

Age Is Not Associated with Hospital Admission or Uncontrolled Symptoms of Asthma if Proper Treatment Is Offered

Eduardo Vieira Ponte^a Rafael Stelmach^b Rosana Franco^c
Carolina Souza-Machado^d Adelmir Souza-Machado^e Alvaro A. Cruz^c

^aFaculdade de Medicina de Jundiaí, ^bInstituto do Coração, ^cNúcleo de Excelência em Asma, ^dEscola de Enfermagem and ^eInstituto de Ciências da Saúde, Universidade Federal da Bahia, Jundiaí, Brazil

Key Words

Asthma · Age · Hospital admission · Inhaled corticosteroids

Abstract

Background: Aging modifies immune response and respiratory physiology. Few studies evaluate the effect of age on asthma. The aim of our study was to evaluate whether age is associated with uncontrolled symptoms and hospital admissions due to asthma in a setting where patients were receiving proper treatment. **Methods:** We enrolled 401 patients with uncontrolled asthma who were inhaled corticosteroid-naïve. The follow-up period was 1 year. They received medications for asthma, performed spirometry, a symptoms questionnaire, and all emergency room visits and hospital admissions due to asthma were reported. The primary end point was hospital admission during the follow-up period. **Results:** Baseline data demonstrated that subjects >55 years of age had a later onset of asthma and a longer duration of symptoms. Adjusted logistic regression models demonstrated that older age at enrollment did not predict asthma control in the follow-up: hospital admission due to asthma [odds ratio (OR) 1.7 and 95% confidence interval (CI) 0.6–4.7], symptoms score (OR 0.6 and 95% CI 0.3–1.1) and emergency room visits due to asthma (OR 0.9 and 95% CI 0.6–1.3). Older age was associ-

ated with worse lung function (OR 1.8 and 95% CI 1.1–3.3). **Conclusion:** This study allows us to conclude that older age is associated with a later onset of asthma and a longer duration of symptoms. Age does not predict hospital admissions or poor control of asthma symptoms if proper treatment is offered. It does, however, predict worse lung function.

© 2014 S. Karger AG, Basel

Introduction

Aging modifies the immune response in healthy subjects. Older subjects have decreased numbers of naive T cells [1, 2], reduced production of antibodies [3] and a reduced cellular immune response [4]. Airway neutrophils in older people produce fewer leukotrienes [5], and eosinophils have a reduced capacity to degranulate and to produce superoxide [6]. Among atopic subjects, IgE [7] and reactivity to skin-prick tests [8] decrease with age. Aging modifies the respiratory physiology. It is associated with reduced lung function [9], loss of elastic recoil of the

This study was conducted in the Núcleo de Excelência em Asma, Universidade Federal da Bahia, Salvador, Brazil.

lungs [10] and more bronchial hyperresponsiveness [11, 12]. Older subjects may have a reduced awareness of acute bronchoconstriction, which could affect the recognition of obstructive lung diseases [12].

There are few studies evaluating the effect of immune and physiologic senescence on allergic respiratory diseases such as asthma. These studies often have contradictory results. Evidence suggests that older subjects with asthma have more airway remodeling [13]. Decline in lung function over time is more pronounced in asthmatic subjects in comparison with healthy subjects [14]. Some studies have found that there is a lower prevalence of self-reported asthma in older subjects [15, 16] while others have found a higher prevalence of asthma in older populations [17]. Whether age predicts outcomes of asthma control has not yet been established. Previous epidemiologic surveys were not conclusive due to their retrospective design and imbalances in treatment [15, 18–20]. The aim of our study is to evaluate whether age is associated with outcomes of asthma control in a prospective cohort of subjects receiving proper treatment.

Material and Methods

Study Population

Asthmatic subjects living in the city of Salvador, Brazil, were screened upon admission to a public program for the control of asthma in a city with a low-income population. Inclusion criteria were uncontrolled asthma and no previous use of inhaled corticosteroids. The diagnosis of asthma was made by a chest physician and was based on typical symptoms (acute episodes of dyspnea and wheezing), lung function (normal or obstructive) and normal chest radiograph. The criteria for uncontrolled asthma were at least one of the following: (1) daily symptoms of asthma or (2) >2 nocturnal awakenings per week due to asthma or (3) >2 puffs/day of short-acting bronchodilator to relieve asthma symptoms [21]. Patients were excluded if they were current smokers, had a smoking history of >9 pack-years or had a diagnosis of other pulmonary morbidities or extrapulmonary disease that could possibly interfere in the evaluation of asthma. To exclude other pulmonary morbidities, complementary exams like high-resolution computed tomography of the chest were performed according to the discretion of the physician in charge. The study was approved by the institutional review board of the Maternidade Clémio de Oliveira – Universidade Federal da Bahia. Subjects gave their signed informed consent.

Study Design

This was a prospective study of consecutive patients. The subjects who were enrolled were followed up for 1 year. They had five study visits throughout the follow-up, i.e. visits I–V. The interval between study visits was 3 months. The enrollment period was from January 2004 to January 2006.

At visit I, the inclusion/exclusion criteria were checked. Subject evaluation and approach to management were conducted by a

physician, a nurse and a pharmacist. All subjects received medications for asthma, performed lung function tests and reported any emergency room visits and hospital admissions due to asthma in the previous 12 months. The initial treatment was inhaled budesonide (800 µg/day) and inhaled formoterol (24 µg/day). Patients received inhaled short-acting β-2 agonist to be used on demand.

At follow-up visits II–IV, patients reported all emergency room visits and hospital admissions due to asthma since the previous visit. The physician in charge adjusted treatment. Subjects who reported the above or symptoms of asthma in the last 2 weeks had a 25% increase in treatment, and those who reported none of these had a 25% decrease in treatment. Asthma medication was dispensed on a monthly basis. Pharmacists recorded withdrawal of medication.

At visit V (the last visit), patients answered the Asthma Control Questionnaire (ACQ) [22], the Asthma Quality of Life Questionnaire (AQLQ) [23] and performed a posttreatment lung function test. The ACQ and AQLQ are continuous variables. The Portuguese version of the ACQ has a 0.75 cut-off to identify controlled asthma [24]. The minimal significant difference of the AQLQ is 0.5 [25]. Rhinitis was classified according to ARIA (Allergic Rhinitis and its Impact on Asthma) criteria [26]. Dispensed medications were reviewed to assure that only patients with >80% adherence to treatment were included in the analysis.

Lung Function and Skin-Prick Test

A KoKo spirometer (software PDS Instrumentation, Inc., Louisville, Colo., USA) was used for lung function testing according to the American Thoracic Society recommendations. FEV₁ was expressed as a percentage of predicted value and was used to quantify the degree of airway obstruction.

Atopy was assessed with an immediate-type hypersensitivity skin-prick test with aeroallergen extracts, performed in the forearm. Four antigens were used: dust mites (*Dermatophagoides pteronyssinus* and *Blomia tropicalis*) and cat and dog epithelium (FDA Allergenic, Rio de Janeiro, Brazil), as these are the most common aeroallergens in Salvador, Bahia, Brazil [27]. The wheal diameters were measured 15 min after puncture. The test was considered positive when at least one antigen induced a reaction with a diameter that was 3-mm greater than the control with saline solution. The sum of two larger diameters of reactions to antigens, divided by 2, was used to measure the intensity of the atopic status.

Statistical Analysis

To estimate whether age is associated with outcomes of asthma control, subjects were divided into 2 groups: <55 years and ≥55 years. Previous publications used a cut-off of 55 years [18, 28] or 65 years [15, 29]. We chose 55 years as the cut-off age because it provided a balanced sample size between groups, resulting in more power to identify differences. The primary end point of the study was hospital admission due to asthma because this was associated with increased age in previous studies [15, 18, 19]. Secondary end points were symptoms score (ACQ), quality of life (AQLQ) and lung function recorded at visit V and any emergency room visits due to asthma during the follow-up.

The response to treatment with inhaled corticosteroids was evaluated. The study population was inhaled corticosteroid-naïve

Table 1. Baseline characteristics of 401 patients with uncontrolled asthma

Females	320 (80)
Age of asthma onset, years	12 (4–26)
Patients reporting a smoking history of ≤ 9 pack-years ¹	27 (6)
BMI >35	30 (8)
Duration of asthma, years	28 (17–41)
Positive skin-prick test ²	189 (60)
Rhinitis diagnosis	332 (83)
Number of emergency room visits in the year before enrollment	7 (2–24)
Patients with emergency room visits in the year before enrollment	355 (88)
Number of hospital admission in the year before enrollment	0 (0–1)
Patients with hospital admission in the year before enrollment	115 (29)
FEV ₁ % predicted before treatment	66 (52–82)

Nominal variables are denoted as n (%). Continuous and ordinal variables are depicted as median and interquartile range.

¹ Being a current smoker and having a smoking history >9 pack-years were exclusion criteria.

² A total of 314 patients were evaluated.

before the study. Therefore, reduction in the number of emergency room visits during the study was attributed to the use of the inhaled corticosteroids. We created an index to estimate the response to treatment. The number of emergency room visits in the year before the study, reported at visit I, was the baseline information to estimate the percentual reduction during the study. Subjects were classified into 2 categories, i.e. a $\geq 90\%$ or a $<90\%$ reduction in the number of emergency room visits. A similar analysis was performed for lung function. FEV₁ at visit I was the baseline information to estimate improvement in lung function at visit V. Patients were classified into 2 categories, i.e. a $\geq 10\%$ or a $<10\%$ improvement in FEV₁.

Nominal variables were expressed as proportions. Ordinal and continuous variables were expressed as median and quartiles. The Fisher exact test and the χ^2 test were used to compare nominal variables. The Mann-Whitney U test was used to compare ordinal and continuous variables. A multivariate binominal logistic regression model evaluated the impact of age on end points of asthma control and response to treatment. Statistical analysis was performed using a software program (SPSS for Windows; SPSS Inc., Chicago, Ill., USA).

Results

Table 1 describes the baseline characteristics of 401 subjects enrolled in the study. Most were female and 60% had positive skin-prick test. The frequency of rhinitis was 83%. The frequency of subjects that reported emergency room visits and hospital admissions due to asthma in the year before enrollment was 88 and 29%, respectively. Median and interquartile values of emergency room visits and hospital admissions due to asthma in the year before the study were 7 (2–24) and 0 (0–1) events per pa-

tient, respectively. The median FEV₁ % predicted was 66%.

Table 2 depicts comparisons of baseline data according to age strata. Subjects were not using inhaled corticosteroids at that point in time. Older subjects had a later onset of asthma, a longer duration of symptoms, had reported less emergency room visits for the year before enrollment and had worse lung function. They had a trend toward less atopy in comparison to younger subjects. The groups were similar with regard to gender, smoking history, frequency of rhinitis, BMI (>35) and hospital admissions due to asthma in the year before study enrollment.

Table 3 compares proxies of asthma control and response to treatment in the follow-up while the subjects were on inhaled corticosteroids. Most subjects used ≥ 800 μg of inhaled budesonide during the study. Older subjects used more inhaled corticosteroids (865 ± 216 and 778 ± 274 μg budesonide). The median reduction of emergency room visits in the follow-up was 98% in the group <55 years and 92% in the group ≥ 55 years ($p = 0.02$). Older subjects had a lower lung function and less severe rhinitis at visit V. Young and old subjects were similar with regard to emergency room visits, hospital admissions and improvement in lung function during the follow-up. Symptom control and quality of life at visit V were not different between groups.

Table 4 shows multivariate binominal logistic regression models to evaluate whether age predicted asthma control and response to treatment during follow-up. These analyses were adjusted for emergency room visits and hospital admissions in the year before enrollment in

Table 2. Baseline characteristics of patients with asthma according to age

	Age <55 years (n = 274)	Age ≥55 years (n = 127)	p
Age at enrollment in the study, years	40 (31–47)	62 (56–67)	<0.01
Female gender	222 (81)	98 (77)	0.37
Age of asthma onset, years	8 (3–20)	22 (10–46)	<0.01
Smoking history >9 pack-years ¹	15 (6)	12 (9)	0.15
BMI >35	21 (8)	9 (7)	0.86
Duration of asthma, years	26 (17–36)	38 (16–51)	<0.01
Positive skin-prick test ²	139 (63)	50 (53)	0.10
Intensity of atopy ²	8 (0–13)	5 (0–12)	0.10
Rhinitis diagnosis	232 (85)	101 (80)	0.20
Patients with emergency room visits ³	250 (91)	105 (83)	0.01
Number of emergency room visits ³	10 (3–28)	5 (1–20)	<0.01
Patients with hospital admissions ³	82 (30)	33 (26)	0.35
Number of hospital admissions ³	0 (0–1)	0 (0–1)	0.21
FEV ₁ % predicted before treatment	69 (54–84)	59 (47–78)	<0.01

Continuous and ordinal variables are depicted as median and interquartile range. Nominal variables are depicted as n (%).

¹ Currently smoking and a smoking history of >9 pack-years were exclusion criteria.

² A total of 314 patients were evaluated for this end point.

³ In the year before enrollment.

Table 3. Unadjusted association between age and outcomes of asthma control in the follow-up

	Age <55 years (n = 274)	Age ≥55 years (n = 127)	p
Dose of inhaled corticosteroids (μg/day)	778±274	865±216	<0.01
>800 μg/day of inhaled budesonide during follow-up	219 (80)	119 (94)	<0.01
ACQ score	1.3 (1.9–2.7)	1.0 (1.7–2.7)	0.20
ACQ score >0.75 at visit V	232 (85)	102 (80)	0.28
AQLQ final score at visit V	3.9 (2.8–5.0)	4.1 (2.9–5.6)	0.11
Patients with emergency room visits ¹	126 (46)	56 (44)	0.72
Number of emergency room visits ¹	0 (0–2)	0 (0–2)	0.65
Patients with hospital admissions ¹	9 (3)	7 (6)	0.29
Number of hospital admissions ¹	0 (0–0)	0 (0–0)	0.29
Reduction in the number of emergency room visits ²	98 (72–100)	92 (0–100)	0.02
FEV ₁ % predicted at visit V	71 (60–85)	66 (51–80)	0.02
Improvement in FEV ₁ at the follow-up ³	2 (0–17)	6 (0–19)	0.18
Rhinitis severity ⁴			
No rhinitis	42 (15)	26 (20)	0.01
Mild	135 (50)	75 (60)	
Moderate/severe	95 (35)	26 (20)	

Continuous and ordinal variables are depicted as median and interquartile range, except for the dose of inhaled corticosteroids which is depicted as mean ± SD. Nominal variables are depicted as n (%).

¹ In the year of follow-up.

² Percentual reduction in comparison to the number of events reported by the patients in the year before enrollment.

³ Percentual reduction in comparison to the FEV₁ at visit I.

⁴ According to the ARIA criteria.

Table 4. Adjusted association between outcomes of asthma control and age in the follow-up

	OR (95% CI)
ACQ score >0.75 at visit V ¹	
Age <55 years	–
Age ≥55 years	0.6 (0.3–1.1)
Emergency room visits in the year of follow-up ²	
Age <55 years	–
Age ≥55 years	0.9 (0.6–1.3)
Hospital admission in the year of follow-up ³	
Age <55 years	–
Age ≥55 years	1.7 (0.6–4.7)
<90% reduction in emergency room visits during the follow-up ¹	
Age <55 years	–
Age ≥55 years	1.6 (1.1–2.4)
FEV ₁ % predicted <60% at visit V ⁴	
Age <55 years	–
Age ≥55 years	1.8 (1.1–3.3)
<10% improvement in FEV ₁ at visit V ¹	
Age <55 years	–
Age ≥55 years	1.3 (0.9–3.0)

¹ Adjusted for the dose of inhaled corticosteroids in the follow-up period and the duration of asthma.

² Adjusted for the dose of inhaled corticosteroids in the follow-up period, the number of emergency room visits before enrollment and the duration of asthma.

³ Adjusted for the dose of inhaled corticosteroids in the follow-up period, the number of hospital admissions before enrollment and the duration of asthma.

⁴ Adjusted for the dose of inhaled corticosteroids in the follow-up period, baseline lung function and the duration of asthma.

the study, baseline lung function, the dose of inhaled corticosteroids during the study and the duration of asthma. Older age at enrollment was associated with a <90% reduction in the number of emergency room visits in the follow-up (adjusted OR 1.6 and 95% CI 1.1–2.4) and FEV₁ <60% predicted at visit V (adjusted OR 1.8 and 95% CI 1.1–3.3). However, age did not predict symptoms control, emergency room visits, hospital admissions or improvement in lung function in the follow-up.

Discussion

The medical literature highlights the limited understanding of the relationship between aging and asthma [30]. Our study focused on the clinical aspects of this relationship. We did not find an association between age and hospital admissions due to asthma. Our results were different from previous surveys [15, 18, 19, 30]; we ad-

justed treatment prospectively and controlled our data for confounding factors. The sample size did not affect our conclusion. A post hoc analysis demonstrated that the power of the study for hospital admissions in the follow-up was 88% to detect a 10% difference, considering 5% of events in the case group (i.e. subjects ≥55 years old) and 15% in the control group (i.e. subjects <55 years old). The type I error probability associated with this test was 0.05.

We demonstrated that emergency room visits, ACQ scores and AQLQ scores in the follow-up were not associated with age. Our results demonstrate that age does not predict poor control of asthma symptoms when treatment is appropriate. The TENOR study in the USA found that older subjects experienced better control of asthma symptoms and a better quality of life with more aggressive care [29]. In primary care settings in Spain, age was found to have a borderline association with uncontrolled asthma [31]. A national survey in the USA found an association between older age and poor control of asthma [32]. We consider differences in treatment to be the best explanation for divergences between studies.

Our baseline data demonstrates the differences in the phenotype of asthma between old and young patients. Older subjects had a later onset of asthma and a longer duration of symptoms. Baseline and follow-up differences between groups confirm that our cut-off for age was successful in the identification of two different populations. Nevertheless, it would be advisable to validate our observations for populations consisting of the very old.

Both age groups showed an important reduction in emergency room visits during our study. This is the effect of the regular use of inhaled corticosteroids offered free of charge. Younger subjects had a more pronounced reduction in the number of emergency room visits. Future studies should investigate if the greater reduction in emergency room visits among younger subjects is due to peculiarities of airway inflammation.

Current knowledge demonstrates that lung function decreases with age in healthy subjects [9] and that asthma increases the loss of lung function over time [14]. At the end of our study, the older subjects had worse lung function. Lung function was adjusted for the physiological effect of age because it was expressed as a percentage of predicted values. These data suggest that older patients are more susceptible than younger patients to the effects of asthma on lung function.

Evidence in the literature associates aging with an increase in the rate of nonallergic rhinitis [33]. In our study,

the rate of rhinitis was not associated with age. However, older age was associated with reduced symptoms of rhinitis. Further studies should investigate if these observations are related to differences in the perception of rhinitis symptoms.

The prospective design of our study allowed reliable data in a population susceptible to memory bias. Another positive aspect was the multiple end points for estimating asthma control. Data were adjusted for the duration of asthma because this impacts on asthma outcomes [20]. Although we achieved power of >80% for the primary end point of the study, this might be insufficient for some secondary end points. Assuring free medication for patients enrolled in the study limits the external validity of the results to populations with access to asthma treatment. The predominance of women in our study was to be expected because asthma is more frequent and severe in adult females [34].

Our study enabled us to conclude that asthma at older age is different in some aspects. Older patients have a lat-

er onset and longer duration of asthma and less rhinitis symptoms. Age does not predict hospital admissions due to asthma or poor control of symptoms if proper treatment is offered. Age does predict worse lung function.

Acknowledgements

The authors thank the nurses and physicians of ProAR for their dedication in the clinical assistance for the patients and the Fundação de Amparo à Pesquisa da Bahia (FAPESB) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for their financial support. The Departments of Health of the City of Salvador and the State of Bahia, and Brazilian Ministry of Health also made financial contributions.

Disclosure Statement

All authors declare no conflicts of interest and no financial relationships with companies with an interest in the subject matter of this manuscript. The sponsors did not have a role in the design and conduct of the study.

References

- ▶ 1 Globerson A: T lymphocytes and aging. *Int Arch Allergy Immunol* 1995;107:491–497.
- ▶ 2 Franceschi C, Bonafe M, Valensin S: Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. *Vaccine* 2000;18:1717–1720.
- ▶ 3 Weksler ME: Changes in the B-cell repertoire with age. *Vaccine* 2000;18:1624–1628.
- ▶ 4 Candore G, Di Lorenzo G, Melluso M, Cigna D, Colucci AT, Modica MA, Caruso C: Gamma-interferon, interleukin-4 and interleukin-6 in vitro production in old subjects. *Autoimmunity* 1993;16:275–280.
- ▶ 5 Nyenhuis SM, Schwantes EA, Mathur SK: Characterization of leukotrienes in a pilot study of older asthma subjects. *Immun Ageing* 2010;7:8.
- ▶ 6 Mathur SK, Schwantes EA, Jarjour NN, Busse WW: Age-related changes in eosinophil function in human subjects. *Chest* 2008;133:412–419.
- ▶ 7 Barbee RA, Halonen M, Kaltenborn W, Lebowitz M, Burrows B: A longitudinal study of serum IgE in a community cohort: correlations with age, sex, smoking, and atopic status. *J Allergy Clin Immunol* 1987;79:919–927.
- ▶ 8 Burney PG, Britton JR, Chinn S, Tattersfield AE, Papacosta AO, Kelson MC, Anderson F, Corfield DR: Descriptive epidemiology of bronchial reactivity in an adult population: results from a community study. *Thorax* 1987;42:38–44.
- ▶ 9 Griffith KA, Sherrill DL, Siegel EM, Manolio TA, Bonekat HW, Enright PL: Predictors of loss of lung function in the elderly: the Cardiovascular Health Study. *Am J Respir Crit Care Med* 2001;163:61–68.
- ▶ 10 Janssens JP, Pache JC, Nicod LP: Physiological changes in respiratory function associated with ageing. *Eur Respir J* 1999;13:197–205.
- ▶ 11 Hopp RJ, Bewtra A, Nair NM, Townley RG: The effect of age on methacholine response. *J Allergy Clin Immunol* 1985;76:609–613.
- ▶ 12 Connolly MJ, Crowley JJ, Charan NB, Nielson CP, Vestal RE: Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. *Thorax* 1992;47:410–413.
- ▶ 13 Bai TR, Cooper J, Koelmeyer J, Paré PD, Weir TD: The effect of age and duration of disease on airway structure in fatal asthma. *Am J Respir Crit Care Med* 2000;162:663–669.
- ▶ 14 Lange P, Parner J, Vestbo J, Schnohr P, Jensen G: A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194–1200.
- ▶ 15 Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, Scalia MR, Akinbami LJ: National surveillance for asthma – United States, 1980–2004. *MMWR Surveill Summ* 2007;56:1–54.
- ▶ 16 de Marco R, Pesce G, Marcon A, Accordini S, Antonicelli L, Bugiani M, Casali L, Ferrari M, Nicolini G, Panico MG, Pirina P, Zanolin ME, Cerveri I, Verlato G: 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 Garin N, Olaya B, Perales J, Moneta MV, Miret M, Ayuso-Mateos JL, Haro JM: Multimorbidity patterns in a national representative sample of the Spanish adult population. *PLoS One* 2014;9:e84794.
- ▶ 18 Banerji A, Clark S, Afilalo M, Blanda MP, Cydulka RK, Camargo CA Jr: Prospective multicenter study of acute asthma in younger versus older adults presenting to the emergency department. *J Am Geriatr Soc* 2006;54:48–55.
- ▶ 19 Moorman JE, Mannino DM: Increasing US asthma mortality rates: who is really dying? *J Asthma* 2001;38:65–71.
- ▶ 20 Quadrelli SA, Roncoroni AJ: Is asthma in the elderly really different? *Respiration* 1998;65:347–353.
- ▶ 21 Global strategy for asthma management and prevention, revised 2002. <http://www.ginasthma.com>.
- ▶ 22 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR: Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–907.
- ▶ 23 Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR: Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14:32–38.

- ▶ 24 Leite M, Ponte EV, Petroni J, D'Oliveira A, Pizzichini E, Cruz AA: Evaluation of the Asthma Control Questionnaire validated for use in Brazil. *J Bras Pneumol* 2008;34:756–763.
- ▶ 25 Juniper EF, Guyatt GH, Willan A, Griffith LE: Determining the minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiology* 1994;47:81–87.
- ▶ 26 Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al: Allergic rhinitis and its impact on asthma (ARIA), 2008 update. *Allergy* 2008;63:8–160.
- 27 Medeiros M, Figueiredo JP: Sensitization to allergens in people with bronchial asthma and/or chronic rhinitis in Salvador, Bahia. *Revist Brasil Alergia Imunopatol* 1997;20:143–153.
- ▶ 28 Tsai CL, Lee WY, Hanania NA, Camargo CA Jr: Age-related differences in clinical outcomes for acute asthma in the United States, 2006–2008. *J Allergy Clin Immunol* 2012;129:1252–1258.
- ▶ 29 Slavin RG, Haselkorn T, Lee JH, Zheng B, Deniz Y, Wenzel SE: Asthma in older adults: observations from the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study. *Ann Allergy Asthma Immunol* 2006;96:406–414.
- ▶ 30 Hanania NA, King MJ, Braman SS, Saltoun C, Wise RA, Enright P, et al: Asthma in the Elderly Workshop: current understanding and future research needs – a report of a National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol* 2011;128:S4–S24.
- ▶ 31 González Barcala FJ, de la Fuente-Cid R, Alvarez-Gil R, Tafalla M, Nuevo J, Caamaño-Isorna F: Factors associated with asthma control in primary care patients: the CHAS study. *Arch Bronconeumol* 2010;46:358–363.
- ▶ 32 Talreja N, Baptist AP: Effect of age on asthma control: results from the National Asthma Survey. *Ann Allergy Asthma Immunol* 2011;106:24–29.
- ▶ 33 Yonekura S, Okamoto Y, Horiguchi S, Sakurai D, Chazono H, Hanazawa T, Okawa T, Aoki S, Konno A: Effects of aging on the natural history of seasonal allergic rhinitis in middle-aged subjects in south Chiba, Japan. *Int Arch Allergy Immunol* 2012;157:73–80.
- ▶ 34 Almqvist C, Worm M, Leynaert B: Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy* 2008;63:47–57.