Factors associated with asthma control in 121 preschool children

Short title: Asthma control in preschool children

Leiria-Pinto P[1,2], Carreiro-Martins P[1,2], Peralta I[1], Marques J[1,2], Finelli E[1], Alves C[1], Belo J[3], Alves M[4], Papoila AL[2,4], Neuparth N[1,2]

[1]Immunoallergology Department, Hospital Dona Estefânia – CHULC, EPE, Lisbon, Portugal

[2]NOVA Medical School/Comprehensive Health Research Center (CHRC), Lisbon, Portugal

[3]Centro Hospitalar Universitário Cova da Beira

[4]Centro de Investigação, Hospital Dona Estefânia – CHULC, EPE, Lisbon, Portugal

Corresponding author:

Paula Leiria Pinto

Allergy and Immunology Department, Hospital de Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central

Rua Jacinta Marto, 1169-045 Lisboa

Portugal

E-mail: pleiriapinto@gmail.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0630

Abstract

Background: There are controversial data about risk factors for uncontrolled asthma in preschool children.

Objective: This study aims to explore the association between clinical and functional parameters and the lack of asthma control in preschool children.

Methods: Children 3-5 years-old with asthma and healthy controls were recruited. A questionnaire was used to identify the potential risk factors of uncontrolled asthma as defined by GINA (Global INitiative for Asthma) criteria. Lung function and bronchial reversibility were evaluated through impulse oscillometry (IOS) and spirometry. Adjusted odds ratios (OR) 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: 121 children were included, 107 of which had asthma and 14 were healthy controls. Fifty-three patients (50%) had uncontrolled asthma. After adjustment, the variables associated with an increased risk of lack of control were: "More than 3 flare-ups in last 12 months", "moderate to severe rhinitis", "relative variation in post-bronchodilator FVC and FEV_1". The AUC of the final models that included variation of FVC or FEV_1 were 0.82 and 0.81, respectively. 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 usefulness of the IOS.

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

doi: 10.18176/jiaci.0630

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 GINA (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", "variación relativa en FVC y FEV1 después del broncodilatador". El AUC de los modelos finales que incluyeron variación de la FVC o FEV1 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

doi: 10.18176/jiaci.0630

Introduction

Background

Asthma is one of the most common chronic diseases in paediatric age and it is estimated that, in Portugal, one out of every three to four preschool children has had at least one episode of wheezing in the last year [1], 6.5% have current asthma [1] and approximately 4.5% [2] have a physician diagnosis of asthma.

Previous studies showed that about half of children with asthma have an uncontrolled disease [3,4] and several factors have been reported to be associated with this lack of control, including the presence of more than one 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]. There are discrepancies in the results of these studies, which may be due not only to the heterogeneity of the target population but also to the methodological differences.

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

Assessing lung function in this age group is known to be challenging, since spirometry, considered as the gold-standard to ascertain the presence of airways obstruction, requires patient collaboration [12]. Therefore, the success rate reported by several centres varies between 23% and 95%, showing a positive association with the increasing age of the children [13].

Impulse oscillometry (IOS), a technique that requires less collaboration, is promising in the ability to distinguish those children with lung function impairment [14]. However, several indexes have been reported, both classic – resistance and reactance at 5 Hz, R5

doi: 10.18176/jiaci.0630

and X5, respectively – and more recent – frequency dependence of flow resistance, i.e. the difference between the resistance at 5 and 20 Hz (R5-20), the area under the reactance curve (AX) and the relative difference of R5-20 (R5-20%) – that seeming, the last ones, to be more sensitive in the detection of small airway obstruction [15].

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

Despite the assessment of control based on symptoms and lung function being used in the monitoring of asthma, studies conducted in paediatric age evaluating the association between these two forms of monitoring revealed inconsistencies between the different approaches [16,17].

Objective

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 at the Lung Function Laboratory of our Allergy Department. Healthy controls from a local nursery school have also been included in the study.

Participants

Children from three to five years old with recurrent wheezing to whom lung function tests were prescribed by their physician were recruited consecutively. The healthy control group was a convenient sample based on the criteria used in the Global Lung Function

doi: 10.18176/jiaci.0630

Initiative (GLI) study, i.e. children without a history of allergic respiratory disease, family history of asthma or exposure to passive smoking.

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

The ethics committees of the involved Institutions 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 on the demographic and anthropometric data, personal history of allergic disease including bronchial asthma, onset of symptoms, asthma control, medication and adherence to therapy as well as 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, and food allergy, family history of asthma or other allergic diseases, atopy, and exposure to passive smoking during pregnancy was applied to all the subjects.

In addition, the questionnaire also asked for exposure during the first year of life and the present year to passive smoking, 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 available predicting rules to identify asthma in this age group are of modest value for applying in clinical practice [22].

doi: 10.18176/jiaci.0630

Measurement of lung function

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

Bronchodilator test

A baseline function assessment and another after 15 minutes of the administration of bronchodilator (salbutamol 400 μg) using a spacer were performed. The results were expressed using the absolute value, percentage of predictive value and z-score [23]. All Z-scores above 2 for IOS or below -2 for spirometry parameters were considered abnormal and 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 spirometric and oscillometric parameters [23]. Moreover, meaningful cut-off points for variation of FEV_1 and FVC responses were explored. [13,24].

Impulse oscillometry

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

doi: 10.18176/jiaci.0630

Spirometry

Forced vital capacity (FVC), forced expiratory volume at times intervals of 1 (FEV_1) and 0.75 ($FEV_{0.75}$) seconds and mean expiratory flows (FEF_{25-75}) were evaluated. The reference equations of GLI 2012 were used [26].

Statistical analysis

Demographics and clinical characteristics of children were described using the median and inter-quartile range (25^{th} percentile; 75^{th} percentile) for continuous variables. For categorical variables, frequencies (percentages) were presented. Shapiro Wilk test was used to evaluate the normality of the continuous variables. Nonparametric Chi-Square, Mann-Whitney and Kruskal-Wallis tests were used.

To study the association of lack of asthma control with lung function parameters, demographics and clinical characteristics, generalized additive regression models were used. The age was modelled with splines due to its non-linear association with asthma control. All the variables that attained a p-value ≤ 0.25 were considered for the multivariable analysis. Models' discriminative and predictive abilities were assessed by the area under the receiver-operating characteristic curve (AUC) and by calibration plots, respectively.

In the several fitted models only one of the spirometric 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 the "use of bronchial inhaled corticosteroids in the last three months" because preventive medication was previously adjusted to the asthma control level.

The level of significance $\alpha=0.05$ was considered. All data were analyzed using the

doi: 10.18176/jiaci.0630

Statistical Package for the Social Sciences for Windows 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.) and R (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, year = 2014, http://www.R-project.org.).

Results

Of the 156 children who were eligible and accepted to participate in the study, eight were unable to conclude IOS, 25 were unable to perform basal spirometry and two were unable to complete post-bronchodilator spirometry. As a result, 121 children completed the study, 107 of which had asthma (53 had uncontrolled asthma) and there were 14 healthy controls (fig 1).

Baseline characteristics across subject groups

The demographic, clinical and social characteristics of children were 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=0.011 and 0.040 for age; p=0.014 and 0.038 for height, respectively). The weight of the uncontrolled asthma patients was also higher than that of healthy controls (p=0.008). There are no significant differences between uncontrolled and controlled asthma groups regarding gender and z-scores for height-for-age, weight-for-age and BMI-for-age (Table 2).

Inhaled corticosteroids daily use in the previous four weeks was reported higher in the uncontrolled asthma group. It was pointed out that almost half of our asthmatic children, regardless of the level of control of their disease, took at least one systemic corticosteroid courses in the previous year.

Patients had a statistically significant higher prevalence of "more than three asthma flare-ups in the last 12 months" and "rhinitis with limitation of daily activities" reports in the uncontrolled compared to the controlled asthma group.

Conversely, there were no significant differences between groups of different levels of control 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 spirometric parameters (Tables 1S and 2S of the data supplement (suppl)). Furthermore, there were no significant differences between the groups in the spirometry and IOS at baseline (Table 3S suppl). However, R5-20, R5-20% and AX were more frequently abnormal in asthmatic patients compared to the healthy controls. Z-scores of the referred medians were only statistically significant different between asthmatic and healthy control groups for AX and R5-20 (Table 3).

After bronchodilator, the best cut-offs for ΔFEV_1 and FVC in asthmatic compared to 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 compared to those with controlled asthma, albeit these differences were only significant for FVC. The best cut-off to discriminate uncontrolled asthma was $\Delta FVC > 6.7\%$, with 55% sensitivity and 70% specificity. Regarding $\Delta FEV1$, we did not find a statistically significant cut-off. Although, $\Delta FEV_1 \geq 15\%$ was significantly more common in uncontrolled group (34% vs. 17%, p=0.039).

doi: 10.18176/jiaci.0630

In relation to variations of the oscillometry parameters, no significant differences were detected between all the groups (Table 4).

Association between clinical and functional parameters, and the lack of asthma control

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

Based on these findings, it was possible to build two explanatory models of the lack of asthma control in preschool children that included clinical parameters and a spirometric criterion of the inhaled bronchodilator response. In these multivariable models, after adjusting for age, parental history of asthma decreased the odds of lack of asthma control while children with more than three asthma flare-ups, and with moderate-severe allergic rhinitis in the last 12 months had a 4 to 5-fold increase in the odds of lack of asthma control. Regarding relative variation of FVC and of FEV_1, for each unit increase of these parameters, there was an 8% increase in the odds of lack of asthma control. These multivariable models showed a good discriminative ability to distinguish between uncontrolled and controlled asthmatic children (fig 2).

Discussion

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

Unlike other studies [5,8] , we could not find any 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 by some authors [3,6,8].

doi: 10.18176/jiaci.0630

This evidence, at least partially, emphasizes the "unified airways concept" [27], regardless the presence of atopy [28].

Based on our data, asthma flare-ups appeared as an important risk factor for uncontrolled asthma, supporting the importance of exacerbations in management of the asthma, as pointed up by Valero A et al in a review about controversies in asthma [29].

Regarding ICS, its chronic use was more common in symptomatic asthmatic children, suggesting a probable reverse causality, and weak responsiveness that might be due to the confirmed heterogeneity in ICS response, in this age group [30].

Surprisingly, reported use of systemic corticosteroid courses in the previous year was common, regardless of the level of control of the disease, which may be due to the increased risk of asthma exacerbations in children [31]. Hospitalizations were also not associated with the level of asthma control.

These findings could be explained through the used definitions for controlled asthma and flare-ups, based on symptoms, not taking into account systemic corticosteroid use and hospitalizations, that address a different domain – the risk. This result emphasizes the need for a meticulously detailed clinical evaluation, as the assessment of different disease domains are 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 included children in this study are more likely to have a severe form of asthma because our department is a referral center.

The parental history of asthma showed 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 related with genetic and epigenetic factors that could have influence in disease severity [33] and responsiveness to the preventive therapy [34].

doi: 10.18176/jiaci.0630

Concerning treatment adherence, the high rate found, can be explained by these children were included in a study, and also were being closely followed in a specialized Centre, experienced in assisting asthmatic children [35]. Another possible explanation is a possible over-reporting of "good adherence", given the self-reported methodology used in the study [10].

One of the strengths of the study is the assessment of the lung function in all children with asthma, both controlled and uncontrolled, through oscillometry and spirometry, and the inclusion of a healthy control group, without 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 the possibility of the reference values used, based on the Nordic populations not being applicable to this Portuguese sample. Despite this limitation and similarly to Knihtila et al., the R5, one of the oscillometry parameters that is frequently reported in studies involving asthma in children, did not detect any differences between children with controlled and uncontrolled asthma nor between asthma patients and the controls [14]. However, asthma patients presented higher R5-20% and AX than those in the healthy group, a difference that does not appear to be dependent on the level of asthma control, as suggested by Shi Y [15], but is probably due to the ability for detecting airway obstruction, a common finding in asthma [17].

Limitations of the study are the reduced number of healthy controls included, the cross-sectional design, that consequently did not allow the establishment of whether IOS is more sensitive in detecting the presence of airways obstruction than spirometry [36] and if these changes of small airways 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].

doi: 10.18176/jiaci.0630

Contrary to the results of the studies with adolescents and adults [37], our study, in children, found no differences in several spirometric parameters, including FEV_1/FVC ratio, to the prediction of asthma control level, probably translating a very weak association between the level of asthma control and lung function in this age group [17]. However, the reversibility of spirometric parameters FEV_1 and FVC seemed to be useful in the assessment of asthma control [38]. The higher ΔFEV_1 found in non-controlled in comparison with controlled asthmatic children, was in line with Ferrer et al [38] findings. Despite this, only a $\Delta FEV_1 \geq 15\%$ was associated with uncontrolled asthma. We also highlight the discriminative ability of ΔFVC in response to bronchodilator inhalation, not reported in literature for this age group. In COPD patients a higher ΔFVC was associated with the reduction of the hyperinflation [39].

The two models aim to explain the absence of asthma control and may bring a novel complementary tool for assessing the risk of lack of asthma control in children at preschool age, and emphasizes the importance of the inclusion of bronchial reversibility in this new approach. As in young children, symptoms are exclusively reported by parents, integration of the number of asthma flare-ups in last year, the presence and severity of rhinitis, the history of parental asthma, and the response to bronchodilator through lung function tests (spirometry or IOS) could provide additional information in the clinical setting.

In conclusion, an integrated clinical and functional assessment approach 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.

doi: 10.18176/jiaci.0630

Acknowledgments

The authors express their gratitude to the participant children, their parents, and caregivers for their essential contribution. The authors would also like to thank to Dr. Daniel Virella for the support in the design conception.

Funding

The authors declare that no funding was received for the present study.

Conflicts of interest

The authors declare that they have no conflicts of interest, financial or otherwise to this work.

References

1. Ferreira-Magalhães M, Pereira AM, Sa-Sousa A, Morais-Almeida M, Azevedo I, Azevedo LF, et al. Asthma control in children is associated with nasal symptoms, obesity, and health insurance: A nationwide survey. Pediatr Allergy Immunol. 2015;26:466–73.

2. Carreiro-Martins P, Papoila AL, Caires I, Azevedo S, Cano MM, Virella D, et al. Effect of indoor air quality of day care centers in children with different predisposition for asthma. Pediatr Allergy Immunol. 2016;27:299–306.

3. Ferreira-Magalhães M, Sá-Sousa A, Morais-Almeida M, Pité H, Azevedo LF, Azevedo MI, et al. Asthma-like symptoms, diagnostic tests, and asthma medication use in children and adolescents: A population-based nationwide survey. J Asthma. 2016;53:269-76.

4. Papwijitsil R, Pacharn P, Areegarnlert N, Veskitkul J, Visitsunthorn N, Vichyanond P, et al. Risk factors associated with poor controlled pediatric asthma in a university hospital. Asian Pacific J Allergy Immunol. 2013;31:253-7.

5. de Blic J, Boucot I, Pribil C, Robert J, Huas D, Marguet C. Control of asthma in

children: still unacceptable? A French cross-sectional study. Respir Med. 2009;103:1383–91.

6. Jung S, Lee SY, Yoon J, Cho HJ, Kim YH, Suh DI, et al. Risk factors and comorbidities associated with the allergic rhinitis phenotype in children according to the ARIA classification. Allergy, Asthma Immunol Res. 2020;12:72–85.

7. Lang JE, Fitzpatrick AM, Mauger DT, Guilbert TW, Jackson DJ, Lemanske RF, et al. Overweight/obesity status in preschool children associates with worse asthma but robust improvement on inhaled corticosteroids. J Allergy Clin Immunol. 2018;141:1459-1467.e2.

8. Sasaki M, Yoshida K, Adachi Y, Furukawa M, Itazawa T, Odajima H, et al. Factors associated with asthma control in children: Findings from a national Web-based survey. Pediatr Allergy Immunol. 2014;25:804–9.

9. Lu KD, Phipatanakul W, Perzanowski MS, Balcer-Whaley S, Matsui EC. Atopy, but not obesity is associated with asthma severity among children with persistent asthma. J Asthma. 2016;53:1033-44.

10. Klok T, Kaptein AA, Duiverman EJ, Brand PL. Long-term adherence to inhaled corticosteroids in children with asthma: Observational study. Respir Med. 2015;109:1114-9.

11. Global Initiative for Asthma: Global strategy for asthma management and prevention 2020. Available from: www.ginasthma.org

12. Gallucci M, Carbonara P, Pacilli AMG, di Palmo E, Ricci G, Nava S. Use of symptoms scores, spirometry, and other pulmonary function testing for asthma monitoring. Front Pediatr. 2019;7. DOI: 10.3389/fped.2019.00054

13. Raywood E, Lum S, Aurora P, Pike K. The bronchodilator response in preschool children: A systematic review. Pediatr Pulmonol. 2016;51:1242-50.

14. Knihtilä H, Kotaniemi-Syrjänen A, Pelkonen AS, Kalliola S, Mäkelä MJ, Malmberg LP. Sensitivity of newly defined impulse oscillometry indices in preschool children. Pediatr Pulmonol. 2017;52:598-605.

15. Shi Y, Aledia AS, Tatavoosian A V., Vijayalakshmi S, Galant SP, George SC. Relating small airways to asthma control by using impulse oscillometry in children. J Allergy Clin Immunol. 2012;129:671-8.

16. Green RJ, Klein M, Becker P, Halkas A, Lewis H, Kitchin O, et al. Disagreement among common measures of asthma control in children. Chest. 2013;143:117-22.

17. Lee MS, Kao JK, Lee CH, Tsao LY, Chiu HY, Tseng YC, et al. Correlations between pulmonary function and childhood asthma control test results in 5-11-year-old children with asthma. Pediatr Neonatol. 2014;55:218-24.

18. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): Rationale and methods. Eur Respir J. 1995;8:483-91.

19. Gern JE, Calatroni A, Jaffee KF, Lynn H, Dresen A, Cruikshank WW, et al. Patterns of immune development in urban preschoolers with recurrent wheeze and/or atopy. J Allergy Clin Immunol. 2017;140:836-844.e7.

20. Ducharme FM, Jensen ME, Mendelson MJ, Parkin PC, Desplats E, Zhang X, et al. Asthma Flare-up Diary for Young Children to monitor the severity of exacerbations. J Allergy Clin Immunol. 2016;137:744-749.e6.

21. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med. 2013;107:1481–90.

22. Savenije OEM, Kerkhof M, Koppelman GH, Postma DS. Predicting who will have asthma at school age among preschool children. J Allergy Clin Immunol. 2012;130:325–

31.

23. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HGM, Aurora P, et al. An Official American Thoracic Society/European Respiratory Society Statement: Pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007;175:1304–45.

24. Rosenfeld M, Allen J, Arets BHGM, Aurora P, Beydon N, Calogero C, et al. An official American Thoracic Society workshop report: Optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheezing in children less than 6 years of age. Ann Am Thorac Soc. 2013;10:S1-S11.

25. Dencker M, Malmberg LP, Valind S, Thorsson O, Karlsson MK, Pelkonen A, et al. Reference values for respiratory system impedance by using impulse oscillometry in children aged 2-11 years. Clin Physiol Funct Imaging. 2006;26:247–50.

26. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. Eur Respir J. 2012;40:1324–43.

27. Serrano CD, Valero A, Bartra J, Roca-Ferrer J, Muñoz-Cano R, Sánchez-López J, et al. Nasal and Bronchial Response After Nasal Allergen Challenge Nasal and Bronchial In ammation After Nasal Allergen Challenge: Assessment Using Noninvasive Methods. J Investig Allergol Clin Immunol. 2012;22:351-6.

28. Bonner K, Roberts G. Does allergy explain why some children have severe asthma? Clin Exp Allergy. 2018;48:1594–605.

29. Valero A, Olaguibel J, Delgado J, Plaza V, Álvarez F, Molina J, et al. Dilemmas and new paradigms in asthma management. J Investig Allergol Clin Immunol. 2019;29:15–23.

30. Fitzpatrick AM, Jackson DJ, Mauger DT, Boehmer SJ, Phipatanakul W, Sheehan WJ, et al. Individualized therapy for persistent asthma in young children. J Allergy Clin

Immunol. 2016;138:1608-1618.e12.

31. Mahut B, Trinquart L, Delclaux C. Influence of age on the risk of severe exacerbation and asthma control in childhood. J Asthma. 2011;48:65–8.

32. Hamelmann E, von Mutius E, Bush A, Szefler SJ. Addressing the risk domain in the long-term management of pediatric asthma. Pediatr Allergy Immunol. 2020;31:233–42.

33. Hernandez-Pacheco N, Pino-Yanes M, Flores C. Genomic predictors of asthma phenotypes and treatment response. Front Pediatr. 2019;7. DOI: 10.3389/fped.2019.00006

34. Vijverberg SJH, Farzan N, Slob EMA, Neerincx AH, Maitland-van der Zee AH. Treatment response heterogeneity in asthma: the role of genetic variation. Expert Rev Respir Med. 2018;12:55–65.

35. Ngahane BHM, Pefura-Yone EW, Mama M, Tengang B, Nganda MM, Wandji A, et al. Evaluation of factors affecting adherence to asthma controller therapy in chest clinics in a sub-Saharan African setting: A cross-sectional study. Afr Health Sci. 2016;16:194–200.

36. Knihtilä H, Kotaniemi-Syrjänen A, Mäkelä MJ, Bondestam J, Pelkonen AS, Malmberg LP. Preschool oscillometry and lung function at adolescence in asthmatic children. Pediatr Pulmonol. 2015;50:1205–13.

37. Heijkenskjöld Rentzhog C, Janson C, Berglund L, Borres MP, Nordvall L, Alving K, et al. Overall and peripheral lung function assessment by spirometry and forced oscillation technique in relation to asthma diagnosis and control. Clin Exp Allergy. 2017;47:1546–54.

38. Ferrer Galván M, Javier Alvarez Gutiérrez F, Romero Falcón A, Romero Romero B, Sáez A, Medina Gallardo JF. Is the bronchodilator test an useful tool to measure asthma control? Respir Med. 2017;126:26-31.

39. Quanjer PH, Ruppel GL, Langhammer A, Krishna A, Mertens F, Johannessen A, et al. Bronchodilator Response in FVC Is Larger and More Relevant Than in FEV1 in Severe Airflow Obstruction. Chest. 2017;151:1088–98.

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 (EVW)** [11] **Multiple-trigger wheeze (MTW)** [11]	Wheezing only at the time periods of 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 two of three symptoms (cough, difficulty breathing, or wheezing) for more than 24 hours
Asthma control (in the last 4 weeks) (GINA criteria [11])	Classified into "controlled" and "uncontrolled"; including patients with "partly controlled" asthma in the latter group
Adherence to the treatment (self-reported [21])	- Good adherence": taking ≥ 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*

ISAAC - International Study of Asthma and Allergies in Childhood; GINA - Global INitiative for Asthma;

* Inhalant allergens - Dermatophagoides pteronyssinus, Dermatophagoides farinae, Lepidoglyphus destructor, cat epithelium, dog epithelium, Alternaria alternata, mixture of grasses, Parietaria judaica and olive tree.

doi: 10.18176/jiaci.0630

Table 2. Baseline characteristics of the children, by group

	Uncontrolled asthma (n=53)	Controlled asthma (n=54)	Healthy controls (n=14)	p-value
Age, years	5.1* (4.4; 5.5)	4.8** (4.4; 5.4)	4.3 (3.6; 5.1)	0.014[a]
Male gender, n (%)	27 (51)	34 (63)	7 (50)	0.403
Height, cm	110.0* (105.0; 114.0)	108.3** (104.0; 112.3)	104.3 (100.8; 107.5)	0.017[a]
Height / age *z-score*	0.15 (-0.47; 0.74)	0.04 (-0.73; 0.66)	-0.22 (-0.62; 0.24)	0.357[a]
Weight, kg	20.0* (17.0; 21.0)	18.5 (17.0; 20.0)	17.0 (16.8; 18.0)	0.009[a]
Weight / age *z-score*	0.38 (-0.05; 0.87)	0.34 (-0.44; 0.96)	0.04 (-0.42; 0.43)	0.342[a]
BMI (age-adjusted z-score)	0.42 (0.06; 1.07)	0.49 (-0.27; 1.20)	0.32 (-0.14; 1.20)	0.699[a]
>3 asthma flare-ups/12 months, n (%)	26 (49)	11 (20)	-	0.002
Episodic Viral Wheeze, n (%)	24 (45)	25 (46)		0.916
≥1 OCS course/12 months, n (%)	24 (45)	26 (48)	-	0.766
≥1 emergency visit/12 months, n (%)	29 (55)	33 (61)	-	0.503
Hospitalization/12 months, n (%)	2 (4)	2 (4)	-	0.985
ICS ≥3 months, n (%)	28 (53)	15 (28)	-	0.008
ICS in the last 4 weeks, n (%)	29 (55)	15 (28)	-	0.005
LTRA in the last 4 weeks, n(%)	23 (43)	20 (37)	-	0.557
Adherence to preventive therapy, n (%)	37/42 (88)	31/32 (97)	-	0.170
Rhinitis, n (%)	46 (87)	40 (74)	-	0.098
Moderate to severe rhinitis, n (%)	14 (26)	6 (11)	-	0.042
Atopic eczema, n (%)	25 (47)	19 (35)	-	0.208
Rhinitis and eczema in the previous 12 months, n (%)	23 (43)	14 (26)	-	0.057
Atopy, n (%)	26 (49)	26 (48)	-	0.772
Passive smoking, n (%)	9 (17)	6 (11)	-	0.382

Values are expressed as median and inter-quartile range (P_{25}; P_{75}); BMI – body mass index; OCS – oral corticosteroids; ICS – inhaled corticosteroids; LTRA – Leukotriene receptor antagonists; [a]Kruskal–Wallis test, remaining p values were obtained by Chi-square test; *significant differences between uncontrolled asthma and healthy controls; **significant differences between controlled asthma and healthy controls.

doi: 10.18176/jiaci.0630

Table 3. Baseline lung function of the children

	Uncontrolled asthma (n=53)	**Controlled asthma (n=54)**	**p-value [a]**	**Healthy controls (H) (n=14)**	**Asthma (A) (n=107)**	**p-value [a] H vs. A**
FEV_1 % pred	93.2 (85.4; 99.7)	95.5 (88.1; 107.0)	0.295	97.1 (91.2; 106.2)	94.3 (86.5; 106.1)	0.476
$FEV_{0.75}$ % pred	91.3 (84.0; 99.6)	93.9 (84.6; 104.4)	0.441	100.4 (90.9; 107.2)	92.7 (84.1; 102.3)	0.149
FVC % pred	94.4 (86.1; 105.9)	99.0 (91.2; 110.1)	0.140	99.8 (90.4; 104.7)	97.5 (89.3; 107.8)	0.974
FEV_1/FVC % pred	97.9 (93.1; 101.8)	97.1 (92.0; 101.3)	0.658	99.3 (96.1; 100.2)	97.3 (92.4; 101.5)	0.427
$FEF_{25-75\%}$ % pred	70.2 (59.6; 91.5)	74.0 (65.9; 86.4)	0.350	89.3 (62.0; 109.3)	72.6 (61.8; 87.5)	0.079
R5 ***z-score***	0.91 (0.27; 1.56)	1.20 (0.50; 2.20)	0.073	0.83 (-.09; 1.52)	1.07 (0.39; 1.82)	0.303
R5-20 ***z-score***	2.26 (1.16; 3.59)	2.62 (1.41; 3.86)	0.174	1.44 (1.07; 2.76)	2.42 (1.34; 3.85)	0.101
R5-20% ***z-score***	2.72 (1.31; 4.09)	3.01 (1.68; 4.56)	0.319	1.66 (1.11; 2.55)	2.81 (1.61; 4.30)	0.029
AX ***z-score***	5.01 (3.13; 8.20)	6.13 (3.81; 10.19)	0.198	3.66 (1.70; 4.63)	5.95 (3.41; 9.43)	0.009

Values are expressed as median and inter-quartile range ($P_{25;}$ P_{75}); FEV_1 - forced expiratory volume in 1 s; $FEV_{0.75}$ - forced expiratory volume in 0.75 s; FVC - forced vital capacity; FEF25-75 - forced expiratory flow at 25% to 75% of the FVC; 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; AX - area under the reactance curve;.[a]Mann-Whitney test; * Asthma - Uncontrolled asthma+Controlled asthma.

doi: 10.18176/jiaci.0630

Table 4. Response to bronchodilator in different groups

	Uncontrolled asthma (n=53)	Controlled asthma (n=54)	p-value[a]	Healthy Controls (H) (n=14)	Asthma[*] (A) (n=107)	p-value[a] H vs. A
FEV_1 (Var %)	10.2 (4.6; 17.8)	7.3 (3.2; 12.6)	0.078	1.9 (-1.1; 10.2)	8.8 (3.8; 14.8)	0.032
$FEV_{0.75}$ (Var %)	11.1 (6.9; 17.3)	9.8 (4.9; 16.3)	0.380	3.8 (-1.7; 10.5)	11.0 (5.2; 17.1)	0.006
FVC (Var %)	7.6 (0.4; 15.3)	3.9 (0.0; 8.7)	0.045	-0.7 (-4.1; 2.5)	5.3 (0.0; 11.3)	0.007
$FEF_{25-75\%}$ (Var %)	19.4 (9.3; 30.7)	23.9 (12.3; 35.4)	0.404	19.5 (6.7; 32.3)	21.2 (10.1; 31.8)	0.795
R5 (Var %)	-18.5 (-13.2; -24.4)	-20.0 (-14.1; -30.4)	0.418	-18.7 (-11.3; -25.7)	-19.1 (-13.8; -27.6)	0.734
R5-20 (Var %)	-39.4 (-22.9; -50.2)	-42.0 (-26.7; -59.6)	0.254	-34.0 (-23.3; -49.7)	-40.0 (-23.8; -53.6)	0.549
R5-20% (Var %)	-32.2 (-14.9; -45.0)	-37.2 (-19.8; -53.9)	0.241	-23.6 (-11.0; -40.7)	-33.6 (-17.6; -46.1)	0.230
AX (Var %)	-48.7 (-30.6; -56.1)	-46.2 (-34.8; -65.6)	0.276	-51.3 (-36.7; -60.1)	-47.7 (-34.2; -60.8)	0.758

Values are expressed as median and inter-quartile range (P_{25}; P_{75}); FEV_1 - forced expiratory volume in 1 s; $FEV_{0.75}$ - forced expiratory volume in 0.75 s; FVC - forced vital capacity; FEF_{25-75} - forced expiratory flow at 25% to 75% of the FVC; 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; AX - area under the reactance curve; [a]Mann-Whitney test; [*]Asthma - Uncontrolled asthma+Controlled asthma.

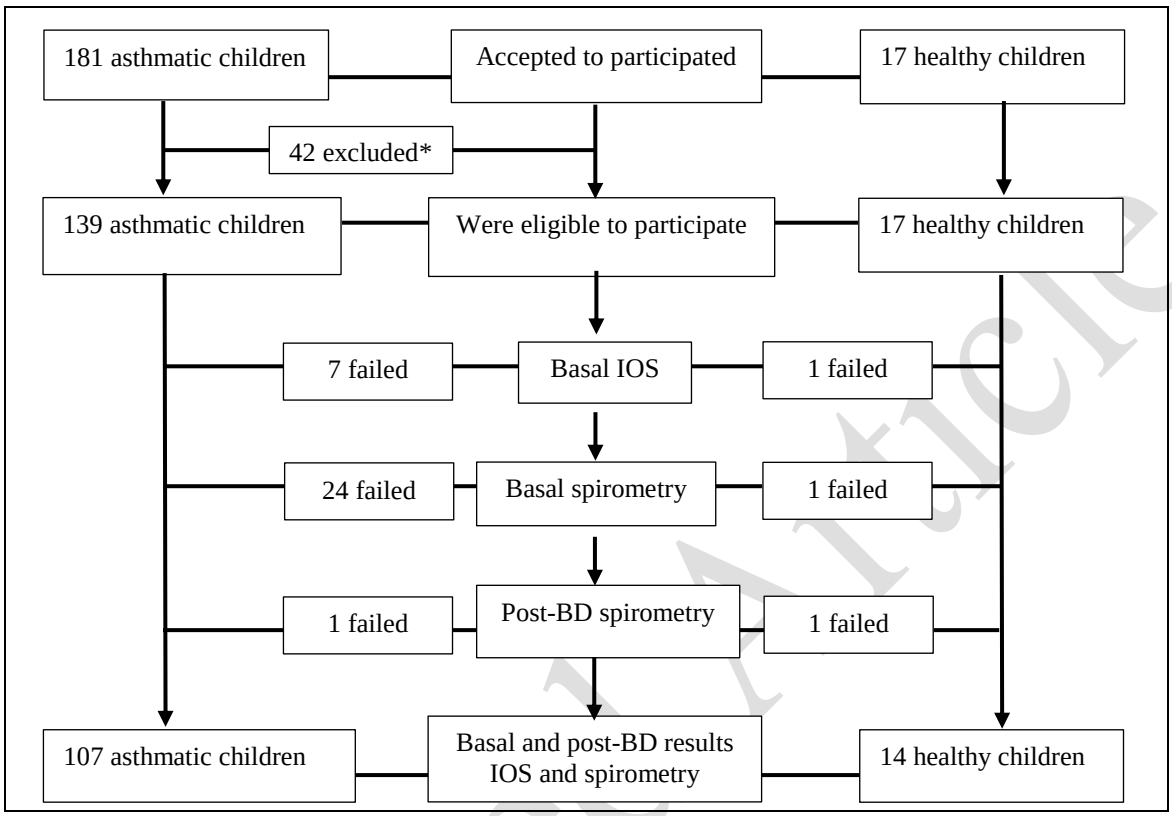
Table 5. Multivariable analysis of lack of asthma control considering FVC (Model A) and FEV_1 (Model B).

Variables	OR estimates	95% CI	p-value
Model A			
Parents with asthma	0.29	(0.11; 0.78)	0.014
>3 flare-ups/12 months	5.16	(1.82; 14.60)	0.002
Moderate to severe rhinitis	4.85	(1.32; 17.76)	0.017
FVC (Var %)	1.08	(1.02; 1.15)	0.007
Model B			
Parents with asthma	0.34	(0.13; 0.88)	0.027
>3 flare-ups/12 months	4.78	(1.74; 13.13)	0.002
Moderate to severe rhinitis	5.49	(1.53; 19.79)	0.009
FEV_1 (Var %)	1.08	(1.01; 1.15)	0.002

FEV_1 - forced expiratory volume in 1s; FVC - forced vital capacity; OR – odds ratio; CI – confidence interval; p- values were obtained by generalized additive regression models; Model A – with clinical characteristics and relative variation of FVC; Model B – with clinical characteristics and relative variation of FEV_1.

doi: 10.18176/jiaci.0630

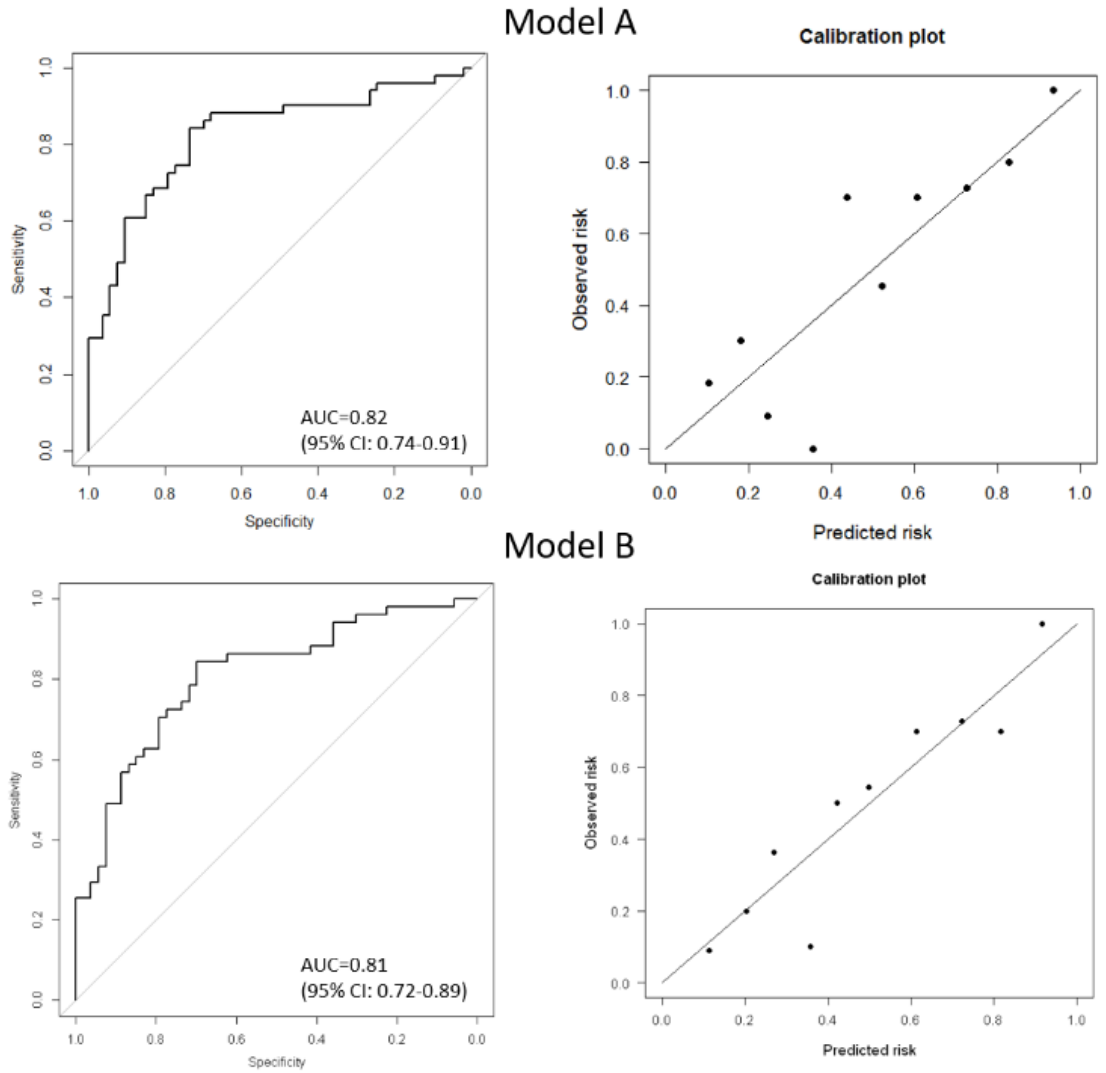
Figure 1. Study flow-chart



* More common exclusion criteria: non-caucasian ethnicity, prematurity and /or low birth weight, and refusal to participate.

* More common exclusion criteria: non-caucasian ethnicity, prematurity and /or low birth weight, and refusal to participate.

Figure 2. Lack of asthma control models' performance



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