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Classification and implementation of asthma phenotypes in elderly patients

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ABSTRACT

Background: No attempt has yet been made to classify asthma phenotypes in the elderly population. It is essential to clearly identify clinical phenotypes to achieve optimal treatment of elderly patients with asthma. **Objectives:** To classify elderly patients with asthma by cluster analysis and developed a way to use the resulting cluster in practice.

Methods: We applied k-means cluster to 872 elderly patients with asthma (aged ≥ 65 years) in a prospective, observational, and multicentered cohort. Acute asthma exacerbation data collected during the prospective follow-up of 2 years was used to evaluate clinical trajectories of these clusters. Subsequently, a decision-tree algorithm was developed to facilitate implementation of these classifications.

Results: Four clusters of elderly patients with asthma were identified: (1) long symptom duration and marked airway obstruction, (2) female dominance and normal lung function, (3) smoking male dominance and reduced lung function, and (4) high body mass index and borderline lung function. Cluster grouping was strongly predictive of time to first acute asthma exacerbation (log-rank $P = .01$). The developed decision-tree algorithm included 2 variables (percentage of predicted forced expiratory volume in 1 second and smoking pack-years), and its efficiency in proper classification was confirmed in the secondary cohort of elderly patients with asthma.

Conclusions: We defined 4 elderly asthma phenotypic clusters with distinct probabilities of future acute exacerbation of asthma. Our simplified decision-tree algorithm can be easily administered in practice to better understand elderly asthma and to identify an exacerbation-prone subgroup of elderly patients with asthma.

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Introduction

The population of individuals aged 65 years or older is increasing faster than the total population in nearly all areas of the world.¹ Accordingly, asthma in elderly people is not a rare disorder.² Although asthma mortality and hospitalization rates have decreased in the past decade,³ mortality and hospitalization rates

remain high within this particular population.^{4,5} However, a comprehensive study is lacking for a better management of elderly patients with asthma.

It is widely believed that asthma is a heterogeneous airway disease with various clinical phenotypes.⁶ Such heterogeneity poses significant clinical challenges, particularly with regard to long-term prognosis and acute exacerbation prediction. To overcome this problem, many investigators have identified asthma subtypes using computational classification tools, such as cluster analysis, with the hope of finding prognostic factors or developing customized treatments specific to subtypes.^{7–9} However, these studies did not have prospective follow-up evaluation and, thus, failed to reveal the utility of their classification results in clinical practice.

We established a prospective, observational cohort of Korean elderly people with asthma in 2009.¹⁰ In the current study, we identified meaningful clusters of elderly patients with asthma with distinct clinical trajectories in terms of acute exacerbations during the 2 years of follow-up. In addition, we developed a decision-tree algorithm to facilitate implementation of our classifications and tested its utility in an independent cohort.

Methods

Establishment and Design of the Cohort of Elderly Patients with Asthma

Our primary cohort is a prospective, observational, and multi-centered cohort. Patients 65 years or older with asthma had been recruited from 9 centers in Korea: Seoul National University Hospital, Bundang Seoul National University Hospital, Asan Medical Center, Samsung Medical Center, Chungang University Hospital, Hanyang University Hospital, Dankook University Hospital, Busan University Hospital, and Chosun University Hospital. Written informed consent was obtained from each study participant, and the protocol of this cohort was approved by the institutional review boards of the respective centers.

A patient was considered to have asthma if the medical record review documented the presence of a reversible airway obstruction with a positive bronchodilator response or a 12% or more improvement in forced expiratory volume in 1 second (FEV₁) after anti-asthmatic treatments. Patients with proven diagnosis of mental and behavioral disorders, including dementia and depression (*International Statistical Classification of Diseases, 10th Revision* [ICD-10] codes F00–F99), cerebrovascular diseases (ICD-10 codes I60–I69), heart failure (ICD-10 code I50), pulmonary tuberculosis (ICD-10 code A15), and bronchiectasis (ICD-10 code J47) that might influence study outcomes were excluded. Asthmatic patients regularly taking medications who had a controlled status assessed by the Global Initiative for Asthma (GINA) guideline were enrolled.¹¹ We defined asthma exacerbations according to the official American Thoracic Society/European Respiratory Society Statement (severe asthma exacerbation).¹² The definition of asthma exacerbation included at least one of the following: (1) use of systemic corticosteroids (tablets, suspension, or injection) or an increase from a stable maintenance dose for at least 3 days and/or (2) a hospitalization or emergency department visit because of asthma that required systemic corticosteroids. Variables measured at baseline included demographic factors, asthma symptom duration, body mass index, smoking status, atopy, presence of chronic rhinosinusitis, history of previous exacerbations, and postbronchodilator lung functions. In addition, cognitive function was assessed using the Korean version of the Mini-Mental State Examination (KMMSE), and mood status was assessed using the Korean version of the Geriatric Depression Scale Short Form (GDSSFk) because depression or cognitive dysfunction were frequently encountered in elderly patients with asthma^{13,14} and might affect medication use and therefore

exacerbations. We did not exclude individuals based on the KMMSE and GDSSFk scores but checked whether those 2 scores were significantly different among clusters we found.

To reflect the reality that more than half of asthmatic patients in Korea are current or ex-smokers¹⁵ and that asthma and chronic obstructive pulmonary disease coexist in a substantial proportion of general population,¹⁶ we did not exclude smoking elderly patients with asthma from the present analysis. After baseline evaluations, elderly patients with asthma were treated for 2 years with conventional medications according to the level of asthma control proposed by the GINA guideline.¹¹ During the follow-up period, medications were adjusted accordingly if the control status of elderly patients with asthma was changed. Patients were supposed to visit the respective health centers regularly every 3 months (SD, 30 days). At every visit, allergy specialists adjusted patients' medication based on the current asthma control status and carefully checked the occurrences of asthma exacerbations during the last 3 months.

Statistical Analysis

To identify meaningful clusters, Ward's hierarchical methods were used to estimate the number of likely clusters, and then k-means nonhierarchical cluster analysis was performed. Comparisons between clusters were performed with a 1-way analysis of variance or a χ^2 test. We next assessed the predictive relevance of the derived cluster designations by performing survival analysis (Kaplan-Meier estimates of cumulative probability and Cox proportional hazards models) of time to the first acute asthma exacerbation during 2 years. To facilitate clinical implementation of our clustering results, we tested whether a smaller subset of variables could serve to classify elderly patients with asthma into their respective clusters using recursive partitioning trees. To prune our original set of 9 cluster-building variables to the minimum informative amount, we selected the right complexity parameter value. The right complexity parameter is a threshold point at which increased cost for further splitting outweighs reduction in lack of fit. All analysis was performed with R version 2.15.3 (www.r-project.org), and $P < .05$ was considered statistically significant.

Assessing the Generalizability of the Decision-Tree Algorithm

To assess the generalizability, we applied our decision-tree algorithm to a secondary cohort, Cohort for Reality and Evolution of Adult Asthma in Korea (COREA).¹⁵ Asthmatic patients enrolled in COREA were recruited by allergists or pulmonologists from 11 referral centers in diverse areas of Korea, and those with a chronological age of 65 years or older were enrolled in the present study. The diagnosis of asthma was made according to the criteria proposed by GINA with symptoms that included episodic coughing and shortness of breath that lasted more than 3 months plus a positive bronchodilator response ($>12\%$ improvement in FEV₁ after administration of 180 μg of albuterol by a metered-dose inhaler) or a positive methacholine bronchial provocation test result (provocative concentration of methacholine causing a 20% reduction in FEV₁ ≤ 16 mg/mL),¹¹ and asthmatic patients regularly taking medications with a controlled asthma status were enrolled. At enrollment, the number of previous exacerbations was measured by the careful review of medical records during the past 12 months.

Results

A total of 872 elderly patients with asthma were successfully followed up for 2 years and included in the analysis of the primary cohort. At baseline, 1,030 elderly patients with asthma were enrolled; the dropout rate was 15.3%. The baseline characteristics were not different between the patients who dropped out and those who remained in the study (data not shown). A total of 429

Table 1
Baseline characteristics of the 2 cohorts^a

Characteristic	Primary (n = 872)	Secondary (COREA) (n = 429)
Male, %	47.2	51.3
Age, y	75.1 (5.5)	70.2 (4.2)
BMI	24.3 (3.5)	24.7 (3.2)
Asthma symptom duration, y	4.9 (6.4)	11.8 (14.9)
Atopy, ^b % of positivity	18.9	31.9
CRS, ^c % of positivity	37.4	NA
Smoking, % of current or ex-smoker	33.2	34.5
Smoking pack-year	14.4 (30.9)	13.9 (22.8)
Previous exacerbation, ^d % of positivity	12.3	27.7
Postbronchodilator % predicted FEV ₁	78.6 (23.7)	75.0 (24.9)
Postbronchodilator FEV ₁ /FVC ratio	69.6 (14.2)	66.8 (13.2)

Abbreviations: BMI, body mass index; COREA, Cohort for Reality and Evolution of Adult Asthma in Korea; CRS, chronic rhinosinusitis; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, not assessed.

^aData for continuous variables are presented as mean (SD).

^bAtopy was defined as a condition with positive skin prick test response (allergen/histamine ratio >1.0 plus a mean wheal size >3 mm) to one or more aeroallergens.

^cThe definition of CRS was a symptom-based definition made by allergy specialist.

^dHistory of a previous exacerbation (yes or no) was assessed by a careful review of medical records during the 3 months leading up to enrollment in the primary cohort and 12 months before enrollment in the secondary cohort.

elderly patients with asthma from COREA were included for the generalizability analysis. The baseline characteristics of elderly patients with asthma from both cohorts are summarized in Table 1.

Cluster Analysis

The essential features of each cluster of the 4-cluster model can be characterized as follows: (1) long symptom duration and marked airway obstruction (cluster 1), (2) female dominance and normal lung function (cluster 2), (3) smoking male dominance and reduced lung function (cluster 3), and (4) high body mass index and borderline lung function (cluster 4). All 9 cluster-building variables were significantly different across the clusters (Table 2). Statistically significant differences in the MMSE and GDSSFK scores were not observed across the cluster groups (data not shown). Kaplan-Meier analysis confirmed that cluster grouping was strongly predictive of time to first acute asthma exacerbation (Fig 1, log-rank $P = .01$). The hazard ratios for each group were as follows: 1.0 for cluster 1, 0.428 for cluster 2 (1 vs 2, $P = .002$), 0.725 for cluster 3 (1 vs 3, $P = .20$), and 0.580 for cluster 4 (1 vs 4, $P = .02$).

Decision-Tree Algorithm for Efficient Classification of Elderly Patients with Asthma

To prune our initial set of 9 cluster-building variables to the minimum informative amount, we set the complexity parameter

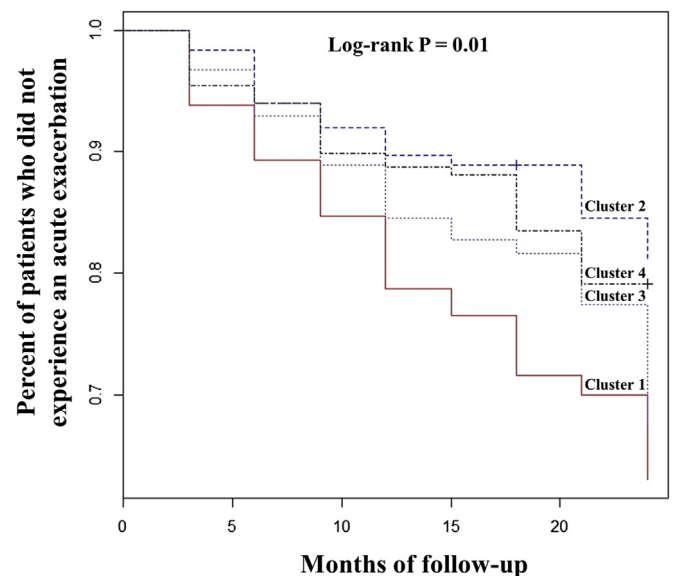


Figure 1. Kaplan-Meier plots by cluster of the cumulative probability of a first acute asthma exacerbation in the primary cohort. Cluster 1 indicates long symptom duration and marked airway obstruction; cluster 2, female dominance and normal lung function; cluster 3, smoking male dominance and reduced lung function; and cluster 4, high body mass index and borderline lung function.

value as 0.03. The developed classifier included percentage of predicted FEV₁ and smoking pack-years (Fig 2). Nodes and branches represent clinical variables used in the model and their cut points, respectively. End nodes represent the number of elderly patients with asthma belonging to each cluster. The table located at the bottom of the Figure 2 gives the sensitivity, specificity, positive predictive value, and negative predictive value of the decision-tree algorithm.

Assessing the Generalizability of the Decision-Tree Algorithm

We evaluated the generalizability of decision-tree algorithm in elderly patients with asthma enrolled from COREA cohort. By applying criteria shown in Figure 2, we identified the 4 clusters in the secondary cohort. The results are presented in Table 3. Similar to cluster 1 of the primary cohort, elderly patients with asthma belonging to cluster 1 had a significantly longer duration of symptom, severe airway obstruction, and a higher number of exacerbations during 1 year before enrollment when compared with those of other clusters. Cluster 2 was characterized by female dominance, preserved lung functions, and a significantly lower

Table 2
Clusters identified in the primary cohort^{a,b}

Characteristic	Cluster 1 (n = 145)	Cluster 2 (n = 237)	Cluster 3 (n = 182)	Cluster 4 (n = 308)	P value
Male, No. (%)	95 (65.5)	41 (17.3)	175 (96.2)	101 (32.8)	<.001
BMI	23.1 (3.6)	24.6 (3.3)	23.5 (3.2)	25.2 (3.4)	<.001
Asthma symptom duration, y	16.0 (7.4)	3.9 (5.3)	4.9 (6.3)	8.8 (5.3)	<.001
Atopy, No. (%)	28 (19.3)	37 (15.6)	48 (26.4)	52 (16.9)	.03
CRS, No. (%)	41 (28.3)	99 (41.8)	53 (29.1)	133 (43.2)	.001
Pack-years	7.7 (12.2)	1.9 (6.9)	55.7 (46.1)	2.7 (7.6)	<.001
Previous exacerbation, ^c No. (%)	24 (16.6)	18 (7.6)	27 (14.8)	38 (12.3)	.04
Postbronchodilator % predicted FEV ₁	49.0 (11.3)	106.9 (12.7)	66.8 (18.1)	77.8 (10.1)	<.001
Postbronchodilator FEV ₁ /FVC ratio	55.0 (12.1)	79.5 (10.0)	62.6 (12.6)	73.2 (10.5)	<.001

Abbreviations: BMI, body mass index; CRS, chronic rhinosinusitis; FEV₁, forced expiratory volume in 1 second; FVC, forced expiratory capacity.

^aData for continuous variables are presented as mean (SD).

^bCluster 1 indicates long symptom duration and marked airway obstruction; cluster 2, female dominance and normal lung function; cluster 3, smoking male dominance and reduced lung function; and cluster 4, high body mass index and borderline lung function.

^cHistory of a previous exacerbation (yes or no) was assessed by the careful review of medical records during the 3 months leading up to enrollment.

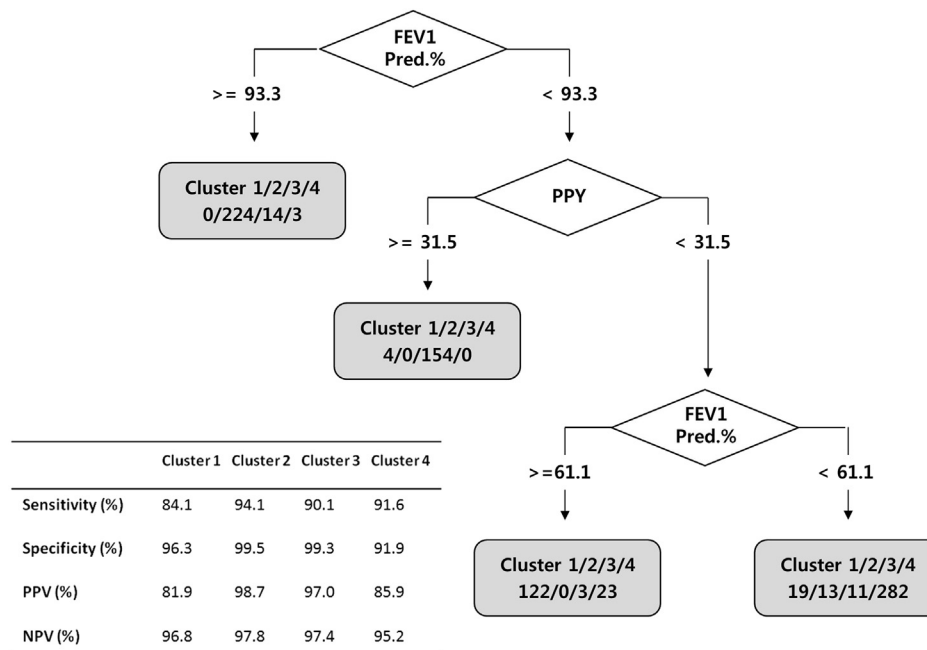


Figure 2. Decision-tree algorithm for the classification of elderly patients with asthma in the primary cohort. Cluster 1 indicates long symptom duration and marked airway obstruction; cluster 2, female dominance and normal lung function; cluster 3, smoking male dominance and reduced lung function; and cluster 4, high body mass index and borderline lung function. NPV indicates negative predictive value; PPV, positive predictive value; and PPV indicates pack-year.

number of asthma acute exacerbations. Both cluster 3 and cluster 4 had characteristics similar to those identified in the primary cohort.

Discussion

To understand the heterogeneous features of asthma, many investigators have used statistical classification methods that incorporate multiple clinical factors and identify peculiar asthma subtypes.^{7–9} However, these studies did not provide a longitudinal validation and practical utility of their classification. In the present study, we verified 4 discrete phenotype clusters of elderly asthmatic patients, which were associated with prospective risk stratification in terms of acute asthma exacerbation. In addition, we proposed a simplified decision algorithm that can be administered in real practice to better understand asthma in elderly patients and to identify an exacerbation-prone subgroup of elderly patients with asthma. We confirmed the effectiveness of our decision algorithm in a secondary independent cohort of elderly patients with asthma. To the best of our knowledge, this study is the first to classify elderly patients with asthma by cluster analysis.

We assigned the following names to these 4 clusters based on their distinguishing characteristics: long symptom duration and marked airway obstruction (cluster 1), female dominance and normal lung function (cluster 2), smoking male dominance and reduced lung function (cluster 3), and 'high body mass index and borderline lung function (cluster 4). Lung function decreases with increasing age. In addition to aging, long duration of asthma and smoking were recognized as factors that contribute to accelerated lung function decline in patients with asthma.^{17,18} Along with this, we found that long symptom duration and smoking coincided with reduced lung functions in elderly patients with asthma even after bronchodilator inhalation. Each of these features independently contributed to different clusters (cluster 1 and cluster 3), which suggests that underlying pathophysiologic mechanisms and clinical outcomes of these 2 clusters may be different, although they were similarly characterized by reduced lung function. However, in terms of the time to first acute exacerbation, we could not find any significant difference. Thus, a large-scale prospective study is needed to define the role of smoking and long symptom duration in elderly patients with asthma with reduced lung function.

Table 3
Clusters identified in the secondary cohort by applying a decision-tree algorithm^{a,b}

Characteristic	Cluster 1 (n = 94)	Cluster 2 (n = 92)	Cluster 3 (n = 81)	Cluster 4 (n = 162)	P value
Male, No. (%)	53 (56.4)	22 (23.9)	73 (90.1)	64 (39.5)	<.001
BMI	24.4 (3.3)	24.5 (2.7)	23.7 (3.2)	25.2 (3.3)	<.001
Asthma symptom duration, y	15.2 (18.5)	8.5 (11.7)	10.0 (12.0)	11.2 (15.2)	.01
Atopy, No. (%)	26 (27.7)	23 (25.0)	45 (55.6)	43 (26.5)	<.001
Pack-years	6.7 (9.5)	1.9 (5.7)	53.6 (22.3)	4.7 (9.2)	<.001
No. of previous exacerbations ^c	0.64 (1.14)	0.26 (0.72)	0.46 (0.85)	0.45 (0.93)	.04
Postbronchodilator % predicted FEV ₁	46.7 (10.3)	107.5 (11.4)	62.6 (23.3)	79.1 (8.9)	<.001
Postbronchodilator FEV ₁ /FVC ratio	56.8 (13.4)	76.9 (6.6)	60.0 (14.8)	70.6 (8.4)	<.001

Abbreviations: BMI indicates body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced expiratory capacity.

^aData for continuous variables are presented as mean (SD).

^bCluster 1 indicates long symptom duration and marked airway obstruction; cluster 2, female dominance and normal lung function; cluster 3, smoking male dominance and reduced lung function; and cluster 4, high body mass index and borderline lung function.

^cNumber of previous exacerbations was assessed by the careful review of medical records during the 12 months leading up to enrollment in the secondary cohort.

In our previous study with asthmatic adults in Korea, we found that asthma associated with smoking was a distinct asthma subtype.¹⁵ The cluster of smoking patients with asthma (cluster 3) in the current study revealed a greater reduction in lung function compared with that from our previous study. It is widely thought that both asthma and chronic obstructive pulmonary disease overlap and converge in elderly patients with asthma.¹⁹ We believe that cluster 3 is closely related with this overlap state. Cluster 3 was characterized by male predominance and propensity for acute asthma exacerbation. So far, previous studies of asthma have only analyzed nonsmokers to exclude the effect of smoking and smoking-related airway diseases. In clinical practice, however, the proportion of smoking patients with asthma is considerable.¹⁵ Likewise, elderly patients with asthma who smoke comprised as much as 20% of the entire elderly asthma population in the present study. Moreover, smoking was reported to be significantly associated with hospitalization²⁰ and mortality⁵ in elderly patients with asthma. On the basis of these factors, we propose that this distinct cluster needs to be further evaluated in other ethnic groups.

Implementation of phenotyping approaches in clinical practice is achievable by developing physician-friendly applications. For this reason, we suggest a simplified classifier with which we can reliably classify elderly patients with asthma into the 4 clusters identified in the analysis. Although only 2 clinical features are incorporated in our classifier, the sensitivity and specificity are within acceptable ranges. This finding suggests that other clinical variables used for the cluster analysis were successfully loaded to the 2 variables: postbronchodilator percentage of predicted FEV₁ and smoking pack-years. Like other clinical classifiers, such a tool would require independent validation. We have demonstrated that our classifier could identify 4 clusters in an independent cohort, which is characterized by clinical features similar to the primary clusters. We hope that our classifier help physicians identify meaningful clusters of elderly patients with asthma and individualize care of each patients according to the classification.

We could identify a more reliable model if we had included more relevant variables in our analysis. However, for simplicity and ease of application in real practice, we excluded comorbidities, adherence, cognitive dysfunction and depression from the cluster, and classifier analysis. These features are frequently encountered in elderly patients with asthma and reported to affect the clinical course of asthma in elderly patients.^{10,13,14,20} Therefore, this aspect should be remembered when interpreting the results, although we could not find any significant difference in the KMMSE and GDSSFK scores that reflected cognitive function and depression. We think that identified clusters and a simplified classifier in the present study provided a broad outline for understanding of asthma in elderly patients. For more elaborate management of asthma in elderly patients, other factors need to be considered, such as comorbid disease, cognitive dysfunction, depression, presence of caregiver, and adherence. In addition, relatively short durations of asthma in the primary and secondary cohorts need to be considered in applying our results to general management of asthma in elderly patients.

We did not incorporate any variables obtained from biologic samples of participants, and thus we were not able to propose

pathophysiologic mechanisms underlying different features among 4 clusters. A previously reported subgroup that has a differential response to asthma medications (eg, obese women with adult-onset asthma who have neutrophilic inflammation in the Severe Asthma Research Program⁷) possibly would be hidden in our cluster models. Molecular phenotyping of our clusters is now ongoing, and we will be able to provide their pathophysiologic background in the near future.

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References

- [1] United Nations. 2001. World Population Ageing: 1950–2050. <http://www.un.org/esa/population/publications/worldageing19502050>. Accessed July 14, 2014.
- [2] Urso DL. Asthma in the elderly. *Curr Gerontol Geriatr Res*. 2009;858415.
- [3] Szeffler SJ. Advancing asthma care: the glass is only half full! *J Allergy Clin Immunol*. 2011;128:485–494.
- [4] Australian Institute of Health and Welfare. Asthma in Australia 2008. <http://www.aihw.gov.au/publication-detail/?id=6442468169>. Accessed July 14, 2014.
- [5] Bellia V, Pedone C, Catalano F, et al. Asthma in the elderly: mortality rate and associated risk factors for mortality. *Chest*. 2007;132:1175–1182.
- [6] Lin TY, Poon AH, Hamid Q. Asthma phenotypes and endotypes. *Curr Opin Pulm Med*. 2013;19:18–23.
- [7] Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med*. 2010;181:315–323.
- [8] Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. 2008;178:218–224.
- [9] Amelink M, de Nijs SB, de Groot JC, et al. Three phenotypes of adult-onset asthma. *Allergy*. 2013;68:674–680.
- [10] Park HW, Kim TW, Song WJ, et al. Prediction of asthma exacerbations in elderly: results of a one-year prospective study. *J Am Geriatr Soc*. 2013;61:1631–1632.
- [11] The Global Initiative for Asthma. The guideline for asthma management and prevention 2010. <http://www.ginasthma.org/guidelines-pocket-guide-for-asthma-management.html>. Accessed July 14, 2014.
- [12] Reddel HK, Taylor DR, Bateman ED, et al. American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59–99.
- [13] Ng TP, Chiam PC, Kua EH. Mental disorders and asthma in the elderly: a population-based study. *Int J Geriatr Psychiatry*. 2007;22:668–674.
- [14] Jelicic M, Kempen GL. Cognitive function in community-dwelling elderly with chronic medical conditions. *Int J Geriatr Psychiatry*. 1997;12:1039–1041.
- [15] Kim TB, Park CS, Bae YJ, et al. Factors associated with severity and exacerbation of asthma: a baseline analysis of the cohort for reality and evolution of adult asthma in Korea (COREA). *Ann Allergy Asthma Immunol*. 2009;103:311–317.
- [16] de Marco R, Pesce G, Marcon A, et al. The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle-aged and elderly people from the general population. *PLoS One*. 2013;8:e62985.
- [17] Cassino C, Berger KI, Goldring RM, et al. Duration of asthma and physiologic outcomes in elderly nonsmokers. *Am J Respir Crit Care Med*. 2000;162:1423–1428.
- [18] Lange P, Parner J, Vestbo J, et al. A 15 year follow-up study of ventilatory function in adults with asthma. *N Engl J Med*. 1998;339:1194–1200.
- [19] Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet*. 2010;376:803–813.
- [20] Diette GB, Krishnan JA, Dominici F, et al. Asthma in older patients: factors associated with hospitalization. *Arch Intern Med*. 2002;162:1123–1132.