

Comparative Clinical, Physiological, and Inflammatory Characteristics of Elderly Subjects With or Without Asthma and Young Subjects With Asthma



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BACKGROUND: Asthma seems to present in the elderly as a specific phenotype that remains to be further described. In this prospective observational study, we aimed to assess the multi-dimensional aspects of asthma in the elderly.

METHODS: In young (18 to 35 years old) subjects with mild to moderate asthma and elderly subjects (aged ≥ 60 years) either with or without mild to moderate asthma, we compared asthma control, health care and medication use, lung function, markers of airway and systemic inflammation, and adherence to therapy.

RESULTS: Fifty subjects were recruited in each group. Elderly people with asthma showed more marked airway obstruction compared with young people with asthma and elderly people without asthma. They also had poorer asthma control, mainly associated with a lower FEV₁, compared with young people with asthma, although airway responsiveness, health care use, prescribed doses of inhaled corticosteroids, and adherence to treatment were similar in both groups. Elderly subjects had an increase in some markers of systemic inflammation and bronchial epithelial dysfunction compared with young people with asthma. Blood eosinophils were higher in both asthma groups, particularly in elderly people with asthma. Sputum neutrophils were increased in both groups of elderly subjects and sputum eosinophils were increased in elderly people with asthma compared with the other two groups.

CONCLUSIONS: Asthma in the elderly presents as a specific phenotype associated with increased airway obstruction and mixed airway inflammation in addition to signs of systemic inflammation.

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KEY WORDS: aging; airway inflammation; airway obstruction; asthma; biomarkers

ABBREVIATIONS: ACSS = Asthma Control Scoring System; CC16 = Clara-cell protein 16; CCL18-PARC = ratio of CC-chemokine ligand 18/pulmonary and activation-regulated chemokine; CRP = C-reactive protein; ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonist; SP-D = surfactant-associated protein D; VAS = visual analog scale

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Asthma affects more than 10% of patients older than 60 years of age.^{1,2} These subjects have more frequent hospital admissions, greater morbidity, and increased mortality rates related to asthma compared with younger people with asthma.³⁻⁵ Underdiagnosis, undertreatment, and various management problems may explain this poor asthma outcome in the elderly.^{6,7} Indeed, significant care gaps have been observed in elderly people with asthma in regard to the treatment offered, treatment adherence, inhaler use, and other inappropriate behaviors and attitudes toward this illness.⁸⁻¹⁰ It has been suggested, however, that age was not associated with poorer outcomes if proper treatment of asthma symptoms was offered.¹¹

There is increasing evidence that asthma in the elderly represents a different phenotype of asthma, usually characterized by more marked airway obstruction¹² and reduced response to treatment, possibly related to an increased neutrophilic airway inflammation.¹³⁻¹⁵ The fixed component of airway obstruction commonly observed in elderly people with asthma may also reflect a progressive decline in lung function in long-standing asthma, or a more severe disease in subjects with more recent-onset asthma.¹⁶

Because elderly subjects have often been excluded from studies on asthma, there is a need to better define the characteristics of asthma in this population and characterize the possible subphenotypes of the disease. A few authors have assessed the features of elderly people with asthma compared with young people with asthma,

but they did not include elderly control patients without asthma¹⁷ and often did not look at the multiple features of asthma either by not incorporating variables associated to comorbidities, lung volumes, markers of systemic inflammation,¹⁸ or lower airway inflammation.¹⁹ Furthermore, although serum levels of proinflammatory biomarkers such as IL-1 β , IL-6, and tumor necrosis factor alpha have been shown to be increased in the elderly, there is a need to identify biomarkers involved in asthma-specific processes. These include markers of systemic inflammation such as C-reactive protein (CRP), epithelial damage or dysfunction such as surfactant-associated protein D (SP-D) or Clara-cell protein 16 (CC16), regulators of leukocyte movements such as pulmonary and activation-regulated chemokine (PARC) or TH2 processes such as CC-chemokine ligand 18 (CCL18), in addition to markers of atopy (IgE). Hence, comprehensive studies addressing the various features of asthma in the elderly are still needed. Furthermore, severe asthma was usually included in those studies, making conclusions difficult to make for milder forms of asthma.

In this study, we aimed to assess the multidimensional clinical features of asthma in the elderly by evaluating clinical, physiological, and inflammatory changes potentially contributing to a different asthma phenotype in elderly subjects with asthma compared with younger subjects with asthma and elderly control subjects without asthma.

Methods

Subjects

Nonsmoking subjects with asthma were recruited from the outpatient clinics and nonsmoking subjects without asthma were recruited from advertisements between October 2013 and February 2016: (1) young (18-35 years of age) subjects with mild-to-moderate asthma and elderly subjects (≥ 60 years of age); (2) with mild-to-moderate asthma; or (3) without asthma. Asthma severity was defined by medication needs. Mild asthma: Subjects used a bronchodilator on demand only or a low dose of inhaled corticosteroids (ICS) equivalent to ≤ 250 mcg/d beclomethasone HFA. Moderate asthma: Subjects were on a moderate dose of ICS equivalent to >250 mcg/d but ≤ 500 mcg/d of beclomethasone HFA, alone or in combination with additional therapy such as a long-acting β_2 -agonist (LABA) and/or a leukotriene receptor antagonist. All subjects with asthma had stable disease with unchanged asthma medication for at least 4 weeks before study entry. Inclusion and exclusion criteria are described in [e-Appendix 1](#). Written informed consent was obtained from all subjects and the study was approved by the Ethics Committee of the Quebec Heart and Lung Institute (CÉR 20936).

Study Design

This was a cross-sectional study comparing asthma phenotype, as defined by clinical, physiological, and inflammatory characteristics, among the three subject groups.

Procedures

Detailed procedures are provided in [e-Appendix 1](#). Briefly, demographic, disease-related data, and self-reported comorbid conditions, associated to appropriate medication use or a doctor's diagnosis, were recoded. The frequency of asthma exacerbations was documented for the past year. Asthma control was determined using the Asthma Control Scoring System (ACSS)^{20,21} and adherence to asthma therapy was determined using two instruments: a visual analog scale (VAS) and a modified version of the Morisky scale.²² Spirometry was performed and lung volumes and carbon monoxide diffusion capacity were measured, as were reversibility to bronchodilator. All lung measurements were performed according to the recommendations of the American Thoracic Society/European Respiratory Society Task Force; quality and reproducibility of the measurements were assessed according to these guidelines.²³⁻²⁵ Airway responsiveness to methacholine was determined²⁶ and

perception of induced chest tightness and breathlessness was recorded. Lower airway inflammation was assessed with fractional exhaled nitric oxide measurements²⁷ and induced sputum analysis.^{28,29} CBC, fibrinogen, CRP, and serum IgE levels were analyzed to assess systemic inflammation. Serum was obtained from clotted blood. The following biomarkers were measured in serum: the ratio of CCL-18/ PARC (R&D Systems) and CC16, SP-D, and periostin (all Biovendor LLC) according to the manufacturers' instructions.

Statistical Analyses

Data were expressed as means $\pm$ SD for continuous variables, as numbers (%) for categorical variables or as median (25th-75th percentiles) for nonnormally distributed variables. Phenotype was determined by comparing the various characteristics between elderly and young people with asthma and elderly people without asthma. Groups of subjects were compared using χ^2 or Fisher exact test for categorical variables and one-way analysis of variance for continuous

variables. For some variables, a statistical model with heterogeneous variances among groups was performed using the Satterthwaite degree of freedom for statistical analyses. Posteriori comparisons were performed using the Tukey comparison technique. The univariate normality assumptions were verified with the Shapiro-Wilk test on the error distribution from the statistical model. Correlations between continuous variables were expressed using Spearman correlation coefficients. Subanalyses were also performed to compare all studied parameters between subjects with asthma according to the duration of asthma (≤ 5 vs ≥ 15 years) and between elderly subjects according to age categories (between 60 and 69 vs ≥ 70 years). Because elderly people with asthma had had asthma for a longer time, statistical analyses were performed to compare young and elderly subjects with asthma adjusting for duration of asthma. The results were considered significant with $P < .05$. All analyses were conducted using the statistical package SAS v9.4 (SAS Institute Inc).

Results

The flowchart of subjects' recruitment is shown in Figure 1. The final sample of 150 subjects was equally

divided into three groups: (1) young people with asthma, (2) elderly people with asthma, and (3) elderly people without asthma.

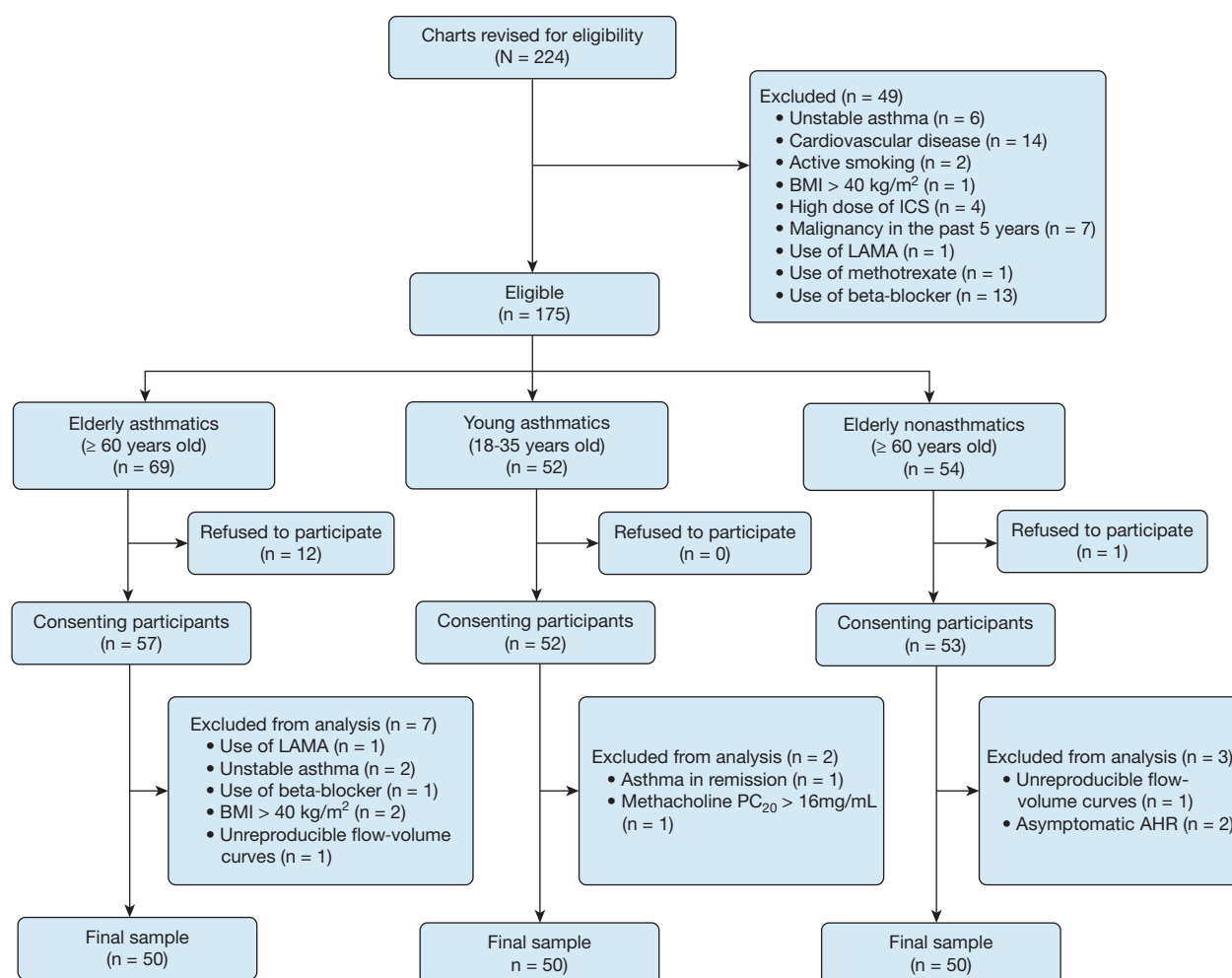


Figure 1 – Flow diagram of participants' recruitment. AHR = airway hyperresponsiveness; LAMA, long-acting muscarinic antagonist; PC20 = provocative concentration inducing a 20% fall in FEV₁.

Subjects' Demographics and Comorbidities

Subjects' demographics and comorbidities are presented in [Table 1](#). Elderly people with and without asthma had a mean age of 69 and 70 years, respectively, compared with young people with asthma, whose mean age was 26 years. In the elderly people with asthma group, there were 24 subjects aged between 70 and 79 years and two aged ≥ 80 years. Similar numbers were observed in the elderly people without asthma group, with 22 subjects aged between 70 and 79 years and four aged ≥ 80 years. Both groups of elderly subjects included a higher proportion of ex-smokers compared with the young subjects group, leading to a higher number of pack-years in elderly vs young, although all groups had a <5 pack-years smoking history. When both groups with asthma were compared, elderly subjects had longer asthma duration and a lower ACSS global score (lower degree of asthma control) compared with young subjects. Looking at the three subscores, only the physiological score was significantly lower in elderly compared with young people with asthma. More elderly people with asthma were taking a LABA, although the respective proportions of people with mild and moderate asthma and the daily dose of ICS were similar to that of young people with asthma. There were similar proportions of subjects with low, moderate, and high adherence to asthma treatment in elderly and young people with asthma whether assessed by the VAS or the Morisky scale. Scores were also comparable between groups.

In regard to the prevalence of comorbidities, both groups of elderly subjects reported more chronic rhinosinusitis compared with young subjects with asthma. Atopy was more prevalent in both groups of subjects with asthma compared with elderly subjects without asthma. Allergic rhinitis was more prevalent in young subjects than in elderly subjects, but elderly people with asthma reported a higher prevalence of rhinitis than did elderly people without asthma.

FEV₁, FVC, and FEV₁/FVC were different between groups, with elderly subjects with asthma showing the lowest values ([Table 2](#)). No significant differences were observed between groups for lung volumes or carbon monoxide diffusion. Methacholine provocative concentration inducing a 20% fall in FEV₁ was similar between elderly and young subjects with asthma. Although perception of induced-breathlessness was similar in both of these groups, elderly people with

asthma had a lower perception of induced chest tightness at a 20% fall in FEV₁.

Elderly subjects with asthma showed higher sputum eosinophils compared with young people with and without asthma, whereas both groups of elderly subjects had higher sputum neutrophil counts compared with young subjects ([Table 3](#)). Blood eosinophils were higher in both groups of subjects with asthma compared with elderly people without asthma. Except for serum IgE and periostin, all blood biomarkers were increased in elderly people with asthma compared with young people with asthma ([Fig 2](#)). IgE levels were different among the three groups of subjects, with young people with asthma showing the highest concentrations and elderly people with asthma being intermediate between the other two groups. As well, fibrinogen concentrations were different between groups, with elderly people with asthma having the highest concentrations and young people with asthma having the lowest concentrations. Serum concentrations of CCL18/PARC and SP-D were higher in elderly subjects compared with young subjects, but no difference was observed between elderly people with and without asthma. Serum CC16 concentrations were different among the three groups of subjects, with elderly people without asthma showing the highest concentrations. Periostin concentrations were similar among all groups.

Correlations Between Age and Lung Function or Inflammatory Cells

There were negative correlations between age and baseline FEV₁ and FEV₁/FVC and a positive correlation between age and sputum neutrophil percentage ([Fig 3](#)). No correlations were observed between age and lung volumes, carbon monoxide diffusion, or other blood or sputum inflammatory cells. No correlations were observed between sputum neutrophils and any of the systemic inflammatory markers. Similarly, no correlations were observed between lung function (FEV₁ and FEV₁/FVC) and sputum eosinophils or neutrophils or markers of systemic inflammation.

Subanalysis According to Age

Elderly subjects were analyzed according to age categories (60 to 69 vs ≥ 70 years). This subanalysis showed comparable results to the main analysis. Detailed descriptions of age categories and results are reported in [e-Appendix 1](#).

TABLE 1] Subjects' Demographics and Comorbidities

Variable	Young With Asthma	Elderly With Asthma	Elderly Without Asthma
No. of subjects	50	50	50
Women/men	32/18	31/19	25/25
Age (y), mean $\pm$ SD (range)	26 $\pm$ 5 (18-35) ^a	69 $\pm$ 5 (60-84) ^b	70 $\pm$ 6 (60-90) ^b
BMI (kg/m ²)	24 $\pm$ 5 ^a	28 $\pm$ 5 ^b	27 $\pm$ 4 ^b
Smoking history			
Never smokers	48 ^a	32 ^b	33 ^b
Ex-smokers	2 ^a	18 ^b	17 ^b
Pack-years	0.2 $\pm$ 0.9 ^a	2.3 $\pm$ 3.6 ^b	1.3 $\pm$ 2.4 ^b
Asthma duration (y)	15 $\pm$ 8 ^a	24 $\pm$ 22 ^b	
Asthma severity			
Mild	22	14	...
Moderate	28	36	...
Dose of ICS, equivalent beclomethasone (mcg/d)	400 (250-500)	250 (250-500)	...
LABA	17 ^a	31 ^b	...
Acute care use in the previous year, total No. of events			
Unscheduled medical visits related to respiratory problems	12	11	...
ED visits (<24 h)	0	0	...
Hospitalizations (>24 h)	4	5	...
Treatment use, total No. of events			
Prednisone in the previous year	1	5	...
Rescue bronchodilator use (including SABA and Symbicort-SMART therapy) in the past week	1	4	...
Asthma control			
ACSS global score (%)	86 $\pm$ 11 ^a	77 $\pm$ 16 ^b	...
ACSS clinical score (%)	89 $\pm$ 12	90 $\pm$ 11	...
ACSS physiological score (%)	90 $\pm$ 14 ^a	73 $\pm$ 23 ^b	...
ACSS inflammatory score (%)	64 $\pm$ 27	50 $\pm$ 29	...
Adherence to medication ^d			
VAS			
Low/moderate/high adherence	2/13/19	5/8/25	...
Score (%)	80 (21)	80 (28)	...
Morisky score			
Low/moderate/high adherence	7/18/10	3/16/19	...
Score (No. of yes)	1.3 $\pm$ 1.2	0.8 $\pm$ 1.0	...
Animal at home (yes)	24 ^a	8 ^b	9 ^b
Family history of asthma (yes)	25 ^a	22 ^{a,b}	11 ^b
Family history of allergy (yes)	42 ^a	25 ^b	16 ^b
Comorbidities			
GERD	14	21	10
CRS	2 ^a	10 ^b	9 ^b
Atopy	46 ^a	40 ^a	22 ^b

(Continued)

TABLE 1] (Continued)

Variable	Young With Asthma	Elderly With Asthma	Elderly Without Asthma
AR	42 ^a	21 ^b	10 ^c
OSA	0	4	5
Anxiety	3	5	4
Depression	1	2	0
History of depression	1	5	5

Results are presented as means $\pm$ SD for continuous variables or as No. of subjects for categorical variables unless otherwise stated. ACSS = Asthma Control Scoring System; AR = allergic rhinitis; CRS = chronic rhinosinusitis; ICS = inhaled corticosteroid; GERD = gastroesophageal reflux disease; LABA = long-acting beta-agonist; SABA = short-acting beta-agonist; SMART = Symbicort maintenance and reliever therapy; VAS = visual analog scale.

^{a,b,c}Superscript letters indicate statistical significance between groups $P < .05$.

^dAdherence to medication among subjects using inhaled corticosteroids with or without long-acting beta-agonist and/or leukotriene receptor antagonist to control their asthma.

Subanalysis According to Asthma Duration

A subanalysis according to the duration of asthma was also performed in elderly people with asthma, who were divided into two groups: (1) short asthma duration (diagnosis of asthma ≤ 5 years; $n = 19$, median asthma duration 1 year) and (2) long asthma duration (diagnosis of asthma ≥ 15 years; $n = 29$, median asthma duration 36 years). Most characteristics were similar between these two groups of elderly subjects, except for the severity of asthma, for which the group with a longer duration of asthma included a higher proportion of people with moderate asthma (long asthma duration, 17% people with mild and 83% people with moderate asthma vs short asthma duration, 47% people with mild

and 53% people with moderate asthma, $P = .046$). In addition, elderly subjects with long asthma duration had a lower FEV₁/FVC (long asthma duration: 0.64 ± 0.08 vs short asthma duration: 0.67 ± 0.06 , $P = .047$), higher total IgE concentrations (long asthma duration: 352 ± 795 vs short asthma duration: 73 ± 120 IU/mL, $P = .01$), and lower adherence to medication according to VAS (long asthma duration: $74 \pm 31\%$ vs short asthma duration: $92 \pm 13\%$, $P = .03$).

Discussion

This study reports the characteristics of mild-to-moderate asthma in the elderly compared with subjects without asthma of the same age and with

TABLE 2] Pulmonary Function Tests and Airway Responsiveness

Variable	Young People With Asthma	Elderly People With Asthma	Elderly People Without Asthma
Spirometry			
FEV ₁ (% predicted)	92 $\pm$ 9 ^a	83 $\pm$ 15 ^b	105 $\pm$ 13 ^c
FVC (% predicted)	104 $\pm$ 9 ^a	97 $\pm$ 13 ^b	110 $\pm$ 13 ^c
FEV ₁ /FVC	0.75 $\pm$ 0.07 ^a	0.66 $\pm$ 0.08 ^b	0.73 $\pm$ 0.05 ^a
Reversibility to BD (%)	6.3 $\pm$ 5.5	8.8 $\pm$ 9.3	...
Lung volumes			
RV (% predicted)	101 $\pm$ 25	101 $\pm$ 22	92 $\pm$ 18
FRC (% predicted)	93 $\pm$ 17	97 $\pm$ 16	96 $\pm$ 18
TLC (% predicted)	102 $\pm$ 7	100 $\pm$ 11	102 $\pm$ 10
CO diffusion (% predicted)	91 $\pm$ 16	92 $\pm$ 17	92 $\pm$ 18
Airway responsiveness			
PC ₂₀ methacholine, geometric mean (range), mg/mL	2.03 (0.17-16.0)	3.14 (0.09-16.0)	...
PS ₂₀ breathlessness	2.2 $\pm$ 1.6	1.9 $\pm$ 1.7	...
PS ₂₀ chest tightness	2.7 $\pm$ 1.5 ^a	1.7 $\pm$ 1.4 ^b	...

Results are presented as means $\pm$ SD unless otherwise stated. BD = bronchodilator; CO = carbon monoxide; FRC = functional residual capacity; PC₂₀ = provocative concentration giving a 20% fall in FEV₁; PS₂₀ = perception score on the Borg scale at 20% fall in FEV₁; RV = residual volume; TLC = total lung capacity.

^{a,b,c}Superscript letters indicate statistical significance between groups $P < .01$.

TABLE 3] Lower Airway and Systemic Inflammation

Variable	Young People With Asthma	Elderly People With Asthma	Elderly People Without Asthma
Lower airway inflammation			
F _{ENO} (ppb)	22 (14-42)	23 (12-34)	19 (15-23)
Sputum			
No. of samples	17	21	25
Total cell count ($\times 10^6$ cells/g)	3.5 (2.6-6.3)	7.5 (4.3-10.8)	8.2 (3.6-13.5)
Eosinophils (%)	1.0 (0.5-6.1) ^b	2.8 (2.0-10.8) ^a	0.5 (0-1.8) ^b
Neutrophils (%)	15.9 (8.1-39.0) ^a	44.8 (30.0-64.5) ^b	54.0 (44.0-68.8) ^b
Systemic inflammation			
WBC ($\times 10^9$ /L)	6.4 (4.9-7.4)	6.2 (5.4-7.3)	6.1 (5.3-7.1)
Neutrophil ($\times 10^9$ /L)	3.8 (2.5-4.4)	3.8 (3.2-4.7)	3.8 (3.1-4.8)
CRP (mg/mL)	1.2 (0.5-2.5)	1.7 (0.9-3.0)	1.1 (0.4-2.2)
IgE (IU/mL)	119.0 (71.0-271.3) ^a	70.5 (23.0-189.3) ^b	23.0 (9.5-61.8) ^c
Fibrinogen (g/L)	2.7 (2.5-3.0) ^a	3.2 (2.9-4.1) ^b	3.1 (2.8-3.4) ^c
Serum biomarkers			
CCL18/PARC (ng/mL)	47.0 (35.2-63.2) ^a	78.3 (55.9-109.5) ^b	71.6 (47.0-90.8) ^b
CC16 (pg/mL)	7.5 (5.4-10.7) ^a	9.9 (7.4-13.3) ^b	12.9 (9.8-15.9) ^c
SP-D (ng/mL)	100.3 (69.1-136.1) ^a	144.2 (84.1-192.0) ^b	146.6 (101.5-187.8) ^b
Periostin (ng/mL)	14.8 (13.0-21.6)	14.8 (11.7-18.7)	14.1 (12.3-16.4)

Results are presented as medians (25th-75th percentiles). CC16 = Clara-cell protein 16; CCL18= CC-chemokine ligand 18; CRP= C-reactive protein; F_{ENO}= exhaled nitric oxide; PARC: pulmonary and activation-regulated chemokine, SP-D= surfactant-associated protein D.

^{a,b,c}Superscript letters indicate statistical significance between groups $P < .01$.

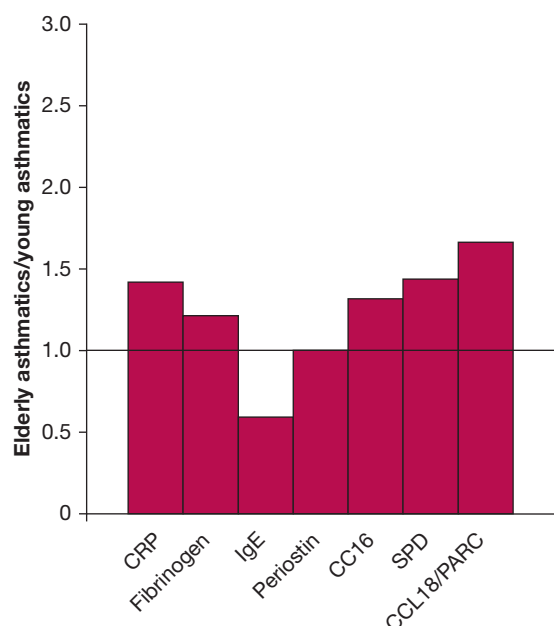


Figure 2 – Ratio of elderly people with asthma's over young people with asthma's blood biomarkers median concentrations. CC16 = Clara-cell protein 16; CCL18 = CC-chemokine ligand 18; CRP, C-reactive protein; PARC = pulmonary and activation-regulated chemokine; SP-D = surfactant-associated protein D.

younger subjects with asthma. It shows that elderly people with asthma have different asthma features, supporting the notion that asthma in the elderly presents as a specific phenotype or different subphenotypes that remain to be further described, probably reflecting the influence of senescence on asthmatic processes and possibly additional influences over time. Our study confirms some previous observations in elderly subjects with asthma but adds further data on many other components of mild-to-moderate asthma in this population, particularly serum biomarkers and differentiation between long vs short asthma duration.

In the present study, elderly people with asthma showed poorer asthma control, despite higher use of LABA, similar use of ICS, and similar adherence to asthma controller therapy than young people with asthma. Analyzing these variables according to asthma duration, however, we showed that elderly subjects with a long asthma duration reported significantly lower medication adherence compared with elderly subjects with short asthma duration for similar asthma control. This suggests that some of these subjects may have been overtreated or that they

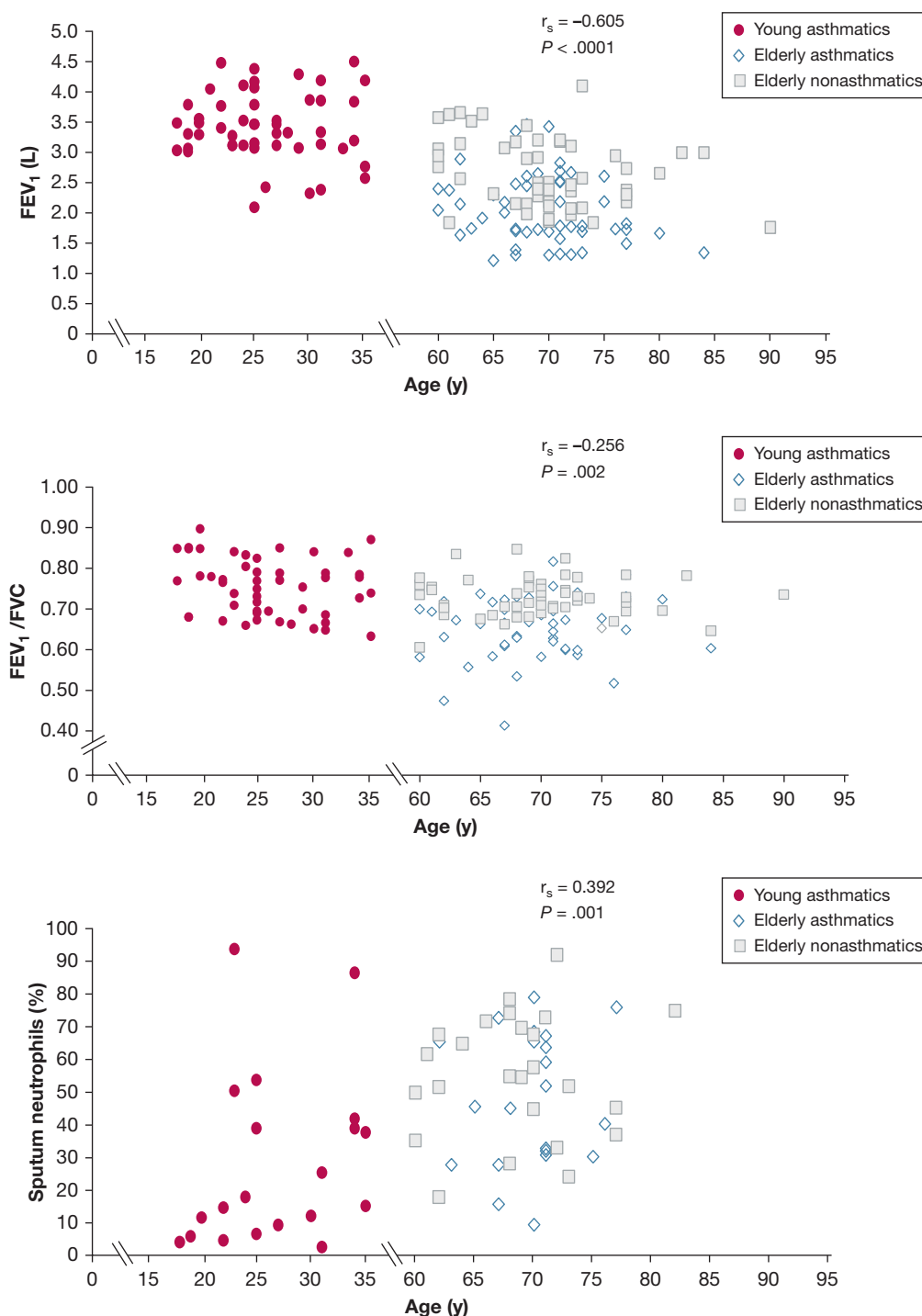


Figure 3 – Correlations between age and (A) FEV₁, (B) FEV₁/FVC, and (C) sputum neutrophils in the entire study sample.

had a temporal adaptation to their asthma symptoms. Nevertheless, this worse control in elderly compared with young subjects did not seem to affect health care use because we found no increase in such outcome in the elderly, these events being rare in both groups of people with asthma. These observations may suggest

that the lower control scores for expiratory flows represent chronic changes and that, although the elderly had more eosinophils, such an increase in inflammation may not be so detrimental, possibly because of a reduced function of eosinophils, as discussed later.

Because nonadherence to treatment has been associated with increasing age,^{30,31} the results of previous studies showing marked increases in morbidity and mortality in elderly people with asthma could be due to asthma management problems and insufficient adherence to treatment. Poorer asthma control and underdiagnosis of asthma in the elderly has been previously explained by a lack of symptoms reported or an inadequate symptoms perception in this population.³² Indeed, as compared with young people with asthma, previous studies have suggested that elderly people with asthma have a blunted perception of breathlessness and wheezing during induced bronchoconstriction.^{33,34} In our study, however, elderly subjects had only a trend toward lower perception of breathlessness compared with young subjects and perceived significantly less chest tightness for a similar degree of bronchoconstriction. Because the difference in mean scores between both groups was 1 point, this could be considered clinically significant.^{35,36} Poorer asthma control in the elderly was mainly from lower lung function; however, even if perceived, symptoms of asthma may be misinterpreted or not reported, often being considered to be due to aging. Although perception of symptoms is a cornerstone for asthma management, spirometry should be included as part of asthma control assessment.³⁷ Our results extend this recommendation to the elderly population.

Airway obstruction was more marked in elderly people with asthma compared with young people with asthma and elderly people without asthma. This is in keeping with others who observed a lower FEV₁ and FEV₁/FVC in elderly people with asthma compared with elderly people without asthma^{7,17} or to young people with asthma.³⁸ Nevertheless, because we included age-matched elderly control patients and younger asthma subjects, our results add to previous findings by suggesting an additive effect of asthma and older age in lung function decrease. Our results support those of others reporting a marked airway obstruction in elderly patients with asthma,³⁹ probably reflecting long-term changes in airway structure, such as airway remodelling and loss of elastic recoil.⁴⁰⁻⁴⁴ Although the number of patients in each subgroup may seem small, the results from our post hoc subanalysis comparing elderly subjects with asthma according to the duration of disease showed that elderly patients with longer asthma duration had more airway obstruction than those with shorter duration, which is in line with what has been

shown in a general population of asthma patients.⁴⁵ Whether these characteristics contribute to a worse prognosis in elderly patients with longer asthma duration should be further explored in a larger cohort of patients.

Immune responses change with age.⁴⁶ In this study, by comparing elderly people with asthma with their age-matched control patients and their younger counterparts, we observed several features suggestive of a switch toward a less allergic and more neutrophilic asthma phenotype. First, although atopy was as prevalent in elderly people with asthma as in younger ones, serum IgE levels and prevalence of allergic rhinitis were intermediate between elderly people without and young people with asthma. Second, although sputum eosinophils were higher than in the other two groups and blood eosinophils were similar to young people with asthma, sputum neutrophils were also increased, being higher than in young people with asthma and similar to elderly people without asthma. This supports previous findings that inflammation evolves to a more mixed phenotype with increasing age.^{18,47} Nevertheless, it would have been of interest to assess the function of these eosinophils because age-related changes in eosinophils' function have been reported.⁴⁸ We and others have previously reported increased sputum neutrophil percentages in elderly subjects with asthma, whatever the severity of asthma, whereas in younger subjects, this increase is observed in severe asthma only.¹⁴ This could be related to the senescence process, possibly through a change in microbiome⁴⁹ and/or to persistent systemic inflammation, either from subclinical infection or other causes. Indeed, changes in the elderly airway microbiome can modulate immune responses, and such changes could be responsible for the persistence of airway inflammation in these patients and explain their increase in airway neutrophil numbers. This could have consequences on their treatment response and outcome; however, it should be further explored. In our study, CRP, a marker of systemic inflammation, was not significantly different among all three groups, and levels of fibrinogen, another marker of chronic low grade inflammation, was in the normal range, although higher in elderly people with asthma compared with the other two groups.

Markers of epithelial damage or dysfunction such as SP-D or CC16 were increased in elderly subjects with

and without asthma, suggesting alterations in airway epithelium with age. Animal studies have suggested a shift from a Th2 to Th1 gene and protein expression with time.⁵⁰ We therefore wanted to explore if Th2 markers would be decreased in elderly compared with young patients. We observed similar concentrations of periostin, a Th2-driven asthma biomarker, in the three groups studied. In addition, increased levels of CCL18/ PARC in elderly patients were observed compared with young patients, although there was no significant difference between elderly people with and without asthma. In keeping with our results, Han et al⁵¹ previously showed a negative relationship between CCL18 concentrations and age in asthma. The involvement of such biomarkers in elderly asthma should be further explored.

This study has some limitations. First, it is cross-sectional, preventing evaluation of the stability of our findings. Second, the generalizability of our results may be limited by our study population being from a single institution and that sputum samples could not be obtained from all participants. Third, we did not include young control patients; thus, we could not evaluate the effect of aging separately. Fourth, the age 60 cutoff may be questionable, and an American Thoracic Society workshop report referred to those >65 years of age as elderly.⁵² Because there is evidence that the senescence process becomes more significant after 60 years old⁵³ and because this cutoff has been used in previous

studies,^{18,47} we believe that age 60 years was a valid lower age limit for elderly subjects. Nevertheless, mean age of both elderly groups in this study was 70 years. Last, subjects with asthma were recruited from a tertiary care center, which might limit the generalizability of the results. There is indeed a possibility that control of asthma in the elderly could be more problematic in primary care. In spite of these limitations, we believe it gives a valuable screenshot at the multidimensional picture of asthma in the elderly. Finally, we excluded severe asthma because it is often considered a separate entity. Indeed, patients with severe asthma have many comorbidities interfering with measures and they cannot often perform all tests, such as bronchoprovocation, having difficulties withholding medications for a sufficient duration before these tests.⁵⁴ To our knowledge, it is the first study to compare such a wide range of characteristics in a population of well-defined elderly and young patients with asthma and of elderly control patients. Because phenotypes are still not well identified in the aging population with asthma, we believe that our study brings novel findings to the multidimensional picture of asthma in the elderly.

In conclusion, asthma in the elderly shows specific characteristics, different from asthma in younger patients. The clinical implications of this change in phenotype, particularly on response to therapy, remain to be studied.⁵⁵ This could allow better targeting of interventions and reduce disease burden.

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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Comparative Clinical, Physiological, and Inflammatory Characteristics of Elderly Subjects With or Without Asthma and Young Subjects With Asthma

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e-Appendix 1.

METHODS

Subjects

Inclusion criteria: All subjects had to: 1) be non-smokers or ex-smokers, defined as <10 pack-years of smoking and no smoking for at least one year before inclusion into the study, 2) have a body mass index (BMI) <40 kg/m², and 3) be able to adhere to study procedures and to provide written informed consent to participate in the study, in accordance with good clinical practice requirements.

In addition, asthmatic subjects must have had: 1) a diagnosis of asthma confirmed according to the criteria of the Canadian Asthma Consensus Guidelines (1) and 2) mild-to-moderate asthma as defined by medication needs. *Mild asthma:* used only a bronchodilator on demand or a low dose of inhaled corticosteroids (ICS) equivalent to ≤250 mcg/day beclomethasone HFA. *Moderate asthma:* were on a moderate dose of ICS equivalent to >250 but ≤500 mcg/day of beclomethasone HFA, alone or in combination with additional therapy such as a long-acting b2-agonist (LABA) and/or a leukotriene receptor antagonist (LTRA), 3) stable asthma with unchanged asthma medication for at least 4 weeks before study entry.

Exclusion criteria included: any respiratory condition, apart from asthma for asthmatic subjects, which could have significantly interfered with the tests, such as cardiovascular diseases such as heart failure or unstable coronary heart disease; smoking-induced chronic obstructive pulmonary disease (COPD); interstitial pulmonary disease or other disorders causing dyspnea; unstable diabetes; any active chronic inflammatory disease; bleeding disorders; evidences of active and/or treated malignancy within the previous 5 years; any significant concomitant illness or injury and any evidence of respiratory infection within four weeks of entry in the study.

Prohibited medication for all participants included: 1) anticholinergics, 2) systemic immunosuppressive or immunomodulatory drug therapy, 3) beta-blockers, and 4) any concomitant medication that, in the opinion of the investigator, could affect the outcome of the study.

Demographics and comorbidities

Data were collected on the duration of asthma, allergen exposure, active or secondary smoking, family history of asthma and atopy, and severity of the disease. Frequency of hospital admissions, unscheduled medical and emergency department visits, and use of oral corticosteroids for at least

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3 days, or an increase from a maintenance dose, were documented for the last year. Current self-reported comorbid conditions such as gastro-oesophageal reflux disease, chronic rhinosinusitis, allergic rhinitis, obstructive sleep apnea, anxiety, and depression were recorded. Atopy was also determined from skin prick tests, performed with 26 common aeroallergens. Normal saline and histamine were used as negative and positive controls, respectively. Skin wheal diameter was recorded after 10 minutes and a positive response was defined as a skin wheal diameter equal or greater than 3 mm.

Asthma control

Asthma control was determined using the asthma control scoring system which assesses three types of parameters: symptoms/rescue medication needs, expiratory flows and lower airway inflammation from induced sputum analysis (2, 3). The different parameters are quantified to obtain a total score of 100% each and a global score is determined using the means of these parameters.

Adherence to asthma medication

For the VAS, subjects were asked about their best guess of how much of their ICS or LTRA they had taken over the past 6 months on a scale from 0 to 100 (where 0=0% of prescribed medication taken and 100=100% of prescribed medication taken). Low adherence was defined as intake of less than 50% of prescribed doses, moderate adherence as 50%-80%, and high adherence as >80% (4).

The modified version of the Morisky scale includes 4 questions: 1) Do you ever forget to take your ICS or asthma pills? 2) Are you ever careless about taking your ICS or asthma pills? 3) When you feel better, do you sometimes stop taking your ICS or asthma pills? 4) Sometimes, if you feel worse when you take your ICS or asthma pills, do you stop taking them? Positive and negative answers were rated 1 and 0, respectively. Low adherence was defined as a score of 3 or 4, medium adherence as a score of 1 or 2, and high adherence as a score of 0 (4).

Lung function and volumes

Baseline forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured according to the American Thoracic Society (ATS) criteria (5) and the predicted values

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were obtained from the European Respiratory Society (ERS) Global Lung Function Initiative (GLI-2012) (6, 7). Airway obstruction was defined as a FEV₁ <80% of predicted values and a FEV₁/FVC ratio <0.7. Reversibility of airway obstruction was measured after administration of 200 mcg of inhaled salbutamol. Lung volumes and carbon monoxide (CO) diffusion capacity were measured as per ATS/ERS standards (8, 9).

Airway responsiveness and perception of bronchoconstriction

Methacholine challenge was done according to the method described by Juniper *et al.* (10) Briefly, following 0.9% saline inhalation, increasing concentrations of methacholine, up to 16 mg/ml, were inhaled for 2 minutes, at 5-minute intervals, through a Wright nebulizer. Airway hyperresponsiveness (AHR) was defined as a provocative dose of methacholine inducing a 20% fall in FEV₁ (PC₂₀) <16mg/ml.

Breathlessness and chest tightness were recorded before each FEV₁ measurement on a modified Borg scale (0 = no symptom, 10 = maximum symptom). The perception score on the Borg scale at 20% fall in FEV₁ (PS₂₀) was determined for each subject by interpolation of the two last perception scores, before and after the 20% fall in FEV₁ (11).

Inflammation

FeNO measurements were performed according to ATS recommendations, using a NiOXmino handheld analyzer (Aerocrine, Morrisville, NC, USA) (12). Sputum was induced by inhalation of hypertonic saline and processed using the method described by Pin *et al.* (13) and modified by Pizzichini *et al.* (14). Briefly, mucus plugs were selected from saliva, weighed, and treated with dithiothreitol (DTT). Following filtration, total cell count and viability were determined. Two slides were prepared and stained with Diff-Quik for differential cell count.

RESULTS

Sub-analysis according to age

Elderly subjects were analyzed according to categories of age: 1) between 60 and 69 years old and 2) ≥70 years old. Five groups were therefore analysed on the basis of asthma status and age: 1) young asthmatics (*N*=50), 2) elderly asthmatics aged between 60 and 69 years (*N*=24), 3) elderly asthmatics aged ≥70 years (*N*=26), 4) elderly non-asthmatics aged between 60 and 69 years (*N*=24), and 5) elderly non-asthmatics aged ≥70 years (*N*=26). Results from this sub-analysis were similar to those obtained from the main analysis (data not shown), suggesting that elderly

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asthmatic subjects aged 60 to 69 years (mean age: 65 years) and those aged ≥ 70 years (mean age: 73 years) do not have different asthma characteristics.

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