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Factors Associated With Asthma Control in 121 Preschool Children

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■ Abstract

Background: Data on risk factors for uncontrolled asthma in preschool children are controversial.
Objective: This study aims to explore the association between clinical and functional parameters and the lack of asthma control in preschool children.
Methods: Children aged 3-5 years with asthma and healthy controls were recruited. A questionnaire was used to identify potential risk factors for uncontrolled asthma, as defined by the Global INitiative for Asthma criteria. Lung function and bronchial reversibility were evaluated through impulse oscillometry and spirometry. Adjusted odds ratios were estimated based on multivariable generalized additive regression models. The discriminative ability of the models was measured by the area under the receiver operating characteristic curve (AUC).
Results: The study population comprised 121 children (107 with asthma and 14 healthy controls). Fifty-three patients (50%) had uncontrolled asthma. After adjustment, the variables associated with an increased risk of lack of control were as follows: "More than 3 flare-ups in the last 12 months", "Moderate to severe rhinitis", and "Relative variation in postbronchodilator FVC and FEV_1". The AUC of the final models that included variation in FVC or FEV_1 were 0.82 and 0.81, respectively. The R5-20, R5-20%, and AX z-score values of the healthy group were lower than those of children with asthma.
Conclusion: In preschool children, clinical and functional parameters are associated with uncontrolled asthma. More studies are needed to confirm the usefulness of impulse oscillometry.

Key words: Asthma. Asthma control. Lung function tests. Preschool asthma. Risk factors.

■ Resumen

Antecedentes: Existe controversia sobre los factores de riesgo de asma no controlada en niños en edad preescolar.
Objetivo: Este estudio tiene como objetivo explorar la asociación entre los parámetros clínicos y funcionales y la falta de control del asma en niños en edad preescolar.
Métodos: Se reclutaron niños de 3-5 años con asma y controles sanos. Se utilizó un cuestionario para identificar los posibles factores de riesgo de asma no controlada según lo definido por los criterios de la GINA (*Global Initiative for Asthma* [Iniciativa global para el asma]). La función pulmonar y la reversibilidad bronquial se evaluaron mediante oscilometría de impulsos (IOS) y espirometría. Los *odds ratios* ajustados (OR) se estimaron en base a modelos de regresión aditiva generalizada multivariable. La capacidad discriminativa de los modelos se midió por el área bajo la curva de características operativas del receptor (AUC).
Resultados: Se incluyeron 121 niños, 107 de los cuales tenían asma y 14 eran controles sanos. Cincuenta y tres pacientes (50%) tenían asma no controlada. Después del ajuste, las variables asociadas con un mayor riesgo de falta de control fueron: "Más de 3 reagudizaciones en los últimos 12 meses", "rinitis moderada a grave"y "variación relativa en FVC y FEV_1 después del broncodilatador". El AUC de los modelos finales que incluyeron variación de la FVC o FEV_1 fueron 0,82 y 0,81, respectivamente. Los valores de R5-20, R5-20% y AX *z-score* del grupo sano fueron más bajos que los de los niños con asma.
Conclusión: En niños en edad preescolar, los parámetros clínicos y funcionales están asociados con el asma no controlada. Se necesitan más estudios para confirmar la utilidad del IOS.

Palabras clave: Asma. Control de asma. Pruebas de función pulmonar. Asma preescolar. Factores de riesgo.

Introduction

Asthma is one of the most common chronic diseases in children. It is estimated that, in Portugal, 1 out of every 3 to 4 preschool children has had at least 1 episode of wheezing in the previous year [1], 6.5% have current asthma [1], and approximately 4.5% [2] have physician-diagnosed asthma.

Previous studies showed that about half of all children with asthma have uncontrolled disease [3,4]. Several factors have been reported to be associated with this lack of control, including the presence of more than 1 allergic comorbidity [5], moderate to severe rhinitis [3,6], obesity [3,7], low maternal educational level [8], passive exposure to parental smoking [5], atopy [9], and poor adherence to therapy [10]. The results of these studies are contradictory, not only because of the heterogeneity of the target population, but also because of methodological differences.

In clinical practice, the assessment of asthma control among preschool children is based on subjective parameters such as symptoms, which can be over- or underestimated by parents and caregivers. Objective markers such as lung function, as recommended in children aged above 5 years, are not taken into account [11].

Assessing lung function in this age group is challenging, since spirometry, long considered the gold standard approach to ascertaining the presence of airway obstruction, requires patient collaboration [12]. Therefore, the success rate reported by centers varies between 23% and 95% and is positively associated with the increasing age of the children [13].

Impulse oscillometry (IOS) requires less collaboration and is promising in its ability to identify children with impaired lung function [14]. Several indices have been reported. These include classic parameters (resistance and reactance at 5 Hz [R5 and X5, respectively]) and more recently used parameters, namely, frequency dependence of flow resistance (ie, the difference between resistance at 5 and 20 Hz [R5-20]), the area under the reactance curve (AX), and the relative difference R5-20 (R5-20%). The more recent parameters seem to be more sensitive for the detection of small airway obstruction [15].

The use of the bronchodilator test and the choice of optimal method (spirometry or IOS) to evaluate bronchodilation in preschool children are controversial [13].

Despite assessment of control based on symptoms and lung function in asthma, studies conducted in children evaluating the association between both forms of monitoring revealed inconsistencies between them [16,17].

The aim of this study was to explore the association between clinical and functional respiratory parameters and the lack of asthma control in preschool children.

Methods

Study Design and Setting

A cross-sectional study was carried out between July 2014 and October 2016 in the Lung Function Laboratory of our Allergy Department. Healthy controls from a local nursery school were also included in the study.

Participants

We consecutively recruited children aged from 3 to 5 years with recurrent wheezing to whom lung function tests were prescribed by their physician. The healthy control group was a convenience sample based on the criteria used in the Global Lung Function Initiative (GLI) study, ie, children without a history of allergic respiratory disease, family history of asthma, or exposure to passive smoking.

We excluded children with cardiac, metabolic, or neurological conditions or orofacial deformities, children born with less than 37 weeks of gestation or with a birth weight below the 5th percentile (<2500 g), and children who were unable to undergo lung function testing. Only data from White children were analyzed.

The ethics committees of the participating centers approved this study, and patients' informed consent was obtained from parents or legal representatives after a detailed explanation of the study.

Study Procedures

Clinical questionnaire

A questionnaire was completed to record the following: demographic and anthropometric data; personal history of allergic disease including bronchial asthma; onset of symptoms; asthma control; medication and adherence to therapy; the number of flare-ups; courses of oral corticosteroids; visits to the emergency department and hospitalizations within the last 12 months; allergic rhinitis and its severity; atopic eczema; food allergy; family history of asthma and other allergic diseases; atopy; and exposure to passive smoking during pregnancy.

In addition, the questionnaire asked about exposure to passive smoking during the first year of life and the present year and humidity and pets at home. The operational definitions used in this study are presented in Table 1.

For the purpose of the present study, all children with recurrent wheeze were classified as asthmatic, considering that the current rules for predicting asthma in this age group are of modest value in clinical practice [22].

Measurement of lung function

IOS and spirometry were performed using a Jaeger Master Screen (v4.6., Jaeger Co). All tests were performed according to American Thoracic Society guidelines by a qualified technician trained in both procedures [23]. Spirometry flow volume curves were obtained using software with incentives to encourage children to conduct maximum expiratory maneuvers. To avoid possible bronchoconstrictor responses induced by forced expiratory maneuvers, IOS was always performed before spirometry. Bronchodilator medication was withdrawn during the 24 hours that preceded the respiratory tests. If the child was taking salbutamol as rescue medication or had had a respiratory infection in the previous 2 weeks, the assessment was postponed.

Bronchodilator test

A baseline function assessment was performed, followed by another 15 minutes after administration of

Table 1. Operational Definitions of the Variables Included in the Study

Variables (sources of the questions [Ref number])	Definition
Wheezing (ISAAC questionnaire [18])	Positive answer to the question "Has your child ever had wheezing or whistling in the chest at any time in the past?"
Recurrent wheeze [19]	Presence of 2 or more lifetime wheezing episodes, with at least 1 episode occurring in the last 12 months
Wheezing phenotypes (ERS Task Force) Episodic viral wheeze [11] Multiple-trigger wheeze [11]	Wheezing only during a viral cold, with absence of wheeze between episodes Wheezing that shows discrete exacerbations with viral colds, but also symptoms between episodes
Asthma flare-ups (a priori definition [20])	Presence of at least 2 of 3 symptoms (cough, difficulty breathing, or wheezing) for more than 24 hours
Asthma control (in the previous 4 weeks) (GINA criteria [11])	Classified as "controlled" and "uncontrolled"; including patients with "partly controlled" asthma in the latter group
Adherence to treatment (self-reported [21])	- "Good adherence": taking $\geq$ 80% of the doses - "Poor adherence": taking < 80% of the doses
Rhinitis (ISAAC questionnaire [18])	Positive answer to the question "Has you child ever had a problem with sneezing, or a runny, or a blocked nose when he/she DID NOT have a cold or the flu?"
Current rhinitis (ISAAC questionnaire [18])	Presence in the last 12 months of sneezing and/or itchy nose, or a runny, or blocked nose without having a cold or flu
Moderate-to-severe rhinitis (self-reported severity)	Current rhinitis that interfered "a moderate amount" or "a lot" in the child's daily activities in the past 12 months
Atopic eczema (ISAAC questionnaire [18])	Positive answer to the question "Has your child ever had an itchy rash which was coming and going for at least 6 months?"
Food allergy (Self-reported food allergy)	Positive answer to the question "Does the child have allergy to any foodstuff?"
Atopy	Positivity of the skin prick tests and/or specific IgE measurements to one of the inhalant allergens[a]

Abbreviations: ERS, European Respiratory Society; GINA, Global INitiative for Asthma; ISAAC, International Study of Asthma and Allergies in Childhood.
[a]Inhalant allergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Lepidoglyphus destructor*, cat epithelium, dog epithelium, *Alternaria alternata*, grass mix, *Parietaria judaica*, and olive tree.

the bronchodilator (salbutamol 400 µg) using a spacer. The results were expressed as the absolute value, percent predicted, and z-score [23]. All z-scores above 2 for IOS or below –2 for spirometry parameters were considered abnormal, and those above 1.64 or less than –1.64 were interpreted as bronchial obstruction.

Bronchodilator responses were evaluated through the percentage variation from baseline of the various spirometry and oscillometry parameters [23]. Moreover, meaningful cut-off points for variation in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) responses were explored [13,24].

Impulse oscillometry

The parameters R5, R5-20, R5-20%, and AX were evaluated using the reference values reported by Dencker et al [25].

Spirometry

FVC, FEV_1, $FEV_{0.75}$, and forced midexpiratory flows (FEF_{25-75}) were evaluated. The reference equations of GLI 2012 were used [26].

Statistical Analysis

Demographic and clinical characteristics were expressed using median (IQR) for continuous variables. Categorical variables were expressed as frequencies (percentages). The Shapiro-Wilk test was used to evaluate the normality of the continuous variables. The χ^2, Mann-Whitney, and Kruskal-Wallis tests were used.

Generalized additive regression models were used to study the association between lack of asthma control and lung function parameters, demographic data, and clinical characteristics. Age was modelled with splines owing to its nonlinear association with asthma control. All the variables with a P value $\leq$.25 were entered into the multivariable analysis. The models' discriminative and predictive abilities were assessed using the area under the receiver-operating characteristic curve (AUC) and calibration plots, respectively.

In the several fitted models, only one of the spirometry parameters of the response to the bronchodilator test was included to avoid collinearity problems, as these parameters are associated with each other. We also decided to exclude "Use of bronchial inhaled corticosteroids in the last 3 months"

because preventive medication had been previously adjusted to the asthma control level.

Statistical significance was set at P=.05. All data were analyzed using the Statistical Package for the Social Sciences for Windows Version 21.0 (IBM Corp.) and R (R Foundation for Statistical Computing, http://www.R-project.org.).

Results

Of the 156 children who were eligible and agreed to participate in the study, 8 were unable to conclude IOS, 25 were unable to perform baseline spirometry, and 2 were unable to complete postbronchodilator spirometry. As a result, 121 children completed the study (107 with asthma [uncontrolled in 53] and 14 healthy controls) (Figure 1).

Baseline Characteristics Across the Groups

The demographic, clinical, and social characteristics of the children are summarized in Table 2.

The median age and height of the uncontrolled and controlled asthma groups were slightly higher than those of the healthy controls (P=.011 and .040 for age; P=.014 and .038 for height, respectively). The weight of the patients with uncontrolled disease was also higher than that of the healthy controls (P=.008). There were no significant differences between the uncontrolled and controlled asthma groups

Table 2. Baseline Characteristics by Group[a]

	Uncontrolled asthma (n=53)	Controlled asthma (n=54)	Healthy controls (n=14)	P Value
Age, y	5.1[b] (4.4-5.5)	4.8[c] (4.4-5.4)	4.3 (3.6-5.1)	.014[d]
Male sex, No. (%)	27 (51)	34 (63)	7 (50)	.403
Height, cm	110.0[b] (105.0-114.0)	108.3[c] (104.0-112.3)	104.3 (100.8-107.5)	.017[d]
Height/age, z-score	0.15 (–0.47 to 0.74)	0.04 (–0.73 to 0.66)	-0.22 (–0.62 to 0.24)	.357[d]
Weight, kg	20.0[b] (17.0-21.0)	18.5 (17.0-20.0)	17.0 (16.8-18.0)	.009[d]
Weight/age, z-score	0.38 (–0.05 to 0.87)	0.34 (–0.44 to 0.96)	0.04 (–0.42 to 0.43)	.342[d]
BMI, age-adjusted z-score	0.42 (0.06-1.07)	0.49 (–0.27 to 1.20)	0.32 (–0.14 to 1.20)	.699[b]
>3 asthma flare-ups/12 mo, No. (%)	26 (49)	11 (20)	-	.002
Episodic viral wheeze, No. (%)	24 (45)	25 (46)		.916
≥1 OCS course/12 mo, No. (%)	24 (45)	26 (48)	-	.766
≥1 emergency visit/12 mo, No. (%)	29 (55)	33 (61)	-	.503
Hospitalization/12 mo, No. (%)	2 (4)	2 (4)	-	.985
ICS ≥3 mo, No. (%)	28 (53)	15 (28)	-	.008
ICS in the previous 4 wk, No. (%)	29 (55)	15 (28)	-	.005
LTRA in the previous 4 wk, No. (%)	23 (43)	20 (37)	-	.557
Adherence to preventive therapy, No. (%)	37/42 (88)	31/32 (97)	-	.170
Rhinitis, No. (%)	46 (87)	40 (74)	-	.098
Moderate-to-severe rhinitis, No. (%)	14 (26)	6 (11)	-	.042
Atopic eczema, No. (%)	25 (47)	19 (35)	-	.208
Rhinitis and eczema in the previous 12 mo, No. (%)	23 (43)	14 (26)	-	.057
Atopy, No. (%)	26 (49)	26 (48)	-	.772
Passive smoking, No. (%)	9 (17)	6 (11)	-	.382

Abbreviations: BMI, body mass index; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroids.
[a]Values are expressed as median (IQR).
[b]Significant differences between uncontrolled asthma and healthy controls.
[c]Significant differences between controlled asthma and healthy controls.
[d]Kruskal-Wallis test, remaining P values were obtained by the χ^2 test.

regarding sex and z-score for height-for-age, weight-for-age, and BMI-for-age (Table 2).

Daily inhaled corticosteroid use in the previous 4 weeks was higher in the uncontrolled asthma group. Almost half of the asthmatic children, regardless of the level of control of their disease, took at least 1 course of systemic corticosteroids in the previous year.

The prevalence of "More than 3 asthma flare-ups in the last 12 months" and "Rhinitis with limitation of daily activities" was statistically significantly higher in the
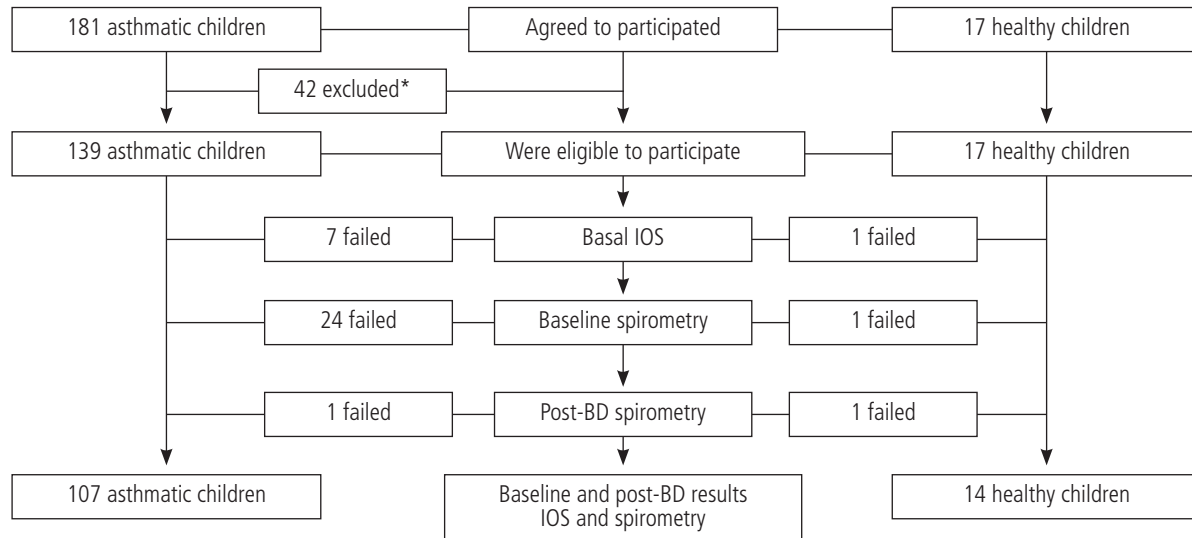
*The most common exclusion criteria were noncaucasian ethnicity, prematurity and/or low birth weight, and refusal to participate.

Figure 1. Study flowchart.

Table 3. Baseline Lung Function[a]

	Uncontrolled asthma (n=53)	Controlled asthma (n=54)	P Value[b]	Healthy controls (H) (n=14)	Asthma[c] (A) (n=107)	P Value[b] H vs A
FEV$_1$, % pred	93.2 (85.4-99.7)	95.5 (88.1-107.0)	.295	97.1 (91.2-106.2)	94.3 (86.5-106.1)	.476
FEV$_{0.75}$, % pred	91.3 (84.0-99.6)	93.9 (84.6-104.4)	.441	100.4 (90.9-107.2)	92.7 (84.1-102.3)	.149
FVC, % pred	94.4 (86.1-105.9)	99.0 (91.2-110.1)	.140	99.8 (90.4-104.7)	97.5 (89.3-107.8)	.974
FEV$_1$/FVC, % pred	97.9 (93.1-101.8)	97.1 (92.0-101.3)	.658	99.3 (96.1-100.2)	97.3 (92.4-101.5)	.427
FEF$_{25-75\%}$, % pred	70.2 (59.6-91.5)	74.0 (65.9-86.4)	.350	89.3 (62.0-109.3)	72.6 (61.8-87.5)	.079
R5, z-score	0.91 (0.27-1.56)	1.20 (0.50-2.20)	.073	0.83 (-.09-1.52)	1.07 (0.39-1.82)	.303
R5-20, z-score	2.26 (1.16-3.59)	2.62 (1.41-3.86)	.174	1.44 (1.07-2.76)	2.42 (1.34-3.85)	.101
R5-20%, z-score	2.72 (1.31-4.09)	3.01 (1.68-4.56)	.319	1.66 (1.11-2.55)	2.81 (1.61-4.30)	.029
AX, z-score	5.01 (3.13-8.20)	6.13 (3.81-10.19)	.198	3.66 (1.70-4.63)	5.95 (3.41-9.43)	.009

Abbreviations: AX, area under the reactance curve; FEF$_{25-75}$, forced expiratory flow at 25% to 75% of the FVC; FEV$_1$, forced expiratory volume in 1 second; FEV$_{0.75}$, forced expiratory volume in 0.75 seconds; FVC, forced vital capacity; R5, respiratory resistance at 5 Hz; R5-20, the difference between respiratory resistance at 5 and 20 Hz; R5-20%, the relative difference of R5-20.
[a]Values are expressed as median (IQR).
[b]Mann-Whitney test.
[c]Asthma = Uncontrolled asthma + Controlled asthma.

uncontrolled asthma group than in the controlled asthma group.

Conversely, there were no significant differences between the controlled and uncontrolled groups regarding the frequency of comorbidities, including rhinitis and/or eczema or atopy (Table 2).

Lung Function Assessment

Significant associations were found between some IOS and spirometry parameters (Supplementary Tables 1S and 2S). No significant differences were observed between the groups in spirometry and IOS at baseline (Supplementary Table 3S). However, R5-20, R5-20%, and AX were more frequently abnormal in asthmatic patients than in the healthy controls. The z-scores of the medians reported were only statistically significantly different between the asthmatic and healthy control groups for AX and R5-20% (Table 3).

After administration of the bronchodilator, the best cut-offs for ΔFEV_1 and FVC in asthmatics compared with healthy children were an increase of at least 5% and 6%, with 64% and 52% sensitivity and 69% and 82% specificity, respectively.

A higher ΔFEV_1, $FEV_{0.75}$, and FVC was found in children with uncontrolled asthma than in those with controlled asthma, although the differences were only significant for FVC. The best cut-off for uncontrolled asthma was $\Delta FVC > 6.7\%$, with 55% sensitivity and 70% specificity. We did not find a statistically significant cut-off for ΔFEV_1. However, ΔFEV_1

$\geq 15\%$ was significantly more common in the uncontrolled group (34% vs 17%, $P=.039$).

No significant differences were detected between all the groups with respect to variations in the oscillometry parameters (Table 4).

Table 5. Multivariable Analysis of Lack of Asthma Control Considering FVC (Model A) and FEV_1 (Model B)

Variables	OR estimates	95%CI	P Value[a]
Model A[b]			
Parents with asthma	0.29	(0.11-0.78)	.014
>3 flare-ups/12 mo	5.16	(1.82-14.60)	.002
Moderate-to-severe rhinitis	4.85	(1.32-17.76)	.017
FVC, Var %	1.08	(1.02-1.15)	.007
Model B[c]			
Parents with asthma	0.34	(0.13-0.88)	.027
>3 flare-ups/12 mo	4.78	(1.74-13.13)	.002
Moderate-to-severe rhinitis	5.49	(1.53-19.79)	.009
FEV_1, Var %	1.08	(1.01-1.15)	.002

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
[a]P values were obtained by generalized additive regression models
[b]Model A: with clinical characteristics and relative variation of FVC.
[c]Model B: with clinical characteristics and relative variation of FEV_1.

Table 4. Response to Bronchodilator by Group[a]

	Uncontrolled asthma (n=53)	Controlled asthma (n=54)	P Value[b]	Healthy controls (H) (n=14)	Asthma[c] (A) (n=107)	P Value[b] H vs A
FEV_1, Var %	10.2 (4.6-17.8)	7.3 (3.2-12.6)	.078	1.9 (−1.1 to 10.2)	8.8 (3.8-14.8)	.032
$FEV_{0.75}$, Var %	11.1 (6.9-17.3)	9.8 (4.9-16.3)	.380	3.8 (−1.7 to 10.5)	11.0 (5.2-17.1)	.006
FVC, Var %	7.6 (0.4-15.3)	3.9 (0.0-8.7)	.045	-0.7 (−4.1 to 2.5)	5.3 (0.0-11.3)	.007
$FEF_{25\%-75\%}$, Var %	19.4 (9.3-30.7)	23.9 (12.3-35.4)	.404	19.5 (6.7-32.3)	21.2 (10.1-31.8)	.795
R5, Var %	−18.5 (−13.2 to 24.4)	−20.0 (−14.1 to 30.4)	.418	−18.7 (−11.3 to 25.7)	−19.1 (−13.8 to 27.6)	.734
R5-20, Var %	−39.4 (−22.9 to 50.2)	−42.0 (−26.7 to 59.6)	.254	−34.0 (−23.3 to 49.7)	−40.0 (−23.8 to 53.6)	.549
R5-20%, Var %	−32.2 (−14.9--45.0)	−37.2 (−19.8 to 53.9)	.241	−23.6 (−11.0 to 40.7)	−33.6 (−17.6 to 46.1)	.230
AX, Var %	−48.7 (−30.6--56.1)	−46.2 (−34.8 to 65.6)	.276	−51.3 (−36.7 to 60.1)	−47.7 (−34.2 to 60.8)	.758

Abbreviations: AX, area under the reactance curve; FEF_{25-75}, forced expiratory flow at 25% to 75% of the FVC; FEV_1, forced expiratory volume in 1 second; $FEV_{0.75}$, forced expiratory volume in 0.75 seconds; FVC, forced vital capacity; R5, respiratory resistance at 5 Hz; R5-20, difference between respiratory resistance at 5 and 20 Hz; R5-20%, relative difference of R5-20.
[a]Values are expressed as median (IQR).
[b]Mann-Whitney test.
[c]Asthma = Uncontrolled asthma + Controlled asthma.

Association Between Clinical and Functional Parameters and Lack of Asthma Control

The results of the univariable and multivariable analyses for lack of asthma control are shown in Supplementary Table 4S and Table 5, respectively.

Based on these findings, it was possible to build 2 explanatory models for the lack of asthma control in preschool children that included clinical parameters and a spirometry criterion (inhaled bronchodilator response). After adjustment for age, the multivariable models showed that parental history of asthma decreased the odds of lack of asthma control, while children with more than 3 asthma flare-ups and moderate-severe allergic rhinitis in the previous

12 months had a 4- to 5-fold increase in the probability of lack of asthma control. Regarding the relative variation in FVC and of FEV_1, for each unit increase in these parameters, there was an 8% increase in the odds of lack of asthma control. The multivariable models had good discriminative ability to distinguish between uncontrolled and controlled asthmatic children (Figure 2).
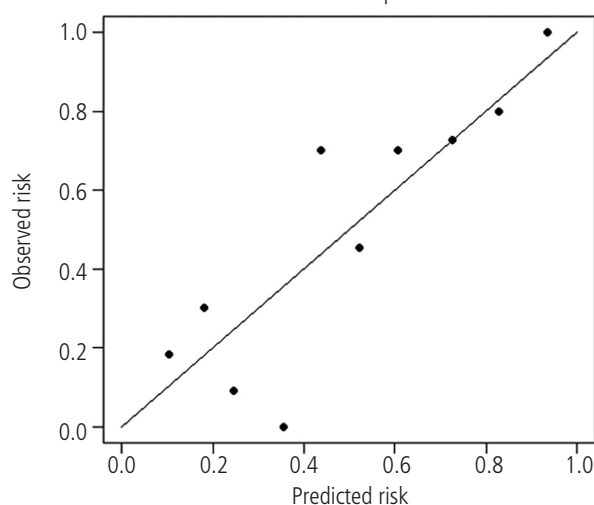
Discussion

Our results confirmed previous findings that nearly half of all children with asthma have uncontrolled disease. This fact should increase awareness of this unacceptable health problem [4],
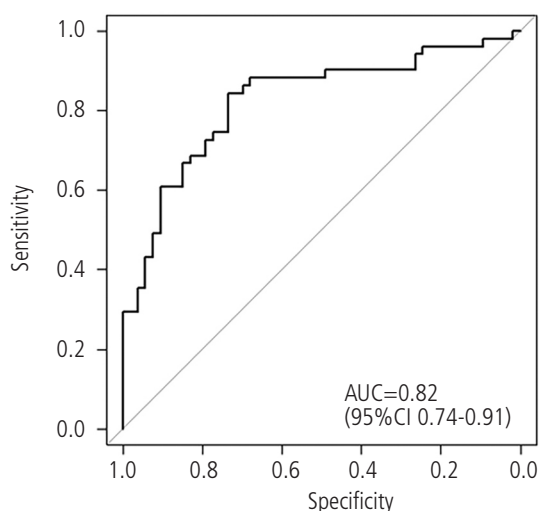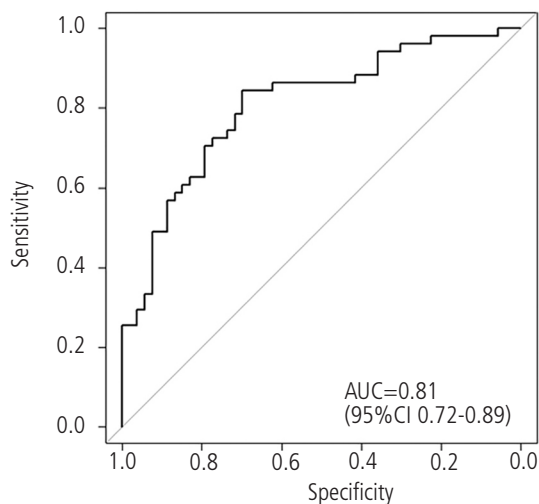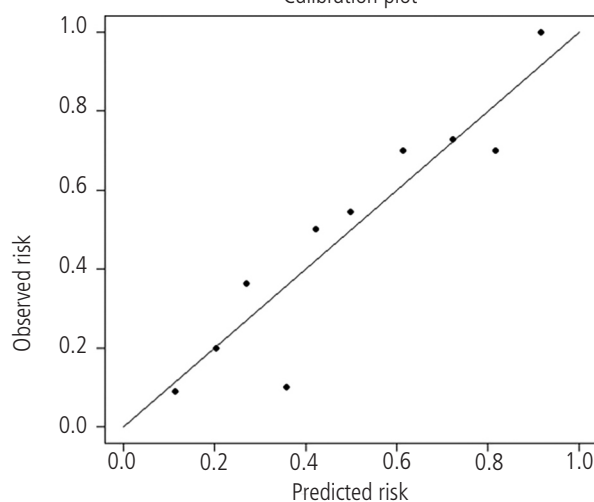

MODEL A: "Parents with asthma", "More than 3 asthma flare-ups in the last 12 months", and "Moderate-severe rhinitis" with the "Relative variation of the FVC.
MODEL B: "Parents with asthma", "More than 3 asthma flare-ups", and "Moderate-severe rhinitis" with the relative variation in FEV_1. An AUC=0.50 is obtained when a model discriminates no better than chance, and a value of 1.0 represents perfect discriminative ability. All dots lying on the 45-degree line represent perfect calibration.

Figure 2. Performance of models for absence of asthma control.

Unlike other studies [5,8], we could not find an association between the lack of asthma control and rhinitis, eczema, or both, although these conditions were more frequent in children with uncontrolled asthma. Nevertheless, moderate to severe rhinitis was associated with the lack of asthma control, as previously reported [3,6,8]. This evidence at least partially emphasizes the "unified airways concept" [27], regardless of the presence of atopy [28].

Based on our data, flare-ups appeared to be a major risk factor for uncontrolled asthma, supporting the importance of exacerbations in management, as indicated by Valero et al [29] in their review of controversies in asthma.

Long-term use of inhaled corticosteroids was more common in symptomatic asthmatic children, suggesting a probable reverse causality and weak responsiveness that might be due to the confirmed heterogeneity in the response to these drugs in this age group [30].

Surprisingly, courses of systemic corticosteroids in the previous year were common, regardless of the level of disease control, possibly owing to the increased risk of asthma exacerbations in children [31]. Similarly, hospitalizations were not associated with the level of asthma control. These findings could be explained by the definitions used for controlled asthma and flare-ups, which were based on symptoms, without taking into account systemic corticosteroid use and hospitalizations, which address a different domain, namely, risk. This result emphasizes the need for a meticulous clinical evaluation, as the assessment of different disease domains is not interchangeable [32].

Furthermore, the relationship between symptom control and flare-ups has not been sufficiently studied in young children [11,29], and all the children included in this study are more likely to have a severe form of asthma because our department is a referral center.

Parental history of asthma had a protective effect on asthma control that was not reported elsewhere. As no differences in the rate of adherence to therapy was found, this effect might be associated with genetic and epigenetic factors that could have an effect on disease severity [33] and responsiveness to preventive therapy [34].

Adherence was good because the children were included in a study and were being closely followed in a specialized center with experience caring for of asthmatic children [35]. However, given the self-reporting methodology used, over-reporting of "good adherence" may also account for this finding [10].

One of the strengths of the study is the assessment of lung function in all children with asthma—both controlled and uncontrolled—through oscillometry and spirometry. In addition, we included a healthy control group, with no known risk factors for asthma.

The high frequency of abnormal values of R5-20, R5-20%, and AX found in healthy children should alert us to possible discrepancies with the reference values used, since these were validated for Nordic populations but not for the Portuguese population. Despite this limitation, and similar to Knihtilä et al [14], R5, which is frequently reported in studies involving asthma in children, did not reveal any differences between children with controlled and uncontrolled asthma or between asthma patients and controls. However, asthma patients had a higher R5-20% and AX than those in the healthy control group, a difference that does not appear to depend on the level of asthma control, as suggested by Shi et al [15], but rather on the ability to detect airway obstruction, a common finding in asthma [17].

Our study is limited by the small number of healthy controls included and the cross-sectional design, which prevented us from determining whether IOS is more sensitive in detecting the presence of airway obstruction than spirometry [36] and whether these changes in small airway limitation were predictive of loss of asthma control [15]. The issue of the unmatched healthy group was minimized through the use of GLI 2012 predicted values or z-scores when expressing lung function results [26].

Contrary to the results of studies with adolescents and adults [37], we found no differences in various spirometry parameters, including FEV_1/FVC ratio, for the prediction of degree of asthma control, probably indicating a very weak association between the level of asthma control and lung function in this age group [17].

However, the reversibility of the spirometry parameters FEV_1 and FVC seemed to be useful in the assessment of asthma control [38]. The higher ΔFEV_1 found in the uncontrolled group than in the controlled group was in line with the findings reported by Ferrer et al [38]. Despite this, only $\Delta FEV_1 \geq 15\%$ was associated with uncontrolled asthma. We also highlight the discriminative ability of ΔFVC in response to bronchodilator inhalation, which has not previously been reported for this age group. In COPD patients, a higher ΔFVC was associated with reduced hyperinflation [39].

The 2 models aim to explain the absence of asthma control and may generate a novel complementary tool for assessing the risk of lack of asthma control in children of preschool age. We also emphasize the importance of including bronchial reversibility in this new approach. As in young children, symptoms are exclusively reported by parents. Useful additional clinical information might include the number of asthma flare-ups in the previous year, the presence and severity of rhinitis, the history of parental asthma, and the response to bronchodilator through lung function tests (spirometry or IOS).

In conclusion, an integrated clinical and functional assessment seems to be useful for asthmatic preschool children. More studies are needed to confirm the clinical and functional parameters identified in the multivariable analysis, as well as the usefulness of the IOS.

Acknowledgments

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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