

Progression of Irreversible Airflow Limitation in Asthma: Correlation with Severe Exacerbations

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What is already known about this topic? Severe exacerbations of asthma have been proposed to induce airway structural changes leading to an accelerated decline in lung function. A reduced bronchodilator response has been used as a surrogate marker for airway remodeling in asthma.

What does this article add to our knowledge? The occurrence of severe asthma exacerbations is correlated with the progression of airflow limitation and reduction in airway reversibility that occurred over time.

How does this study impact current management guidelines? This study suggests that the prevention of asthma exacerbations could have a pivotal role in the attenuation of the long-term adverse consequences of structural and functional changes in the airways.

BACKGROUND: Severe exacerbations of asthma are periods of excess functional and pathological changes in the airways that have been proposed to induce airway remodeling.

OBJECTIVE: The objective of this study was to explore whether severe exacerbations are correlated with the decline in post-bronchodilator forced expiratory volume in 1 second (FEV₁) and loss of bronchodilator reversibility (BDR).

METHODS: We examined the changes in FEV₁ and BDR in 140 nonsmoking patients with well-controlled asthma at baseline and correlated these changes with the frequency of severe asthma exacerbations.

RESULTS: A 3-year follow-up assessment was completed in 128 patients. A total of 28 (21.9%) patients experienced at least 1 severe exacerbation with a mean rate of 0.16 year⁻¹. The exacerbation rate was significantly correlated with an annual rate of decline in FEV₁ ($\rho = 0.49$, $P < .0001$). Both patients with 1 exacerbation and those with 2 or more exacerbations had greater

declines in FEV₁ than patients with no exacerbations (no exacerbation, 13.6 mL/year; 1 exacerbation, 41.3 mL/year; 2 or more exacerbations, 58.3 mL/year; $P < .01$ and $P < .0001$, respectively). The changes in BDR from baseline to the end of the study in patients who did or did not experience an exacerbation were -1.2% and 0.1% , respectively ($P < .0005$). The changes in BDR were significantly correlated with the annual rates of change in FEV₁ ($r = 0.40$, $P < .0001$).

CONCLUSION: The occurrence of severe exacerbations of asthma is correlated with the progression of irreversible airflow limitation over time. This suggests that asthma exacerbations could have the long-term adverse consequences of structural and functional changes in the airways. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:759-64)

Key words: Airway inflammation; Airway remodeling; Airway reversibility; Bronchodilator; Lung function

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A subset of patients with asthma is known to have rapid loss of lung function despite steroid therapy.¹⁻⁴ There is a great need to define targets for attenuation of the progression of airway obstruction. Persistent airflow limitation is believed to be a consequence of structural and functional changes in the airways, possibly due to abnormal injury and repair responses of the airway tissues.^{5,6} Severe exacerbations of asthma are periods of excess pathological and functional changes in the airways that have been proposed to induce airway remodeling.^{7,8} Also, excessive bronchoconstriction often occurs during the exacerbations, and this mechanical stress may have the potential to induce structural changes in the airways.⁹

Structural and functional changes seen in asthmatic patients can include thickening of the basement membrane of the airway wall, formation of an elastic fiber network, angiogenesis, an

Abbreviations used

ACT- Asthma Control Test
 BDR- Bronchodilator reversibility
 FeNO- Exhaled nitric oxide fraction
 FEV₁- Forced expiratory volume in 1 second
 FVC- Forced vital capacity
 GINA- Global Initiative for Asthma
 ICS- Inhaled corticosteroids

increase in airway smooth muscle (ASM) mass, and ASM dysfunction.¹ A reduced bronchodilator response (BDR) has been used as a surrogate marker for airway remodeling in asthma.^{2,10-12} However, no prospective study has examined whether severe exacerbations are correlated with the decline in post-bronchodilator forced expiratory volume in 1 second (FEV₁) and reduction in airway reversibility in asthma.

The FLOAT (Factors affecting the Long-term Asthma Therapy) study is a 3-year, prospective, cohort investigation of patients with well-controlled asthma, which was undertaken to examine the factors associated with changes in asthma control and lung function. Asthma control, severe exacerbations, pre- and post-bronchodilator forced vital capacity (FVC), FEV₁, and exhaled nitric oxide fraction (FeNO) were surveyed during the study. The main results of the FLOAT trial have been reported previously.¹³ The rate of change in FEV₁ among patients with controlled asthma was highly variable and the rapid decline in FEV₁ was associated with a loss of asthma control. We also found that the rapid decliners were more likely to be older, to have higher levels of FeNO, and to have had severe exacerbations.¹³ The FLOAT trial also provided a unique opportunity to examine the associations between the frequency of severe asthma exacerbations and the decline in post-bronchodilator FEV₁ and loss of airway reversibility in a longitudinal, prospective study.

METHODS**Study patients**

The characteristics of the present cohort have been published previously.¹⁴ A total of 250 patients with asthma following inhaled corticosteroids (ICS) therapy for more than 4 years were recruited from the Wakayama Medical University Hospital. All patients had a history of episodic dyspnea, wheezing, and documented significant airway reversibility and/or airway hyperresponsiveness. Current smokers and patients with >10-pack-year smoking history were not included in this analysis. Also, patients with poor adherence to asthma treatment (defined as <80% adherence calculated by dividing the number of days supplied for a medication by the number of days between the visits) or with other pulmonary diseases such as chronic obstructive pulmonary disease were excluded.¹⁴ In this prospective study, 140 patients with well-controlled asthma were selected based on the Global Initiative for Asthma (GINA) guidelines (twice or less/week daytime symptoms, no nocturnal symptoms, no limitation of daily activities, twice or less/week need for reliever, normal lung function [$\geq 70\%$ FEV₁/FVC ratio and $\geq 80\%$ FEV₁ % of predicted], no exacerbation in the previous 1 year).¹ A total of 78 patients with partly controlled asthma (1-2 of these features) and 26 patients with uncontrolled asthma (≥ 3 of these features) were not included. Also, 6 patients under the age of 25 years at recruitment were excluded because lung function normally increases to a maximal value in early adulthood and then declines.¹⁵ The flow diagram of the present study

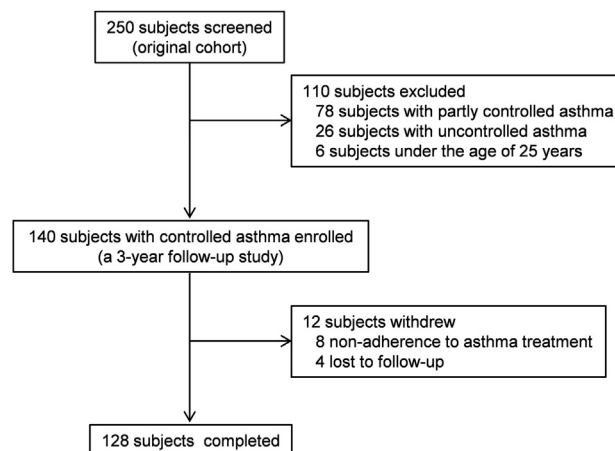


FIGURE 1. Disposition of the study patient population.

is shown in Figure 1. Informed written consent was obtained from each participant.

Study design

The study subjects were followed with Asthma Control Test (ACT), spirometry, and FeNO every 3 months over a 3-year period. Medical records including medication use and adherence to asthma treatment were also obtained. Blood eosinophil numbers and serum specific immunoglobulin E (IgE) for common inhaled allergens (house dust mite, cedar, ragweed, cocksfoot, dog, and cat) were examined. Positive specific IgE to at least 1 allergen was assumed to confirm the presence of atopy. ICS doses and use of other controllers were not fixed during the follow-up period because this was a purely observational study. The study was approved by the ethics committee of Wakayama Medical University (IRB #526) and registered with the University Hospital Medical Information Network (UMIN 000012105).

Study assessments

The FVC and FEV₁ values were measured using a dry rolling seal spirometer. The use of asthma controllers within 24 hours before an examination was prohibited for all study visits. Reversibility of FEV₁ was measured after administration of 400 μ g of salbutamol. The post-bronchodilator FEV₁ was selected to reflect loss of lung function as in other studies following lung function in patients with asthma over time.^{3,8} The annual changes in FEV₁ and BDR were estimated by fitting a least-squares regression line. In total, 3288 FEV₁ measurements were analyzed excluding lung function data during periods of worsening asthma (4 weeks before and 4 weeks after the start of a severe exacerbation). On the basis of the magnitude of change in FEV₁ over a 3-year period, we labeled those of less than the 25th percentile as rapid decliners, and greater than the 25th percentile as nonrapid decliners. All rapid decliners had an estimated rate of decline in FEV₁ of more than 40 mL/year. The FeNO was measured by an online NO analyzer (NIOX MINO; Aerocrine, Solna, Sweden) as previously described.¹⁶ The ACT is a questionnaire that assesses the asthma condition. A validated Japanese translation has been used in some earlier studies in Japan.^{13,14}

Severe asthma exacerbations

A recent American Thoracic Society/European Respiratory Society task force report was used to define exacerbations as events outside the patient's usual range of day-to-day asthma variation, requiring a

TABLE I. Baseline characteristics of patients subdivided by the presence or absence of severe exacerbations

Characteristics	No exacerbation (n = 100)	Exacerbations (n = 28)	P value
Age (y)	44.2 ± 13.8	41.8 ± 13.0	.41
Gender (female/male)	63/37	23/5	.06
Body mass index (kg/m ²)	22.1 ± 3.9	21.7 ± 4.7	.58
Smoking status (never/ex), n	74/26	20/8	.79
Atopy, n (%)	81 (81.0)	21 (75.0)	.49
Duration of asthma therapy (y)	8.6 ± 2.6	9.1 ± 3.0	.39
Dose of inhaled corticosteroids (μg/d)*	328 ± 114	343 ± 103	.54
Use of inhaled long-acting β ₂ -agonist, n (%)	45 (45.0)	16 (57.1)	.26
Use of leukotriene receptor antagonist, n (%)	15 (15.0)	2 (7.1)	.28
Use of theophylline, n (%)	7 (7.0)	2 (7.1)	.98
Asthma control test (points)	23.2 ± 1.0	23.2 ± 1.1	.91
Blood eosinophil numbers (cells/μL)	237 ± 204	249 ± 246	.79
Exhaled nitric oxide fraction (ppb)	28.5 ± 16.8	28.9 ± 19.7	.92
Pre-bronchodilator			
FVC % of predicted (%)	94.7 ± 8.5	94.2 ± 9.5	.77
FEV ₁ /FVC ratio (%)	80.4 ± 6.7	82.4 ± 8.0	.28
FEV ₁ % of predicted (%)	88.7 ± 6.7	89.0 ± 7.4	.80
Post-bronchodilator			
FVC % of predicted (%)	103.4 ± 9.7	103.6 ± 9.6	.92
FEV ₁ /FVC ratio (%)	80.8 ± 6.6	81.4 ± 8.1	.54
FEV ₁ % of predicted (%)	96.9 ± 7.8	97.1 ± 8.1	.47
FEV ₁ reversibility (%)	9.2 ± 4.4	10.1 ± 4.1	.32

FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 second. Data are presented as means ± SD unless otherwise stated. P values compared between the groups.

*Inhaled corticosteroids, expressed as fluticasone propionate equivalent.

change in controller treatment.¹⁷ On the basis of medical history, physical examination, and functional assessments such as peak expiratory flow or FEV₁ and oxygen saturation, the physician then labeled the event as an exacerbation. A severe exacerbation was defined as worsening asthma requiring at least 3 days of treatment with systemic corticosteroids, or as a hospitalization due to asthma.¹⁷ According to the GINA guidelines, 0.5 mg/kg prednisolone was given daily for 5 to 10 days if rapid-acting inhaled β₂-agonist therapy failed to achieve an immediate response, or if the episode was severe.¹

Statistical analysis

In the present study, we dichotomized the subjects into 2 groups based on the presence or absence of severe exacerbations. The clinical characteristics of these 2 groups were compared using the χ^2 test for categorical variables, and unpaired *t* tests or Mann-Whitney *U* tests as appropriate for continuous variables. The χ^2 test was used to estimate odds ratio (OR) with 95% confidence interval (CI) for a rapid decline in FEV₁ (>40 mL/year). Spearman's correlation analysis was used to assess the correlation. A *P* value of <.05 was considered statistically significant.

RESULTS

The 3-year follow-up assessment was completed in 128 patients. The 12 dropouts were from either nonadherence or

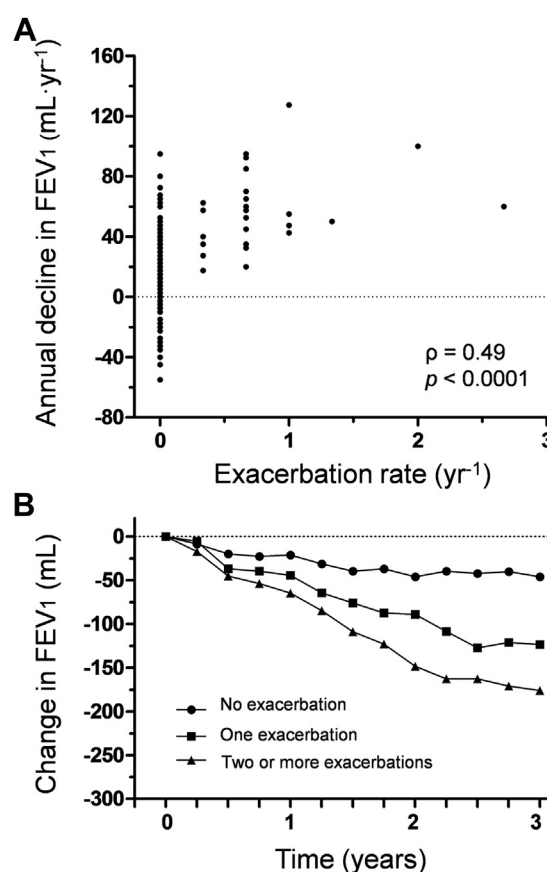


FIGURE 2. A, Relationship between the incidence rate of severe exacerbations and annual decline in forced expiratory volume in 1 second (FEV₁). B, Mean changes in post-bronchodilator FEV₁ by time according to the number of exacerbations during the follow-up period.

because lost to follow-up. The baseline characteristics according to the presence or absence of severe exacerbations are presented in Table I. A total of 28 (21.9%) patients experienced at least 1 severe exacerbation with a mean rate of 0.16 year⁻¹. Clinical characteristics at baseline were not associated with the occurrence of severe exacerbations.

Table II shows the clinical characteristics of study patients during the follow-up period and at the end of the study. Among the 28 patients who experienced exacerbations, 10 had 1 exacerbation and 18 had 2 or more exacerbations despite higher usage rate of the long-acting β₂-agonist (*P* < .01). At the end of the study, the patients with exacerbations had more impaired ACT scores (*P* < .0001) and had lower FEV₁/FVC ratio and FEV₁ values (all, *P* < .05).

As shown in Figure 2, A, the exacerbation rate was correlated significantly with the rate of decline in FEV₁ (*p* = 0.49, *P* < .0001). In patients with no exacerbations, 15% of the patients had a rate of FEV₁ decline of more than 40 mL/year; in 53%, FEV₁ declined by 0 to 40 mL/year, and 32% of the patients had a mean rate of increase in FEV₁. In contrast, in patients with exacerbations, the majority of the patients (65%) had FEV₁ declines of more than 40 mL/year; in 35%, the decline in FEV₁ ranged from 0 to 40 mL/year, and no patients had an increase in FEV₁. Patients with exacerbations had a higher risk of rapid

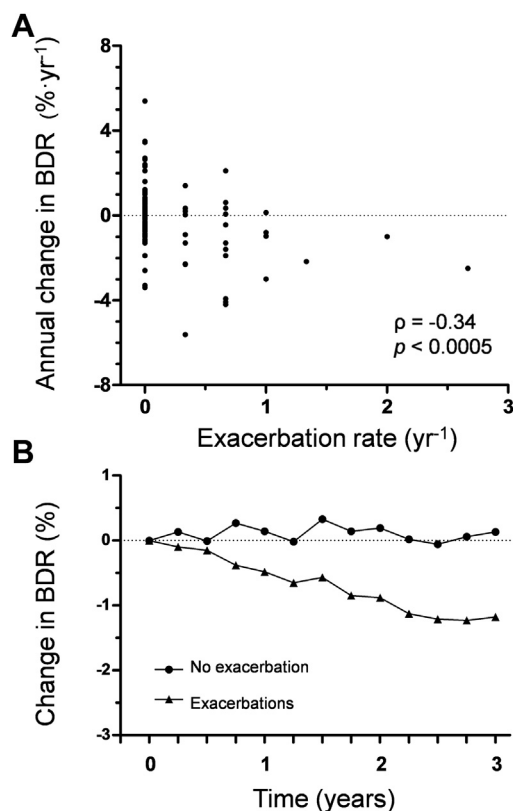


FIGURE 3. **A**, Relationship between the incidence rate of severe exacerbations and annual change in bronchodilator response (BDR). **B**, Mean changes in BDR by time according to the presence or absence of exacerbations.

decline in FEV₁ compared with those with no exacerbations (OR, 5.92; 95% CI, 2.86-12.25; $P < .0001$). As shown in Figure 2, B, both patients with 1 exacerbation and those with 2 or more exacerbations had higher rates of FEV₁ decline than patients with no exacerbations (no exacerbation, 13.6 ± 31.5 mL/year; 1 exacerbation, 41.3 ± 15.1 mL/year; 2 or more exacerbations, 58.3 ± 21.2 mL/year; $P < .01$ and $P < .0001$, respectively), and those with frequent exacerbations had more rapid FEV₁ declines than those with 1 exacerbation ($P < .05$). The changes in FEV₁ before and after the first exacerbations were analyzed in the 26 events. The 2 events were excluded because the next exacerbations were occurred within 12 weeks. The mean ($\pm$ SEM) FEV₁ values decreased significantly from $94.2 \pm 1.5\%$ at 4-12 weeks before the first exacerbation to $89.0 \pm 1.7\%$ at 4-12 weeks after the exacerbation ($P < .05$). This reduction in FEV₁ values showed a slight increase at 16-24 weeks after the exacerbation ($90.9 \pm 1.5\%$) compared with those at 4-12 weeks after the exacerbation ($P = .39$) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Also, the exacerbation rate was significantly correlated with the annual change in airway reversibility ($\rho = -0.34$, $P < .0005$) (Figure 3, A). The changes in BDR from baseline to the end of the study in patients who did or did not experience an exacerbation were $-1.2 \pm 1.8\%$ and $0.1 \pm 1.3\%$, respectively ($P < .0005$) (Figure 3, B). The changes in BDR were significantly correlated with the rates of decline in FEV₁ over a 3-year period ($r = -0.40$, $P < .0001$) (Figure 4).

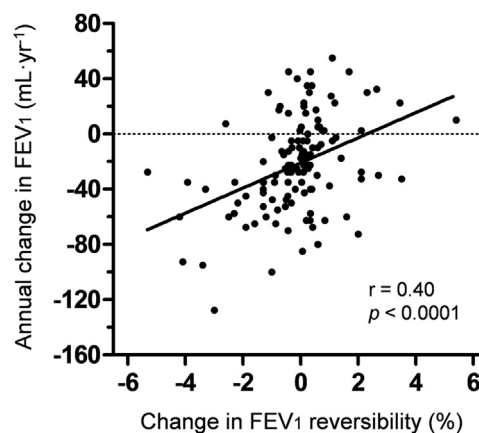


FIGURE 4. Relationship between the change in bronchodilator response and annual change in forced expiratory volume in 1 second (FEV₁). The line corresponds to the fitted regression equation. The r value was Spearman's correlation coefficient.

DISCUSSION

This stratified analysis of data from a prospective FLOAT study identified that the occurrence of severe asthma exacerbations is correlated with a more rapid decline in FEV₁ and loss of BDR, and that there is a significant correlation between the rates of decline in FEV₁ and the reductions in BDR that occurred over time. This study supports the hypothesis that asthma exacerbations, which represent intermittent periods of intense airway inflammation and excess bronchoconstriction, are associated with the progression of airway functional changes that lead to persistent airflow limitation.

The role of asthma exacerbations in the development of airflow limitation is still unclear. Rhinovirus and respiratory syncytial virus infection, which are the major causes of asthma exacerbations, produce dsRNA during viral replication. We recently showed that TLR3 activation by dsRNA causes nitrosative stress.¹⁸⁻²⁰ This leads to excessive release of matrix metalloproteases in lung fibroblasts, which may contribute to airway remodeling.^{18,19} Viruses can also directly modulate ASM function because ASM differentially expresses transcripts for most TLR isoforms.²¹ A recent *in vivo* study showed that epithelial infection with rhinovirus modulated β_2 -adrenoceptor activity in ASM through down-regulation and desensitization of cell surface receptors.²² Also, several *in vivo* studies have shown that Th2 cytokines, including interleukin (IL)-4, IL-5, and IL-13, stimulate epithelial cells and fibroblasts to promote a profibrotic response.²³⁻²⁵ Inflammatory phenotype in asthma may have prognostic relevance. In mouse models, CD8 cells appear to be essential for the influx of eosinophils into the lung during viral infections.²⁶ It has been shown that the decline in FEV₁ can be predicted by the bronchial CD8⁺ cell infiltrate.²⁷ Asthma exacerbations are also characterized by the excessive narrowing of the airway caliber. *In vitro* studies have demonstrated that mechanical stress on the airway epithelium results in structural changes that mimic those related to remodeling *in vivo*.^{28,29} Moreover, a recent human study reported that repeated bronchoconstriction without additional inflammation induces subepithelial collagen-band thickness.⁹

The causality between the occurrence of asthma exacerbations and loss of lung function remains uncertain. Alternatively, it may

TABLE II. Clinical characteristics of patients during the follow-up period and at the end of the study

Characteristics	No exacerbation (n = 100)	Exacerbations (n = 28)	P value
Follow-up period			
Use of inhaled corticosteroids (%) [*]	100 (100.0)	28 (100.0)	1.00
Dose of inhaled corticosteroids (μg/d) ^{†,‡}	330 ± 113	371 ± 98	.08
Use of inhaled long-acting β ₂ -agonist, n (%) [*]	41 (41.0)	20 (71.4)	<.01
Use of leukotriene receptor antagonist, n (%) [*]	14 (14.0)	2 (7.1)	.33
Use of theophylline, n (%) [*]	7 (7.0)	2 (7.1)	.98
No. of patients with 1 exacerbation, n (%)	—	10 (35.7)	—
No. of patients with 2 or more exacerbations, n (%)	—	18 (64.3)	—
At the end of the study			
Asthma control test (points)	23.3 ± 1.7	21.8 ± 1.7	<.0001
Exhaled nitric oxide fraction (ppb)	26.9 ± 16.5	29.9 ± 27.0	.25
Pre-bronchodilator			
FVC % of predicted (%)	92.8 ± 9.9	91.0 ± 9.5	.39
FEV ₁ /FVC ratio (%)	80.4 ± 7.2	78.6 ± 9.1	.27
FEV ₁ % of predicted (%)	86.8 ± 8.3	81.8 ± 7.9	<.01
Post-bronchodilator			
FVC % of predicted (%)	101.9 ± 10.9	98.2 ± 10.3	.11
FEV ₁ /FVC ratio (%)	81.7 ± 7.3	78.1 ± 9.0	<.05
FEV ₁ % of predicted (%)	95.4 ± 9.2	90.4 ± 9.3	<.05
FEV ₁ reversibility (%)	9.3 ± 4.2	8.9 ± 3.6	.66
Annual rates of decline in FEV ₁ (mL/y) [†]	13.6 ± 31.5	53.2 ± 23.5	<.0001
Annual rates of change in FEV ₁ reversibility (%/y) [†]	0.04 ± 0.42	−0.39 ± 0.59	<.0005

FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 second.

Data are presented as means ± SD unless otherwise stated. P values compared between the groups.

^{*}Usage rate of medications during the follow-up period.[†]Mean values during the follow-up period.[‡]Inhaled corticosteroids, expressed as fluticasone propionate equivalent.

be the severity of asthma and/or other patient factors such as asthma treatment and smoking history that are the key determinants of lung function decline and a greater prevalence of persistent airflow limitation.^{2-4,30} A retrospective analysis of data from patients with severe asthma who had been followed at regular intervals without ICS therapy found that frequent severe exacerbations are associated with a more rapid decline in FEV₁ and with a more severe airflow limitation.⁷ A *post hoc* analysis of data from a 3-year, double-blind, placebo-controlled trial reported that asthma exacerbations may contribute to the accelerated decline in lung function and that treatment with ICS is associated with an attenuation of the decline in FEV₁.⁸ In contrast to the previous studies, we recruited the patients with well-controlled asthma, and all patients were treated as clinically appropriate, rather than with treatment and placebo arms to the study. In the present study, patients with exacerbations had a higher risk of decline in FEV₁ of more than 40 mL/year compared with those with no exacerbations. Moreover, we first reported that the occurrence of severe exacerbations was correlated with the progression of irreversible airflow limitation that occurred over time. These findings suggest that severe exacerbations could have the longer term adverse consequences of structural and functional changes in the airways. Patients who experienced exacerbations had similar baseline characteristics to those without any exacerbations. However, it is possible that the individuals in the exacerbation group have a more vulnerable phenotype of asthma than the nonexacerbation group that was not identifiable based on baseline demographic or clinical characteristics (Table I). To date, there are no prospective studies that

demonstrate that the lack of BDR is evidence of airway remodeling. However, a significant positive relationship was observed between BDR and volume fraction of ASM in endobronchial biopsies from children with asthma.¹² Furthermore, the BDR is impaired in steroid-resistant asthma and is associated with a shift in matrix metalloproteinase 9/tissue inhibitor of metalloproteinases 1 ratio.¹⁰

This study had several limitations. First, no biopsy specimens were obtained to examine whether the changes in BDR in our study is correlated with structural changes in the airways. Next, it is possible that treatment could have affected the changes in lung function. In particular, the individuals in the exacerbation group were statistically more likely to have received inhaled long-acting β₂-agonist (Table II). Although this is likely in response to poor control or exacerbation, the difference in inhaled long-acting β₂-agonist between the 2 groups could be confounding. Also, the other major difference between comparison groups is that the definition of severe exacerbation was the receipt of oral corticosteroids. Although of uncertain biological plausibility, we cannot exclude that the use of oral corticosteroids contributed to the decline in lung function. Third, we excluded assessments of FEV₁ made around (±4 weeks) the start of a severe exacerbation, but it is likely that patients with exacerbations had clinical visits close enough to their exacerbations to influence the lung function measurements. In a stability analysis, we defined an alternative, wider censoring interval around the start of an exacerbation (−4 to +12 weeks). The annual rate of decline in FEV₁ was 13.8 ± 30.9 mL/year in patients with no exacerbation and 51.8 ± 24.2 mL/year in patients with exacerbations, results

almost identical to those from our main analysis (Table II). Moreover, we assessed the effects of only severe exacerbations on changes in lung function. This study might have caused an underestimation of the true overall effects.

In conclusion, the present study provided evidence that severe asthma exacerbations have a potential role in the progression of irreversible airflow limitation over time. Although there are no prospective studies that show that the lack of BDR is evidence of remodeling, we suggest that the prevention of asthma exacerbations could have a pivotal role in the attenuation of the long-term adverse consequences of structural and functional changes in the airways.

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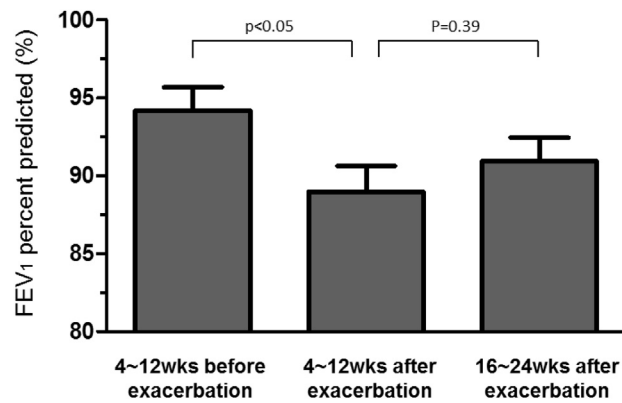


FIGURE E1. The changes in FEV₁ % of predicted before and after the first severe exacerbations of asthma. Data are presented as means ± SEM.

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