and the negative association with current smoking in the AERD group was not mediated by disease severity. The frequency of "cessation within 1 to 4 years before onset" was also higher in the AERD group than the ATA-2 group, which suggested that patients in the AERD group were more likely to develop asthma within 4 years after smoking cessation.

The frequency of past smokers was not different between the AERD and ATA-1 group. In addition, a dose-response relationship was not observed between the AERD and ATA-1 groups. These findings may be related to the insufficient sample size of the ATA-1 group for statistical significance. Another possibility is that the ATA-1 group, in whom the provocation test was performed, represents a distinct patient population from general asthma (the ATA-2 group). Indeed, patients in the ATA-1 group tended to have worse asthma control (Table E1, available in this article's Online Repository at www.jaci-inpractice.org) and a higher frequency of comorbid nasal polyps and/or sinusitis (39.8% vs 16.4%, $P < .001$; data not shown) than those in the ATA-2 group. In addition, because the ATA-1 group were initially suspected to have AERD, but had negative results on the systemic aspirin provocation test, some of these patients had nasal polyps and/or sinusitis or eosinophilia, similar to patients with AERD. We consider the possibility that some ATA-1 patients with nasal polyps share a common pathogenetic background, including prostaglandin status, with AERD, and the inclusion of such a patient in ATA-1 group may have

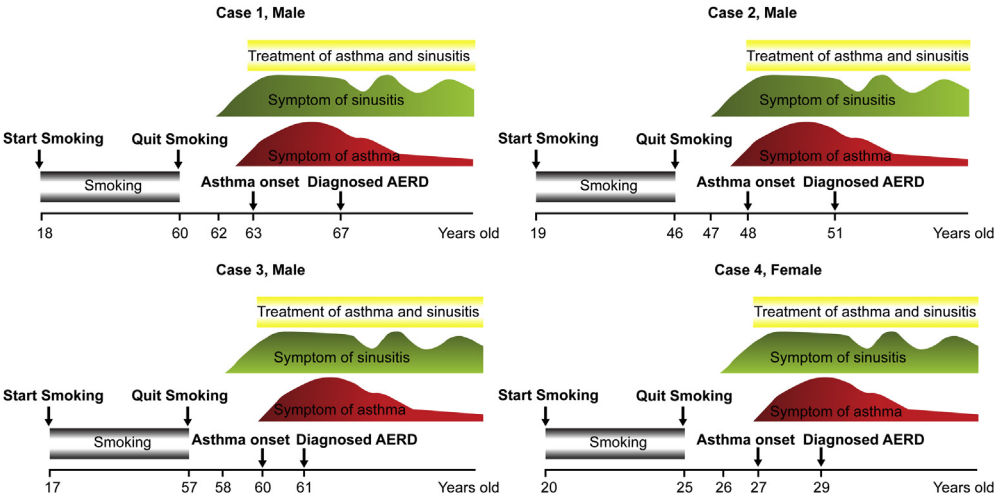

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FIGURE 5. Detailed case histories of the timing of smoking cessation and the onset of respiratory symptoms. The reason for smoking cessation was the risk of future smoking-related health problems in cases 1, 3, and 4 and a nonsmoking policy in the workplace in case 2. *AERD*, Aspirin-exacerbated respiratory disease.

confounded the relationship between smoking and aspirin intolerance.

AERD is characterized by reduced COX-2 expression and subsequent PGE_2 production by airway epithelia.[12-14] PGE_2 activity is mediated by 4 subtypes of E-prostanoid (EP) receptors.[41] Patients with AERD have impaired PGE_2 activity due to the low expression of EP2 receptors on various bronchial inflammatory cells[13] and nasal mucosal inflammatory cells,[14] which may be caused by EP2 gene polymorphisms.[42] Smoking tends to induce an array of inflammatory mediators and cytokines,[43] which also induces COX-2 expression and increases PGE_2 production, both locally in the airway epithelia[23-25] and systemically[26,27] in healthy individuals and asthmatic patients. In addition, smoking increases EP2 receptor expression in lung fibroblasts,[44] neutrophils, and alveolar macrophages.[45] Taken together, these data suggest that smoking increases PGE_2 production and EP2 receptor expression, which may have prevented the development of AERD. In contrast, smoking cessation might diminish PGE_2 production and EP2 receptor expression, which might induce the development of AERD.

In a study of the natural history of AERD,[4] the first reported symptom tended to be rhinosinusitis, and 2 years after developing rhinosinusitis, the first symptoms of asthma appeared. Intolerance to NSAIDs was evident 4 years later.[4] Although polluted air from cigarette smoking is also breathed in through the nose while smoking, the present study did not investigate the association between smoking and the onset of nasal polyps in a case-control manner. However, the case series of 4 patients with AERD who developed asthma within 1 to 4 years after smoking cessation revealed that nasal and lower respiratory symptoms had developed after smoking cessation. Therefore, the development of nasal symptoms was not the reason for smoking cessation in these patients. Indeed, most patients quit smoking for reasons other than physical symptoms. Therefore, we speculate that smoking cessation triggered the pathogenesis of AERD, including nasal symptoms.

There are some limitations to this study. The study design was retrospective, and the source of data was a self-reported questionnaire. However, the same questionnaire was used in all groups. Second, the study included a limited sample number from a single center. Because this study was performed in Japan, results from other ethnic and genetic backgrounds are not available. However, the distribution of age of asthma onset in the AERD group was similar to that previously reported by Szczeklik et al.[4] In addition, the effects of environmental smoke exposure during childhood and adulthood were not considered. Mechanistic investigations such as the role of the arachidonic acid pathway were not conducted and further studies are needed to evaluate the protective PGE_2 theory.

Importantly, it should be emphasized that the results of this study are not intended to have any influence on public policies regarding smoking. Because of its many adverse effects,[46] smoking should not be recommended as a treatment option. However, our findings contribute toward a better understanding of the pathogenesis of AERD and the development of novel strategies to prevent its onset. This study also highlights the need for further intensive investigations into the relationship between the inhalation of cigarette smoke and AERD.

In conclusion, this study indicated that the cessation of cigarette smoke, a natural COX-2 inducer, may be a risk factor for the development of AERD. Further clinical and mechanistic studies are needed to determine the effect of smoking exposure, especially the treatment effect of PGE_2, on the pathogenesis of AERD.

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All authors contributed to this research study. MT developed the study concept and design; HH, CM, KW, YK, KS, and TT were responsible for patient recruitment and data acquisition; EN conducted the statistical analyses; HH wrote the manuscript; and YH, SI, EN, and YF contributed to the critical revision of the manuscript.

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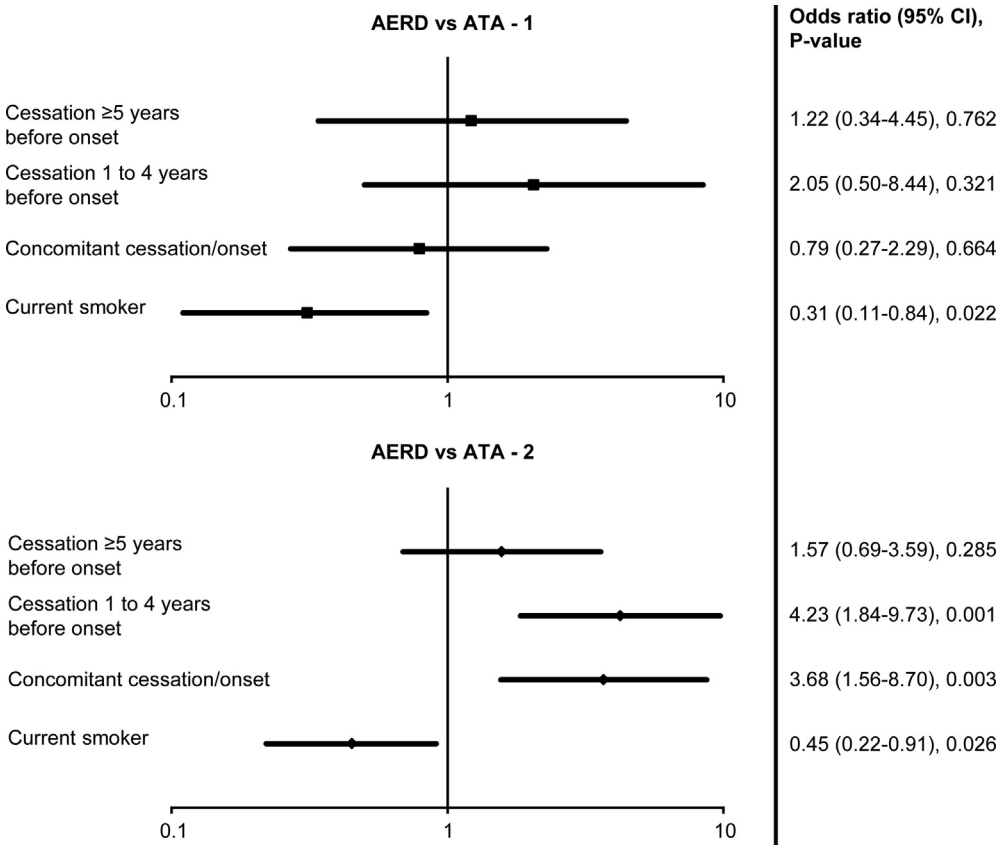

FIGURE E1. Odds ratios for the association between smoking cessation preceding asthma onset and the risk of AERD (smoking classification 2) after adjustment for asthma severity. The reference group was "never smoked." *AERD*, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *CI*, confidence interval.

TABLE E1. Treatment status and asthma control after onset in asthma patients (AERD, ATA-1, and ATA-2)

		Cases	Controls			
			AERD vs ATA-1		AERD vs ATA-2	
		AERD	ATA-1		ATA-2	
Variable	Categories	n = 114	n = 83	*P* value	n = 914	*P* value
GINA treatment step, n (%)	1	9 (7.9)	4 (4.8)	.035	89 (9.7)	<.001
	2	12 (10.5)	23 (27.7)		162 (17.7)	
	3	12 (10.5)	9 (10.8)		221 (24.2)	
	4	65 (57.0)	39 (47.0)		376 (41.1)	
	5	16 (14.0)	8 (9.6)		66 (7.2)	
Asthma control, n (%)	Controlled	61 (53.5)	63 (75.9)	.002	827 (90.5)	<.001
	Partly or uncontrolled	53 (46.5)	20 (24.1)		87 (9.5)	
Urinary leukotriene E_4 (pg/mg of creatinine)	Mean ± SD	574.3 ± 1209.0	165.1 ± 130.7	.001	NA	–

AERD, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *GINA*, Global Initiative for Asthma; *NA*, not available; *SD*, standard deviation.

TABLE E2. Association between smoking status at age of asthma onset and risk of AERD (adjusted by asthma severity)

	AERD vs ATA-1		AERD vs ATA-2	
	Crude OR	Adjusted OR*	Crude OR	Adjusted OR*
Variable at asthma onset age	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Smoking status classification 1†				
Never smoked (never smoked)	1.00	1.00	1.00	1.00
Cessation before onset (past smoker)	1.56 (0.68-3.57)	1.55 (0.55-4.35)	**2.05 (1.22-3.45)**	**2.44 (1.29-4.62)**
Concomitant cessation/onset	0.81 (0.32-2.04)	0.78 (0.27-2.25)	**3.72 (1.80-7.68)**	**3.69 (1.56-8.72)**
Current smoker (current smoker)	0.44 (0.19-1.02)	**0.30 (0.11-0.83)**	**0.41 (0.21-0.79)**	**0.45 (0.22-0.91)**
Smoking status classification 2‡				
Never smoked	1.00	1.00	1.00	1.00
Cessation ≥5 y before onset	1.13 (0.38-3.32)	1.22 (0.34-4.45)	1.25 (0.61-2.54)	1.57 (0.69-3.59)
Cessation 1-4 y before onset	2.20 (0.68-7.17)	2.05 (0.50-8.44)	**4.03 (1.99-8.18)**	**4.23 (1.84-9.73)**
Concomitant cessation/onset	0.81 (0.32-2.03)	0.79 (0.27-2.29)	**3.72 (1.80-7.68)**	**3.68 (1.56-8.70)**
Current smoker	0.44 (0.19-1.02)	**0.31 (0.11-0.84)**	**0.41 (0.21-0.79)**	**0.45 (0.22-0.91)**
Pack-year§				
0	1.00	1.00	1.00	1.00
>0-5	0.9 (0.39-2.08)	0.66 (0.25-1.72)	1.35 (0.75-2.43)	1.07 (0.61-2.08)
>5-10	1.24 (0.43-3.59)	0.89 (0.27-2.94)	1.56 (0.78-3.11)	1.76 (0.74-3.07)
>10	0.68 (0.32-1.41)	0.63 (0.23-1.70)	0.85 (0.50-1.45)	0.97 (0.54-1.90)

AERD, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *CI*, confidence interval; *GINA*, Global Initiative for Asthma; *OR*, odds ratio.
Values in bold are statistically significant ($P < .05$).
Multivariate logistic regression analysis.
*After adjustment for gender, body mass index, asthma onset age, GINA treatment step, and asthma control.
†Smoking status at the age of asthma onset estimated from the age of asthma onset and the age of initiation/cessation of smoking.
‡"Cessation before onset" group of "smoking status classification 1" was classified into 2 subcategories.
§The pack-year at the age of asthma onset.

TABLE E3. Subgroup analysis of dose-response relationship between amount of cigarette consumption and risk of AERD (cessation before onset)

	Cases	Controls			AERD vs ATA-1	AERD vs ATA-2	AERD vs HC
Number of cigarettes smoked per day at asthma onset age	AERD n = 91	ATA-1 n = 56	ATA-2 n = 663	HC n = 1683	Adjusted OR* (95% CI)	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Smoking status classification							
Never smoked	68 (74.7)	46 (82.2)	569 (85.8)	1392 (82.7)	1.00	1.00	1.00
Cessation before onset							
>0-10	9 (9.9)	5 (8.9)	34 (5.1)	80 (4.8)	1.53 (0.44-5.32)	**2.41 (1.08-5.35)**	**3.29 (1.53-7.08)**
>10	14 (15.4)	5 (8.9)	60 (9.1)	211 (12.5)	2.53 (0.74-8.58)	**2.58 (1.24-5.39)**	**3.55 (1.80-6.98)**
P value for trend					.120	.007	<.001

AERD, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *CI*, confidence interval; *HC*, healthy control; *OR*, odds ratio.
Values in bold are statistically significant ($P < .05$).
Multivariate logistic regression analysis.
*After adjustment for gender, body mass index, and asthma onset age.
†After adjustment for gender, body mass index, and age when participating in our previous survey.

TABLE E4. Subgroup analysis of dose-response relationship between cigarette consumption and risk of AERD (current smoker)

	Cases	Controls			AERD vs ATA-1	AERD vs ATA-2	AERD vs HC
Number of cigarettes smoked per day at asthma onset age	AERD n = 79	ATA-1 n = 63	ATA-2 n = 793	HC n = 1998	Adjusted OR* (95% CI)	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Smoking status classification							
Never smoked	68 (86.1)	46 (73.0)	569 (71.7)	1392 (69.6)	1.00	1.00	1.00
Current smoker							
>0-10	5 (6.3)	5 (7.9)	60 (7.6)	175 (8.8)	0.52 (0.14-2.01)	0.63 (0.24-1.64)	0.58 (0.23-1.49)
>10	6 (7.6)	12 (19.1)	164 (20.7)	431 (21.6)	0.40 (0.13-1.26)	**0.33 (0.14-0.80)**	0.50 (0.21-1.22)
P value for trend					.157	.032	.294

AERD, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma; *CI*, confidence interval; *HC*, healthy control; *OR*, odds ratio.
Values in bold are statistically significant ($P < .05$).
Multivariate logistic regression analysis.
*After adjustment for gender, body mass index, and asthma onset age.
†After adjustment for gender, body mass index, and age when participating in our previous survey.

TABLE E5. Smoking cessation after onset in patients with asthma (AERD, ATA-1, and ATA-2) smoking at onset

			Controls			
		Cases	AERD vs ATA-1		AERD vs ATA-2	
		AERD	ATA-1		ATA-2	
Variable	Categories	n = 11	n = 17	*P* value	n = 224	*P* value
Cessation after asthma onset	Yes	8 (72.7)	10 (58.8)	.689	82 (36.6)	.024
	No	3 (27.3)	7 (41.2)		142 (63.4)	

AERD, Aspirin-exacerbated respiratory disease; *ATA*, aspirin-tolerant asthma.