

# An Analysis of Factors that Exacerbate Asthma, Based on a Japanese Questionnaire

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## ABSTRACT

**Background:** It is known that a wide variety of factors exacerbate asthma; however, few studies have investigated the factors that exacerbate asthma from a patient's perspective. The aim of this study was to analyze the factors that exacerbate asthma, based on a questionnaire completed by asthma patients in Niigata Prefecture.

**Methods:** Based on questionnaires given to 3085 patients who visited the medical institutes in the Niigata Prefecture monthly from September through October 2006, groups stratified by sex, age, disease type and disease severity, were analyzed for factors contributing to asthma exacerbation, as described in the guideline of the Japanese Society of Allergology.

**Results:** The leading exacerbating factor chosen by patients was a change in the weather, followed by smoking, allergen exposure, fatigue, stimulants, and air pollutants. Respiratory infection, widely recognized as a critical factor of severe exacerbation, was ranked seventh. Allergen exposure and air pollutants were prominent in younger individuals, whereas respiratory infection tended to be more common in elderly subjects. Allergen exposure, air pollutants, and exercise were significantly more common in atopic-type patients, in contrast with respiratory infection in non-atopic-type patients. According to multiple regression analysis, poor asthma control during the last one year was associated with changes in the weather, whereas the non-atopic disease type was related to exacerbation by respiratory infection. Current smoking was associated with both factors.

**Conclusions:** Many factors exacerbate asthma, depending on the individual case and his/her background. These data suggest that changes in the weather may be more important factor for patients in asthma exacerbation.

## KEY WORDS

asthma exacerbation, questionnaire, respiratory infection, smoking, weather change

## INTRODUCTION

The prevalence of bronchial asthma in Japanese adults is about 5% and is gradually increasing. The mortality due to bronchial asthma, about 3000 deaths per year, is decreasing; however, mortality still remains higher than in Western countries and is considered an important issue in asthma management.<sup>1,2</sup> A review by Alvarez *et al.* states that improper treatment or abrupt cessation of agents such as inhaled

corticosteroids (ICS) are recognized as risk factors for near-fatal or fatal asthma.<sup>3</sup> Other factors are respiratory infection, such as influenza or rhinovirus infection, intolerance of non-steroidal anti inflammatory drugs (NSAIDs), and older age, all thought to be the risk factors for asthma-related death.<sup>4</sup> According to a report on the causes of fatal asthma in the Japanese population, respiratory infection, fatigue and emotional stress were prominent factors.<sup>5</sup> Various factors are recognized as causes of asthma exacerbation as

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well as fatal or near-fatal attacks, and the Japanese Society of Allergology has pointed out 16 factors related to asthma exacerbation. However, no patient has experienced exacerbations from all of these factors; therefore, the recognition and avoidance of factors that cause asthma exacerbation in a particular patient are critical in asthma management. However, the precise recognition of exacerbating factors is not easy, and these factors sometimes occur in combination. For example, a study that examined the association between thunderstorms and asthma exacerbation, reported that increased exposure to antigens such as pollen or certain other allergens, caused by the thunderstorm, contributes to the acute exacerbation,<sup>6</sup> which is therefore a complication of both weather change and allergen exposure. Air pollution and emotional stress are also not thought to be clear-cut factors; therefore, most previous reports regarding these factors might contain some bias because the data contained in the reports originate from the doctor's perspective.

Since 1998, the Niigata Asthma Treatment Study Group has provided an annual questionnaire to asthma patients who reside in the Niigata Prefecture.<sup>7-10</sup> The questionnaire contains various questions such as past and current control of asthma, the existence of aspirin intolerant asthma (AIA) or premenstrual asthma (PMA), smoking status, usage of peak expiratory flow rate (PEFR), and satisfaction with daily life etc. Not only the patients but also their doctors are asked about the disease type, severity, treatment and findings on examination. Although 70 percent of these doctors are pulmonary physicians, and there may therefore be some bias with respect to treatment, these data are thought to reflect the current practice of medicine, to some extent. In this study, the questionnaire was completed by approximately 3000 patients with asthma over a period of 2 months, from September to October 2006, and patients were asked about the factors that induced exacerbations of their asthma, based on the 16 issues that were described in the guideline of the Japanese Society of Allergology. The most noteworthy feature of this study is that patients, not doctors, assessed the factors that exacerbated their asthma. Moreover, multiple regression analysis of "weather change" and "respiratory infection" demonstrated the important association between these factors and asthma-related issues.

## METHODS

The questionnaire used in this study was administered in Niigata Prefecture, Japan, under the *Ethical Principles for Medical Research Involving Human Subjects* in the Declaration of Helsinki, and with the approval of the Ethics Committee of the Niigata University School of Medicine. The institutions involved were 28 large hospitals (200 beds or more), 15 small

hospitals (<200 beds) and 69 clinics (no beds). 3650 questionnaires were prepared and 3085 were answered (response rate: 85%). The questionnaires are shown in Table 1 (originally in Japanese). The questionnaire was distributed over a period of 2 months, from September to October 2006. Subjects were adult patients (aged 16 years and over) with bronchial asthma who regularly visited the participating institutes for asthma management (typically once or twice per month). The recruited patients were asked to complete the questionnaire by themselves.

To investigate factors that exacerbate asthma, patients were asked about their own exacerbating factors with questions such as "Has your asthma ever become worse under the following conditions?" with the possible answers: "allergen exposure", "air pollutants", "respiratory infection", "exercise", "smoking", "weather", "food and food additives", "drugs", "emotional stress", "stimulants", "sulfur dioxide", "menstruation", "pregnancy", "obesity", "alcohol", "fatigue", which are indicated in the Japanese Society of Allergology guideline as factors that exacerbate asthma.

As well as exacerbating factors, patients were asked about the duration of the disease, family history, the presence of asthma in childhood, smoking history, usage of a peak expiratory flow meter and its mean value. The questionnaire also asked patients about the history of their own asthma, such as the frequency of exacerbations during the year prior to the questionnaire, emergency unit visits, hospitalization, and life-threatening events like unconsciousness during an asthma attack, attacks requiring respirator management, and attacks induced by an anti-inflammatory agent (aspirin intolerant asthma: AIA). As an evaluation of current asthma control, the patients were asked about the incidence of asthma exacerbations and asthma-related symptoms during the 2 weeks prior to the questionnaire, such as cough, sputum, and dyspnea in the morning and at night. To evaluate problems in asthma management and treatment related to normal activity levels, the questionnaire asked patients about their satisfaction with daily life.

In addition to completion of the questions by patients, their physicians were asked to supply details of current treatment, primarily identifying controlling medication, and the type of asthma (atopic or non-atopic) in accordance with the level of serum IgE, to identify allergen-related and complicated atopic diseases. We also included a question about the severity of asthma, in accordance with the Japanese Society of Allergology guidelines for the diagnosis and management of bronchial asthma. The definition of asthma we used was essentially the same as that used by the Global Initiative for Asthma.

The results are expressed as arithmetic means ( $\pm$ SD) for continuous variables. A Mann-Whitney U-

## Questionnaire on Exacerbations of Asthma

**Table 1** Questionnaire administered to asthmatic patients in this study (the original was in Japanese)

Age: ( ) years old. Gender: male / female.

Question 1.

When were you first diagnosed as having bronchial asthma? Year: ( ) Month: ( ) Day: ( )

Question 2.

Select your smoking status. (non-smoker, ex-smoker, current smoker)

Question 3.

- 1) Do you use a peak-flow meter? (yes, no)
- 2) What was the average reading on your peak-flow meter during the last 2 weeks?  
Morning: ( ) Night: ( )

Question 4. Select one answer to each of the following questions:

- 1) How often did you have asthma attacks during the last 12 months?  
(frequent attacks, seasonal attacks, few attacks)
- 2) How often did you have asthma attacks during the last 2 weeks?  
(5-7/week, 3-4/week, 1-2/week, absent)
- 3) How well-controlled was your asthma during the last 2 weeks?  
(very good, fairly good, mediocre, slightly bad, bad)
- 4) How severe were your asthma attacks during the last 2 weeks?  
(impossible to move, impossible to lie down, able to lie down, wheeze, dyspnea on exertion)
- 5) Have you ever been hospitalized due to asthma?  
(yes, no)
- 6) Have you ever been brought in by ambulance or visited an emergency room due to an attack?  
(yes, no)
- 7) Have you ever been placed on a respirator due to an asthma attack?  
(yes, no)
- 8) Have you ever been unconscious due to an asthma attack?  
(yes, no)
- 9) Have you ever had an attack induced by anti-inflammatory drugs including painkillers, antipyretics, or cold medicine?  
(yes, no)
- 10) Has your asthma ever been made worse under the following conditions?  
(allergen exposure, air pollutant [outside, inside], respiratory infection, exercise, smoking, weather, food and food additives, drugs, emotional stress, stimulants [smoke, bad smell, steam etc], sulfur dioxide, menstruation, pregnancy, obesity, alcohol, fatigue, other [ ])

Question 5.

Did you have asthma in childhood? (yes, no, I forget)

If yes, how did your childhood asthma change with time? (cured completely, resolved to some extent, continues)

Question 6.

Describe your symptoms during the last 2 weeks:

- 1) In the morning  
(cough, sputum, chest tightness, wheeze, dyspnea, no symptoms)
- 2) At night  
(cough, sputa, chest tightness, wheeze, dyspnea, no symptoms)
- 3) Sleep disturbance  
(sometimes cannot fall asleep due to dyspnea, cannot sleep well due to dyspnea, waking up in the night due to chest tightness, none)

Question 7.

Do you feel satisfied with your daily life?

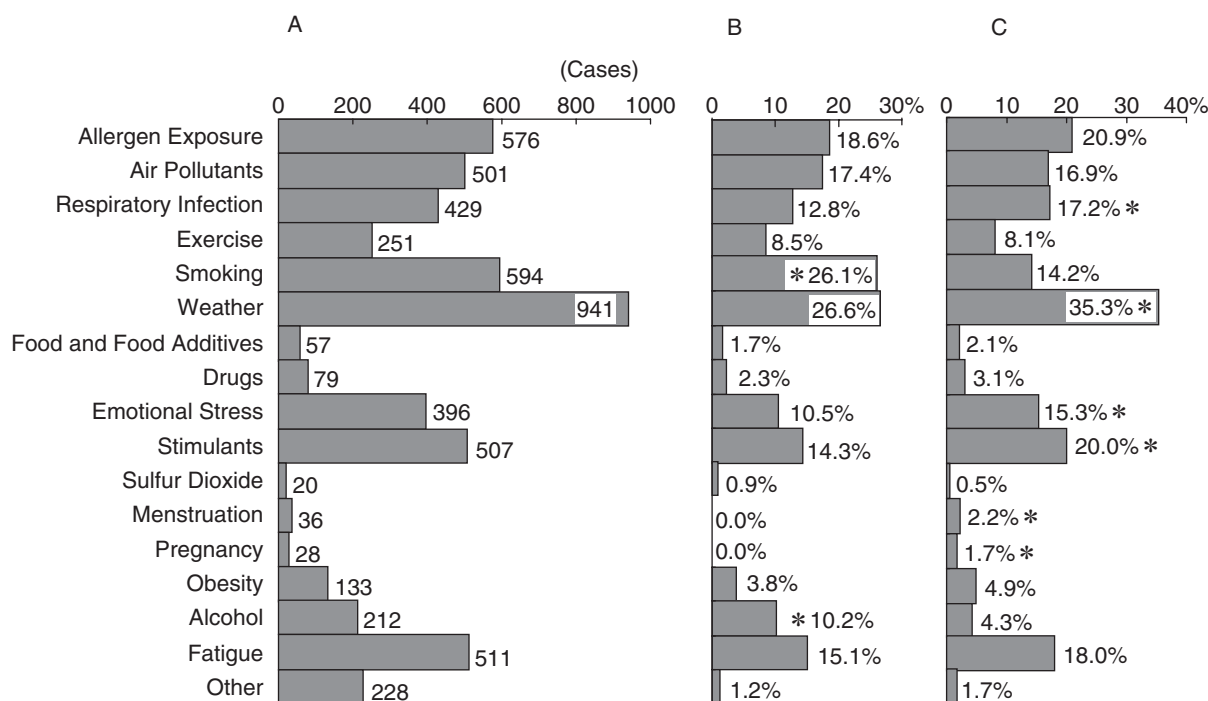
(very satisfied, fairly satisfied, mediocre, slightly dissatisfied, dissatisfied)

test was used to test the equality of distributions of the continuous variables. The differences between dichotomous variables were analyzed by a chi-square test. Multiple regression analysis was used to identify the variables that influenced exacerbating factors. All

statistical analyses were performed with Statview statistical software (PowerPC version 5.0; SAS Institute Inc., Cary, NC, USA). For all statistical analyses, a *P* value < 0.01 was considered to be significant.

**Table 2** Profile of the sample and main results of the questionnaire in this study

Age	57.5+/-17.8 (years old)
Male/Female	1308/1686 (persons)
Disease duration	13.5+/-13.3 (years)
Smoking status (never smoker/ex-smoker/current smoker)	48.8/33.3/13.8 (%)
Disease type (atopic/non-atopic)	66.2/33.8 (%)
Disease severity (step 1/2/3/4)	32.0/32.2/30.0/5.8 (%)
Presence of asthma in childhood	21.1 (%)
Visiting emergency room due to asthma attack	32.6 (%)
Admission due to asthma attack	36.7 (%)
Aspirin tolerant asthma	6.5 (%)
Peak-flow meter usage	28.5 (%)
Oral corticosteroids usage	7.8 (%)
Attack frequency during the last 12 months (frequent/seasonal/few)	12.0/35.2/52.8 (%)
Attack frequency during the last 2 weeks (always/often/sometimes/none)	3.7/5.7/15.3/74.3 (%)
Asthma status during the last 2 weeks (very good/good/mediocre/slightly bad/bad)	18.1/34.6/28.7/15.1/3.5 (%)
Presence of symptoms in morning	45.4 (%)
Presence of symptoms at night	31.5 (%)
Presence of sleep disturbance	14.7 (%)



**Fig. 1** Profiles of factors that exacerbate asthma in all applicants ( $n = 3085$ ) (A) and percentages of factors that exacerbate asthma in male ( $n = 1308$ ) (B) and female patients ( $n = 1686$ ) (C). A: Data are shown as the sum of multiple answers. B and C: \*  $P < 0.01$  comparing the male and female groups.

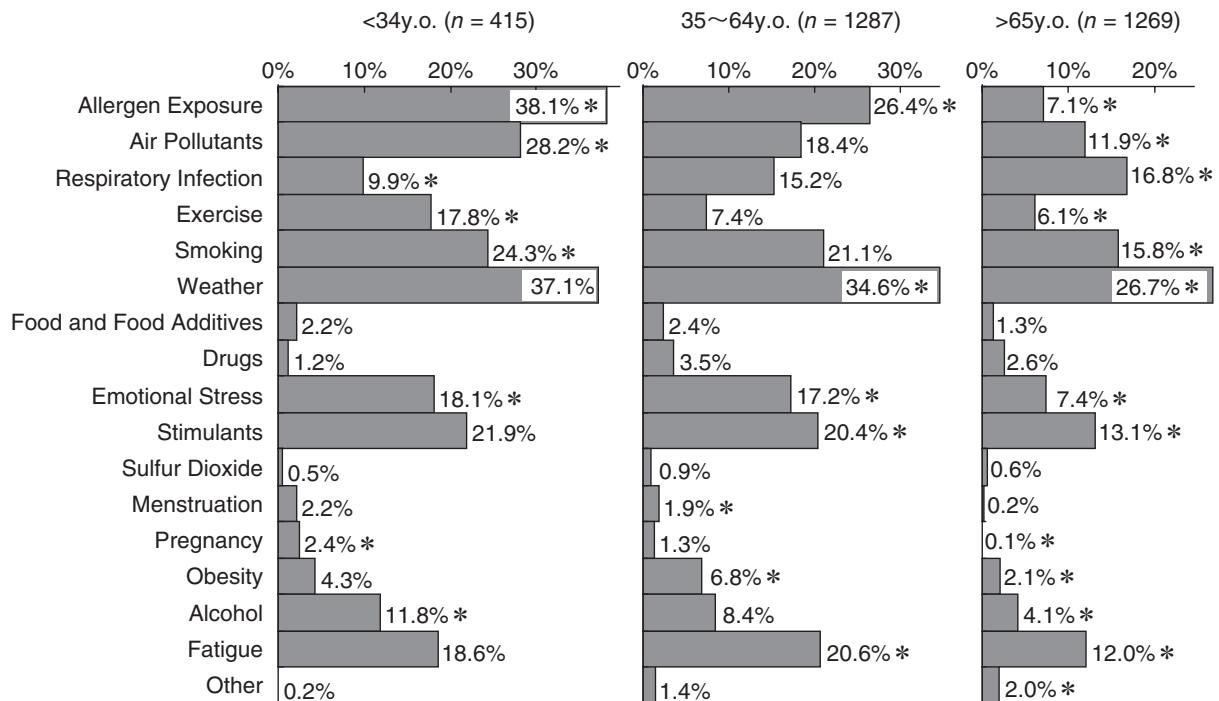
## RESULTS

The subjects of the analysis consisted of 1308 men (42.7%) and 1686 women (55.0%). The mean age was 57.5 years (17.8 SD). Among subjects, 423 subjects

(13.8%) were current smokers (See Table 2 for information about the sample group).

As shown in Figure 1, for patients the most important factor associated with exacerbation of asthma was “weather”. “Allergen exposure” and “smoking”

## Questionnaire on Exacerbations of Asthma



**Fig. 2** Percentages of factors that exacerbate asthma by age group. \*  $P < 0.01$  compared with the remaining groups.

were next most important. Environmental factors such as “air pollutants” and “stimulants” were also major factors as well as personal factors such as “emotional stress” and “fatigue”. Although “respiratory infection” is one of the most prevalent factors that result in asthma exacerbation, it was ranked seventh in the current study (Fig. 1A). In men, “smoking” and “alcohol” were more important factors than in women. In contrast, “respiratory infection”, “weather”, “emotional stress”, and “stimulants” were more common exacerbating factors in women than in men. “Menstruation” and “pregnancy” were clearly exacerbating factors in women alone (Fig. 1B, C).

Analyzing the subjects by age, the younger age group (less than 34 years of age) had a greater number of exacerbating factors, including “allergen exposure”, “air pollutants”, “exercise”, “smoking”, “emotional stress”, and “pregnancy”. “Obesity” and “fatigue” tended to be present in the middle-aged group, whereas “respiratory infection” predominated in the older age group (Fig. 2).

Concerning disease type, atopic subjects regarded “allergen exposure”, “air pollutants”, “exercise”, “emotional stress”, “stimulants”, “alcohol”, and “fatigue” as exacerbating factors, whereas “respiratory infection” played an important role in acute exacerbation in non-atopic subjects (data not shown).

On analyzing the data relevant to severity of asthma, “allergen exposure”, “drugs”, “stimulants”, and “obesity” were conspicuously present in “Step 4” patients, whereas “weather” and “emotional stress” were significantly less common in “Step 1” patients

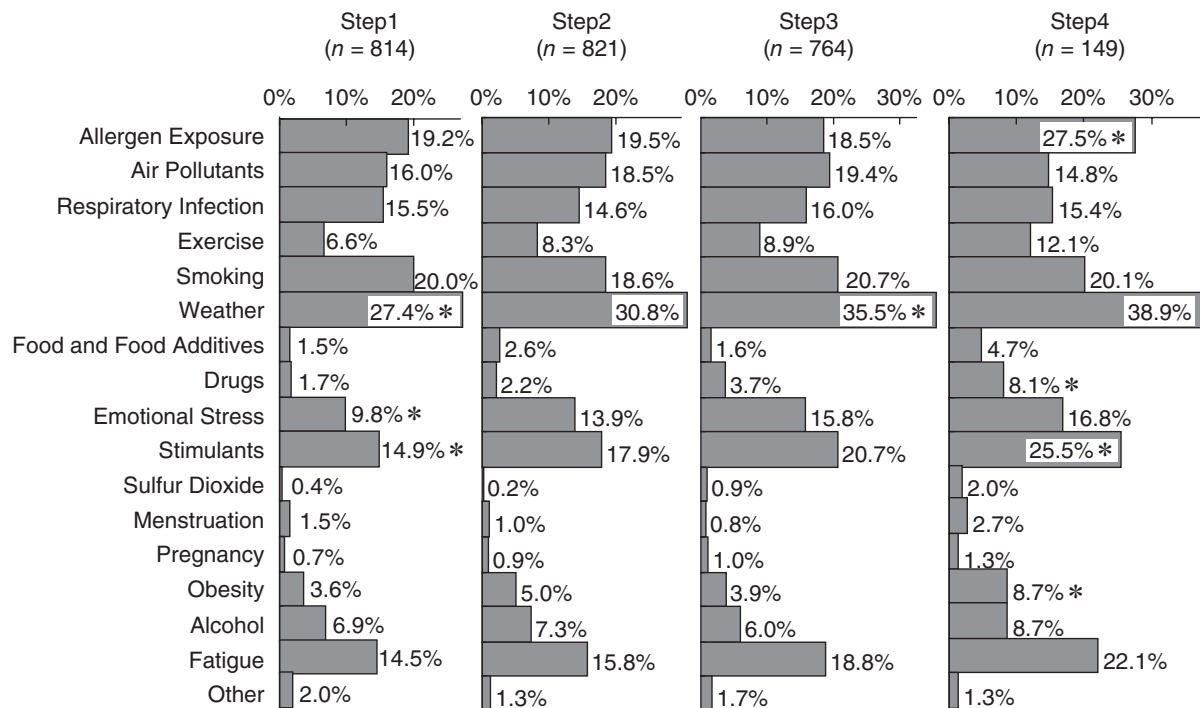
(Fig. 3). These data may reflect the fact that patients with severe disease are susceptible to both internal and external triggers, especially to drugs such as NSAIDs in AIA.

In general, respiratory infection is widely known to be critically important in acute exacerbations of asthma, especially fatal or near-fatal asthma, whereas the weather, the most prominent factor in the current study, is thought to exert a minor influence on acute exacerbations. In order to determine other associations with the exacerbating factors of “weather” and “respiratory infection”, multiple regression analysis was performed. According to multiple regression analysis, poor asthma control during the last one year was associated with “weather”, whereas a non-atopic disease type was relevant to “respiratory infection”. Current smoking was associated with both factors (Table 3A, B).

## DISCUSSION

It is well known that various factors exacerbate asthma; however, the incidence of each factor in clinical medicine is still unclear. Previous studies that described exacerbations of asthma reported relatively severe exacerbations, such as cases requiring admission or an emergency room visit, and were based on the physicians’ perspective, apart from several reports that described a small number of asthma patients.<sup>11-14</sup>

The current study is noteworthy and clinically relevant because we analyzed a questionnaire about factors that exacerbate asthma, and this analysis reflects



**Fig. 3** Percentages of factors that exacerbate asthma by asthma severity based on the GINA guidelines. \*  $P < 0.01$  compared with the remaining groups.

patients' opinions. One weakness of the questionnaire is that the items chosen by the patients as 'exacerbating factors' might be unclear. For example, we do not know whether patients can distinguish between air pollution and sulfur dioxide exposure, nor how they assess a particular factor if several factors were simultaneously present. And in this study, the frequency of each factor was not considered. Even if there was a difference of frequency in some factors, the contributions of these factors were the same in the current study. From this point of view, there are some limitations for recognition of this study. To the best of our knowledge, however, this is the first report to analyze factors associated with exacerbation of asthma in a substantial number of subjects with asthma, based on questionnaire data; the current study is therefore thought to be particularly relevant.

In this study, "weather" was unexpectedly selected by patients as the top-ranking factor. The association with weather as an exacerbating factor for asthma was reported as early as the fifth century BC by Hippocrates,<sup>15</sup> and it is well known in practice that asthma has a tendency for exacerbation when the seasons change or a cold front passes.<sup>16-18</sup> The reasons for this phenomenon are thought to be a dramatic decrease in temperature, qualitative and quantitative change in allergens and particulate matter, and emotional stress. A geographical survey of the prevalence of asthma symptoms in Northern Europe revealed that respiratory symptoms in cold weather,

such as shortness of breath or wheezing, cough induced by cold weather, were more prevalent in the Northern part.<sup>13</sup> Moreover, Girgis *et al.* attributed an increase in emergency-room visits in bad weather to the association between thunderstorms and an increase in pollen counts.<sup>6</sup> As shown in our data, weather change was significantly more frequent in younger people and those with atopy. Exposure to allergens and air pollutants is a significant factor in exacerbations in these categories, and changes in the weather have the potential to modulate exposure to allergens and air pollutants.

In contrast, in this study respiratory infection was ranked seventh as a factor that exacerbates asthma. The association between asthma exacerbations and respiratory infection has been reported both clinically and experimentally in many articles, and it has been shown that the immune response against pathogens such as bacteria or viruses, notably the release of cytokines and chemokines from host cells such as inflammatory, epithelial and smooth muscle cells,<sup>19,20</sup> may contribute to the complex pathogenesis of asthma. Respiratory viral infections are also detected in the great majority of asthma exacerbations in both children (80-90%)<sup>21</sup> and adults (75-80%).<sup>22</sup> The current study shows that patients surprisingly underestimate respiratory infection as a factor in exacerbation of asthma. There may be several reasons for this result. First is that asthma exacerbations may occur more frequently than we imagine. Most such exacerbations

**Table 3A** Multiple regression analysis of respiratory infection vs eleven independent issues

	RC	SE	SRC	t-value	P-value
Interference	0.239	0.044	0.239	5.459	<0.0001
Duration	-0.004	0.024	-0.005	-0.161	0.8718
Severity	-0.008	0.012	-0.019	-0.636	0.525
Disease type	-0.08	0.023	-0.098	-3.571	0.0004
Asthma in childhood	-0.021	0.027	-0.023	-0.768	0.4424
Smoking	-0.051	0.014	-0.097	-3.597	0.0003
OCS use	0.089	0.04	0.064	2.243	0.025
PA (1 year)	0.012	0.018	0.022	0.653	0.5139
PA (2 weeks)	0.036	0.03	0.041	1.206	0.2282
Admission	-0.031	0.023	-0.04	-1.378	0.1684
AIA	0.037	0.039	0.026	0.934	0.3507
Satisfaction with daily life	0.02	0.015	0.036	1.274	0.2029

OCS, oral corticosteroid; PA (1 year), patients experiencing asthma attacks during the year prior to answering the questionnaire; PA (2 weeks), Patients experiencing asthma attacks during the 2 weeks prior to answering the questionnaire; AIA, aspirin intolerant asthma; RC, regression coefficient; SE, standard error; SRC, standardized regression coefficient.

**Table 3B** Multiple regression analysis of weather change vs eleven independent issues

	RC	SE	SRC	t-value	P-value
Interference	0.231	0.055	0.231	4.239	<0.0001
Duration	0.075	0.029	0.076	2.57	0.0103
Severity	0.008	0.015	0.016	0.562	0.5741
Disease type	0.013	0.028	0.012	0.453	0.651
Asthma in childhood	0.042	0.033	0.037	1.256	0.2092
Smoking	-0.055	0.018	-0.083	-3.104	0.002
OCS use	0.029	0.05	0.017	0.588	0.5568
PA (1 year)	0.097	0.022	0.143	4.351	<0.0001
PA (2 weeks)	0.072	0.037	0.066	1.948	0.0516
Admission	0.09	0.028	0.01	0.338	0.7356
AIA	0.01	0.049	0.005	0.196	0.8448
Satisfaction with daily life	0.006	0.019	0.009	0.324	0.7459

are minor, causing a small decrease in PEFV or a tiny change in symptoms that might be attributed to a change in the weather. Second is the possibility of co-existence of several factors. Although respiratory infections might occur together with a change in the weather, fatigue, or emotional stress, patients might tend to underestimate respiratory infection as an exacerbating factor because these other factors might strike them as being more substantial. In regard to the association with weather, change in the weather is generally known to be accompanied with prevalence of upper respiratory infection. It also means that respiratory infection is important as a simultaneous factor with change in the weather.

In the current study, we attempted multiple regression analysis for 11 dependent issues, against both weather and respiratory infection. Both factors had an association with current smoking. Previously Venarske *et al.* reported that patients with asthma exacerbations necessitating hospitalization, who had rhinovirus present in their nasal secretions on reverse

transcription polymerase chain reaction (RT-PCR), were significantly more likely to be smokers and not to be using inhaled corticosteroids.<sup>23</sup> There are no reports which describe any relationship between smoking and the weather; however, a current smoker might have airways that are more susceptible and sensitive to changes in the weather or barometric pressure than those of a non- or ex-smoker.

In summary, we conducted an analysis of factors that exacerbate asthma using a questionnaire completed by approximately 3000 asthma patients over a period of 2 months, from September to October 2006. According to these data, the most prominent factor was “weather”, whereas “respiratory infection”, thought to be the most critical factor in exacerbations of asthma, was ranked seventh. As exacerbating factors, “weather” and “allergen exposure” were more common in younger individuals and in association with an atopic disease type, whereas “respiratory infection” was more common in older persons and associated with a non-atopic disease type. Moreover

multiple regression analysis of associations with “weather” and “respiratory infection”, demonstrated the important association between these factors and worsening asthma control. Further studies are necessary to clarify the association between exacerbation of asthma and particular factors, as such investigation may have a profound impact on the management of asthma.

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