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Differences between asthma in young and elderly: Results from the COREA study

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KEYWORDS

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Summary

Background: There has been no large-scale and comprehensive study of the differences between asthma in elderly asthmatics (EA) and non-elderly (i.e. young) asthmatics (NEA).

Abbreviations: BMI, Body mass index; EA, Elderly asthma; FEV₁, Forced expiratory volume in 1 s; FVC, Forced vital capacity; NEA, Non-elderly asthma; PCA, Principal components analysis.

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Characteristics; Principal components analysis

Methods: We performed principal component analysis (PCA) using 2067 asthmatics (434 EA and 1633 NEA) from the Korean Cohort for Reality and Evolution of adult Asthma (COREA). EA was defined as asthmatics with the chronological age of 65 or more and eleven clinical variables measured at enrollment were used for PCA; symptom score, symptom duration, number of exacerbation during previous one year, smoking pack year, number of controller medications, body mass index, predicted % of FEV₁, predicted % FVC, post-bronchodilator FEV₁/FVC ratio, atopy index and number of eosinophils in peripheral blood.

Results: PCA of all asthmatics showed that EA and NEA were distinctly separated by the first and second principal component on the plot of individual asthmatics according to their scores. For further analysis, we divided all asthmatics into the EA and the NEA group and performed PCA again in each group. The first four principal components with eigenvalues ≥ 1.0 were identified in both groups and they explained 55.5% of the variance in the EA group and 52.4% in the NEA group respectively. Clinical variables showed distinctly different patterns of loading on the first four principal components between the EA and the NEA group.

Conclusion: EA and NEA have different compositional patterns underlying their clinical variables. These observations helped in understanding the differences between EA and NEA from the integrated view covering various clinical aspects.

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Introduction

Elderly asthma usually refers to asthma in people aged 65 years and over. Aging is accompanied with changes in respiratory physiology [1,2] and immunology [3,4]. Therefore, elderly asthmatics (EA) is thought to be distinct from non-elderly (i.e. young) asthmatics (hereafter NEA) and the differences cannot be fully explained by chronological age alone. Compared to patients with NEA, patients with EA have higher rates of airway hyperresponsiveness, more severe asthma, lower prevalence of atopy, and are more difficult to control with corticosteroids [5–9]. Although

these observations are helpful to differentiate EA from NEA, understanding the contribution of multiple clinical variables as a mixture to EA is more challenging. To achieve this purpose, it is desirable to use an indicator that can reflect EA as a complex mixture rather than the sum of individual clinical variables.

Principal component analysis (PCA) is a statistical technique that analyzes a data set in which observations are described by several inter-correlated quantitative dependent variables [10]. Its goal is to extract the important information from a data set, to represent it as a set of new orthogonal variables called principal components, and

Table 1 Baseline characteristics.

Characteristics	EA <i>n</i> = 434	NEA <i>n</i> = 1633	<i>P</i> -value
Male, yes, <i>n</i> (%)	220 (50.7)	736 (45.1)	0.052
Age, years	70.2 $\pm$ 4.2	44.2 $\pm$ 13.0	<0.001
Symptom duration, years	11.8 $\pm$ 14.9	7.8 $\pm$ 10.0	<0.001
Smoking, yes, <i>n</i> (%)	148 (34.1)	350 (21.4)	<0.001
Smoking pack year, years	13.9 $\pm$ 22.8	7.1 $\pm$ 14.0	<0.001
Previous exacerbation, ^a yes, <i>n</i> (%)	119 (27.4)	547 (33.5)	0.016
Number of exacerbation	0.6 $\pm$ 1.5	0.9 $\pm$ 2.0	<0.001
Number of controller medications	0.7 $\pm$ 0.9	0.7 $\pm$ 0.9	0.989
BMI	24.7 $\pm$ 3.2	23.7 $\pm$ 3.4	<0.001
FEV ₁ %Pred.	75.0 $\pm$ 24.9	81.6 $\pm$ 20.2	<0.001
FVC %Pred.	82.2 $\pm$ 19.9	89.6 $\pm$ 17.5	<0.001
Post-BD FEV ₁ /FVC ratio	66.8 $\pm$ 13.2	74.4 $\pm$ 11.9	<0.001
Atopy, yes, <i>n</i> (%)	137 (31.5)	992 (60.7)	<0.001
Atopy index	4.7 $\pm$ 13.8	10.7 $\pm$ 17.9	<0.001
Number of eosinophil	226.5 $\pm$ 240.1	309.4 $\pm$ 339.3	0.558
Symptom score	5.7 $\pm$ 3.0	9.5 $\pm$ 2.8	<0.001

EA, elderly asthma; NEA, non-elderly asthma; BMI, body mass index (kg/m²); FEV₁, Pred.%, % of predicted value of a forced expiratory volume in 1 s; FVC, Pred.%, % of predicted value of a forced vital capacity; Post-BD, post-bronchodilator.

Data indicate means $\pm$ SDs. A statistical significant value (*P* < 0.05) is shown in bold print.

^a During previous one year.

to display the pattern of similarity of the observations and of the variables as points in maps [11]. Using PCA, several clinical variables can be reduced to one or fewer components based on the correlations among the individual clinical variables. In addition to data reduction, PCA can identify compositional patterns that can be used to examine the similarities and differences [11].

In this study, we hypothesized that clinical variables used commonly in practice are differently reduced to underlying similar characteristics in a multidimensional space between EA and NEA. To test our hypothesis, PCA was performed using a cross sectional data set obtained from the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA) [12].

Methods

Study population

Asthmatics enrolled in the COREA were recruited by allergists or pulmonologists from 11 referral centers in diverse areas of Korea [12]. The diagnosis of asthma was made according to the criteria proposed by the Global Initiative for Asthma (GINA) with symptoms including episodic coughing and shortness of breath lasting more than 3 months, plus a positive bronchodilator response [$>12\%$ improvement in forced expiratory volume in 1 s (FEV_1) after administration of 180 μ g of albuterol by a metered-dose inhaler] or a positive methacholine bronchial provocation test [provocative concentration of methacholine causing a 20% reduction in $FEV_1 \leq 16$ mg/mL] [13]. At enrollment, asthmatics were in a stable state with regular medications. Exclusion criteria were destroyed lungs or bronchiectasis on simple chest X-ray and history of lung resection. However, the COREA did not completely exclude smoking asthmatics if their diagnosis was soundly confirmed when they were enrolled [12]. EA was defined as asthmatics with the chronological age of 65 years or more. Written informed consents were obtained from the study participants and the COREA protocol was approved by the Seoul National University Hospital Institutional Review Board.

Clinical variables

Eleven clinical variables in the COREA database were used for PCA: symptom score, symptom duration, number of exacerbation during the previous year, smoking pack year, number of controller medications, body mass index (BMI, kg/m²), predicted % of FEV_1 , predicted % forced vital capacity (FVC), post-bronchodilator FEV_1 /FVC ratio, atopy index, and number of eosinophils in peripheral blood. Symptom score [1–5 scale: most days a week (1), several days a week (2), a few days a week (3), only with chest infections (4), not at all (5)] was based on responses to four statements: "Over the last year, I have coughed"; "Over the last year, I have brought up sputum"; "Over the last year, I have had shortness of breath"; and "Over the last year, I have had attacks of wheezing". An asthma exacerbation was defined by any one of the following criteria: use of systemic corticosteroids or an increase from a stable maintenance dose for at least three days, and asthma-specific unscheduled visits and

emergency department visits or hospitalization. Number of asthma exacerbation was assessed by the careful review of medical records during 1 year prior to enrollment. Controller medications included inhaled corticosteroid with or without long-acting beta-2 agonist, leukotriene modifier, sustained release theophylline, oral corticosteroid and anti-IgE antibody as suggested by the current guideline [13]. Skin prick testing with 11 common aeroallergens (*Dermatophagoides*

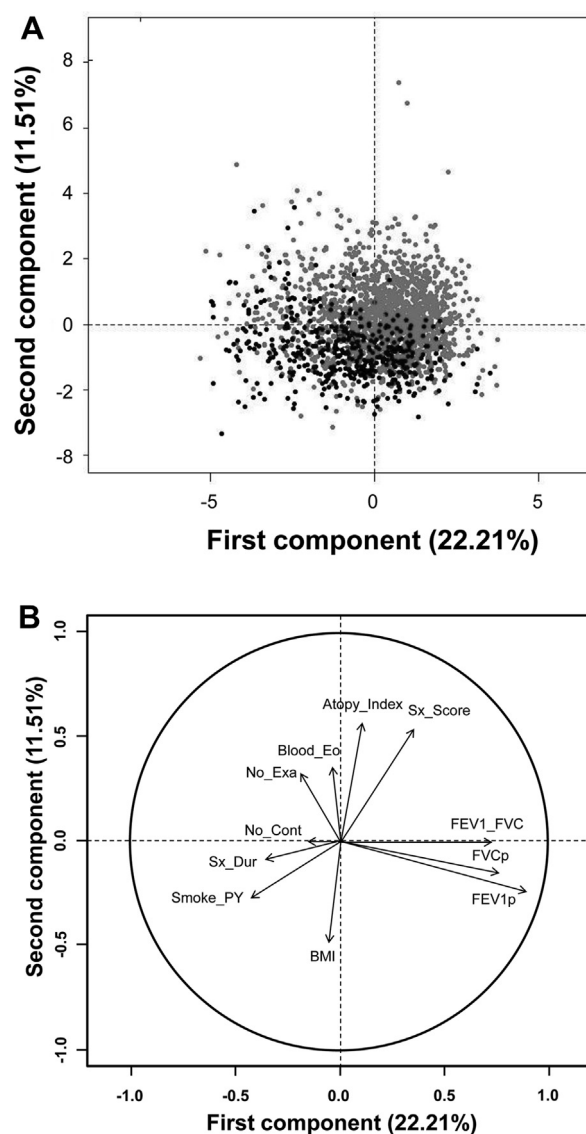


Figure 1 Results of PCA for all asthmatics. (A) A plot of individual asthmatics according to their scores of the first and second principal component. Black dots represent elderly asthma and grey dots represent non-elderly asthma. (B) A circle of correlations and loadings of clinical variables for the first and second principal component. Abbreviations are: FVCp, predicted % forced vital capacity; FEV_{1p} , predicted % of FEV_1 ; FEV_{1_FVC} , post-bronchodilator FEV_1 /FVC ratio; Sx_Score, symptom score; Atopy_Index, atopy index; Blood_Eo, number of eosinophils in peripheral blood; No_Exa, number of exacerbation; No_Cont, number of controller medications; Sx_Dur, symptom duration; Smoke_PY, smoking pack year; BMI, body mass index.

pteronysinus, *Dermatophagoides farinae*, dog fur, cat fur, *Aspergillus*, *Alternaria*, tree pollen mixture, grass pollen mixture, mugwort, ragweed and cockroach; Allergopharma, Reinbek, Germany) was performed. The atopy index was calculated by summing the wheal size of the allergens. The number of eosinophils in peripheral blood was measured using an automated blood cell analyzer. We confirmed that clinical variables of subjects did not differ significantly between hospitals which they were enrolled in.

Statistical analysis

PCA was performed using the 11 clinical variables. PCA is a type of multivariate analysis that reveals the internal structure of the data that best explains the variance in the data [11]. PCA was implemented using the FactoMineR (Factor analysis and data Mining with R, www.cran.r-project.org/web/packages/FactoMineR/index.html) package [14]. In the FactoMineR, the solution maximizing the variance of projected points is kept. The FactoMineR method does not apply any rotation to keep optimal property of the maximization of variance of the projection points, although rotational algorithms help improve the interpretability of the principal components. Loadings (i.e., standard coordinates) are not given by the FactoMineR and they were presently calculated by dividing the coordinates of the variable on a dimension by this dimension's eigenvalue's square root. Only components with an eigenvalue above 1.0 were retained in the solution. When the variables are entirely represented by only two components, the sum of the squared loadings is equal to one. In this case, the points will be positioned on a circle which is called the circle of correlations. When more than two components are required to represent the variable perfectly, the points are positioned inside the circle of correlations. The closer a point is to the circle of correlations, the better we can reconstruct this variable from the two components. Meanwhile, the closer to the center of the plot a point is, the less

important it is for the two components. All analyses were performed with R version 2.15.2 (www.r-project.org).

Results

A total of 2067 asthmatics (434 EA and 1633 NEA) were enrolled for analysis. The baseline characteristics are summarized in Table 1. PCA of all asthmatics identified the first four principal components with eigenvalues ≥ 1.0 and together they explained 53.5% of the variance. Fig. 1 showed a plot of individual asthmatics according to their scores for the first and second principal component and a circle of correlations showing loadings of clinical variables for the first and second principal components. EA and NEA were distinctly separated by the first and second principal component on the plot of individual asthmatics according to their scores. For further analysis, we divided all asthmatics into the EA and the NEA group and performed PCA using 11 clinical variables, the same as the first PCA performed in all asthmatics. In both groups, the first four principal components with eigenvalues ≥ 1.0 were identified and they explained 55.5% of the variance in the EA group and 52.4% in the NEA group. Clinical variables showed different patterns of loading on the first four principal components between the EA and the NEA group (Table 2). A factor loading of 0.4 or greater (or ≤ -0.4) within a particular principal component was used as the cut-off for practical significance, given that the sample size was over 200 [15]. A circle of correlations and plot of loadings of clinical variables for the first and the second principal component is shown in Fig. 2. Variables related with lung function (FEV₁ predicted%, FVC predicted%, and post-bronchodilator FEV₁/FVC ratio) were mainly loaded to the first principal component and closer to circle of correlation in both groups, which suggested that we could reconstruct these variables from the first principal component in the EA group as well as in the NAE group. However, BMI, atopy index, and number of exacerbations showed opposite

Table 2 Factor loadings^a and cumulative variance of the first four principal components in the elderly asthma and non-elderly asthma group.

Variables	Eldery asthma				Non-elderly asthma			
	PC1	PC2	PC3	PC4	PC1	PC2	PC3	PC4
FEV ₁ predicted %	0.570	0.077	-0.078	0.009	0.603	0.246	0.106	0.109
FVC predicted %	0.461	0.109	-0.212	0.336	0.480	0.232	0.083	0.414
Post-BD FEV ₁ /FVC ratio	0.457	0.109	-0.212	0.336	0.458	0.007	0.150	-0.315
Number of controller medications	-0.083	0.620	0.093	-0.044	-0.127	0.202	0.474	-0.451
Number of exacerbations during previous 1 year	-0.103	0.555	0.305	0.184	-0.179	-0.073	0.628	0.213
Smoking (pack year)	-0.278	0.154	-0.518	-0.071	-0.248	0.380	-0.187	0.213
Symptom duration	-0.161	0.003	0.442	0.349	-0.225	0.204	0.438	0.383
Body mass index	0.201	-0.284	0.417	-0.246	-0.062	0.480	-0.107	0.153
Symptom score	0.120	0.011	-0.004	0.651	0.127	-0.334	0.113	-0.029
Atopy index	-0.253	-0.294	0.315	0.242	0.106	-0.476	0.190	0.316
Number of eosinophil in peripheral blood	-0.112	-0.310	-0.289	0.367	-0.047	-0.288	-0.225	0.382
Percent variance explained by factor	23.8	11.8	10.5	9.4	21.3	11.1	10.5	9.5
Cumulative explained variance	23.8	35.6	46.1	55.5	21.3	32.4	42.9	52.4

PC, principal component; Post-BD, post-bronchodilator.

^a Values represent coefficients of correlation between variables and components. Practical significance is shown in bold print.

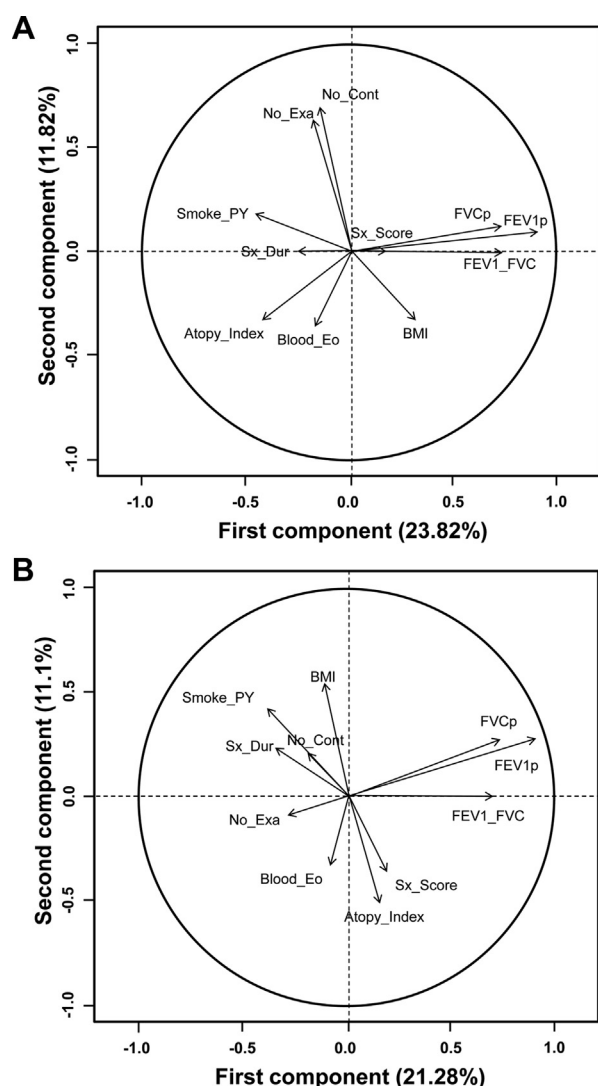


Figure 2 Circle of correlations and plot of loadings of the variables with the first and second principal component for elderly asthmatics (A) and non-elderly asthmatics (B). Abbreviations are: FVCp, predicted % forced vital capacity; FEV1p, predicted % of FEV1; FEV1_FVC, post-bronchodilator FEV1/FVC ratio; Sx_Score, symptom score; Atopy_Index, atopy index; Blood_Eo, number of eosinophils in peripheral blood; No_Exa, number of exacerbation; No_Cont, number of controller medications; Sx_Dur, symptom duration; Smoke_PY, smoking pack year; BMI, body mass index.

directions of loading to the first and the second principal component between the EA and the NEA group. Number of controller medications and number of exacerbations were closer to the center of circle in the NAE group than in the EA group, which implied that those clinical variables were less important for the first two principal components in the NAE group compared to the EA group.

Discussion

One of the goals of PCA is to analyze the structure of the observations and the variables [11]. In the present study, 11

clinical variables were reduced to four major components in all asthmatics, which explained 53.5% of the variability using PCA. Consistent with our *a priori* assumption, we found that EA and NEA were differently located in a two-dimensional space made by the first and the second principal components. Subsequent PCA performed in the EA and the NEA group separately showed that the 11 clinical variables were differently loaded to the first four principal components between two groups, which suggested that unmeasured latent variables underlying EA and NEA might distinctively differ.

EA is a heterogeneous disorder with complex pathophysiologic mechanisms [16]. Thus, comparisons between EA and NEA should be done from the integrated view covering various clinical aspects. Focusing a few clinical variables, we could easily find differences between EA and NEA, as shown in Table 1. Our findings were similar to those shown by previous reports [5–9]. However, we need to understand the contribution of multiple clinical variables as a mixture when we tried to search the difference between EA and NEA. For this reason, we used PCA, because PCA enables us to identify the compositional patterns that underlie EA and NEA and to examine differences based on those patterns. In the present study, based on the patterns of factor loadings, we could summarize the first four principal components identified in the EA group as follows: airway obstruction (the first component), asthma control (the second component), risk factors (the third component), and symptom severity (the fourth component). Likewise, airway obstruction and asthma control were identified as important components in NEA, while we could not characterize the second and the fourth principal component in the NEA group as we did in the EA group due to the heterogeneity in clinical variables with significant factor loadings. Considering clinical variables related with lung function were well constructed from the first principal component in both groups, airway obstruction might be the most important feature for the characterization of EA and NEA. This finding was anticipated and consistent with what we already knew.

However, heterogeneous patterns of loadings found in other clinical variables suggested that clinical variables other than lung function played different roles for the characterization of EA and NEA. Body mass index (BMI) can be a good example. For the first and the second principal component, BMI in the EA group showed the opposite loading patterns to the NEA group. So far, numerous reports consistently have suggested that obesity increase asthma severity [17–19]. However, only children or adult less than 60 years of age were included in those studies and thus we are not sure that same relations may be found in EA. Recently, it was reported that an association between obesity and asthma was significantly modified by age of asthma onset [20]. Moreover, the spirometric values decreased significantly in proportion to the increase of BMI in asthmatics but there was no negative correlation between BMI and FEV1 in the asthmatics over 60 years of age. [21]. Taken together, although BMI is an important variable characterizing EA and NEA (as their values of factor loadings were significant; 0.417 for EA and 0.480 for NEA), the way of its contribution to EA may differ for NEA.

Loading pattern on the first principal component of atopy index in the EA group was opposite to that of atopy index in the NEA group. Moreover, atopy index in the EA group showed no significant values of factor loadings on the four principal components. For many years, EA was characterized by non-atopic [22]. However, recent data from large populations have demonstrated that EA are also atopic [23,24]. Interestingly, it was reported that smoking attenuated the age-related decrease in IgE levels and maintained eosinophilic inflammation [25]. Likewise, atopy index and smoking pack year in the EA group showed same loading patterns on the first principal component, while loading patterns of atopy index and smoking pack year on the first and second principal components were opposite in the NEA group. Taken together, our results suggested that the role of atopy in the pathogenesis of EA should be assessed in the context of correlations with other clinical variables including smoking.

In the present study, we identified four principal components underlying EA and NEA using PCA and found that 11 clinical variables showed distinctly different patterns of loading on the first four principal components between the EA and the NEA group. Our observations helped us to understand differences between EA and NEA from the integrated view covering various clinical aspects. However, it should be kept in mind that our findings may only be applicable to populations of Asian origin. We hope that the results of the current study will be reproduced in another sample set of elderly asthmatics.

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