

# Prediction of Asthma by Common Risk Factors: A Follow-up Study in Cuban Schoolchildren

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## ■ Abstract

**Objective:** To determine which common risk factors, including environmental factors, are predictors for the development of asthma in Cuban schoolchildren.

**Methods:** A longitudinal study was conducted in 1042 schoolchildren without asthma at baseline in 2 Cuban municipalities. Asthma status in 2007, diagnosed using the International Study of Asthma and Allergies in Childhood questionnaire, was related to a set of common risk factors assessed in 2003/2004 in a multivariable logistic regression model. Multiple imputation was used for missing values. The final prediction model was obtained by backward selection ( $P < .15$ ). The model's prognostic accuracy ( $R^2$ ) and discriminative ability (area under the receiver operating characteristic curve [AUC]) were assessed and internal validation by bootstrapping was performed.

**Results:** A family history of atopic diseases (odds ratio [OR], 2.19; 95% CI, 1.19-4.04), allergic sensitization (OR, 1.83; 95% CI, 0.94-3.55), municipality (OR, 0.34; 95% CI, 0.15-0.74), and use of antibiotics in the child's first year of life (OR, 1.66; 95% CI, 0.89-3.11) were predictors for asthma development. The model had an  $R^2$  of 8.0% and a moderate discriminative ability (AUC, 0.69; 95% CI, 0.60-0.78). Internal validation hardly influenced the model's performance.

**Conclusions:** Antibiotics use, genetic predisposition, and allergic sensitization were predictors of asthma in Cuban schoolchildren. Although known as common risk factors they could only partly predict asthma development. Poverty-related factors, such as low income and education, and parasitic infections, did not have an effect. Other or additional environmental predictors need to be identified, as these are potential targets for prevention and control of childhood asthma in affluent as well as nonaffluent countries.

**Key words:** Asthma. Cuba. Prediction model. Predictors. Risk factors. Schoolchildren.

## ■ Resumen

**Objetivo:** Determinar cuáles de los factores de riesgo habituales, incluyendo factores ambientales, tienen capacidad predictiva para el desarrollo de asma en población escolar cubana.

**Métodos:** Estudio longitudinal realizado en una muestra de 1042 escolares cubanos, sin asma al comienzo del estudio, residentes en dos municipios. La presencia de asma en el año 2007, diagnosticada mediante el cuestionario ISAAC, se relacionó con la presencia de factores de riesgo habituales, presentes al inicio del estudio en los años 2003-2004 mediante un modelo de regresión logística multivariable. Se utilizó el criterio de imputación múltiple para los valores no registrados. El modelo final predictivo se obtuvo mediante selección retrógrada. Se evaluaron la capacidad predictiva del modelo ( $R$  cuadrada) y capacidad discriminante (Área bajo la curva ROC) y se realizó una validación interna mediante la técnica de muestreo "bootstrapping".

**Resultados:** Una historia familiar de enfermedades alérgicas (OR 2.19, 95%CI 1.19-4.04), la presencia de sensibilización frente a alérgenos comunes (OR 1.83, 95%CI 0.94-3.55), el municipio de residencia (OR 0.34, 95%CI 0.15-0.74), y el uso de antibióticos en el primer año de vida del niño (OR 1.66, 95%CI 0.89-3.11) fueron todos ellos factores predictivos del desarrollo de asma. La  $R$  cuadrada del modelo fue el 8,0% y poseía una moderada capacidad discriminativa (AUC 0.69, 95%CI 0.60-0.78). La validez interna influencia notablemente el funcionamiento del modelo.

**Conclusiones:** Los antecedentes familiares de enfermedad alérgica, la sensibilización frente a alérgenos comunes y el uso de antibióticos en el primer año de vida fueron factores predictivos de la aparición de asma en los escolares cubanos, si bien solo fueron capaces de explicar en parte esta predisposición. Otros factores relacionados con un nivel socioeconómico bajo, como un nivel de ingresos o de educación bajos o las infecciones por parásitos, no tuvieron ningún efecto. Se hace por tanto necesario, identificar otros o adicionales factores predictivos ambientales, que sean también dianas de programas de prevención y control de la enfermedad asmática tanto en países de niveles económicos altos o bajos.

**Palabras clave:** Asma. Cuba. Modelos Predictivos. Factores predictivos. Factores de riesgo. Escolares.

## Introduction

Childhood asthma is an important public health problem worldwide [1] and its prevalence has increased in the past decades [2]. Risk factors include genetic, environmental, and host factors. Common risk factors are sex, socioeconomic status, and (prenatal) exposure to tobacco smoke [3], exposure to air pollution [4], diet [3,5], climate [4,6], infection [3,7], obesity [8], antibiotic use, allergic sensitization, lung function, breastfeeding, family structure, and exposure to (furry) animals [3], a family history of atopic diseases [3,9], low birth weight [10], premature birth [11], and day-care attendance [12].

To date, most research has focused on the association of asthma with single risk factors. Prediction models based on a set of factors are scarce and have so far only been performed in affluent countries [13,14]. In developing countries other or additional factors, such as socioeconomic status [15] and parasitic infections [16], may be influential.

A family history of atopic diseases or genetic predisposition is known to be an important factor in the etiology of asthma [3]. However, genetics alone cannot explain the global rise in asthma prevalence in the last decades. Environmental factors, alone and by interacting with genes, are also assumed to be responsible [3,17]. Unlike genetic and host factors, environmental factors can be modified, thus making them potential targets for intervention and prevention strategies. Using a prediction model, we aimed to identify which environmental and other common risk factors contribute to the development of asthma in Cuban schoolchildren.

## Methods

### Study Population and Design

A longitudinal study was performed in primary schoolchildren in San Juan y Martínez (SJM) and Fomento, 2 municipalities in Cuba. Using Survey select, SAS version 8.0 (SAS Institute Inc.), primary schools were selected randomly after double stratification for municipality (SJM or Fomento) and area of residence (urban or rural), and all the children from each school were included. The inclusion period was December 2003 to May 2004. In SJM, there were 398 children: 207 (52%) from 2 urban schools and 191 (48%) from 3 rural schools. In Fomento, there were 923 children: 483 (52%) from 2 urban schools and 440 (48%) from 12 rural primary schools. The children were followed up between February and May 2007. Further details have been described elsewhere [18,19]. Of these 1321 children only those who did not have asthma at the start of the study (n=1042) were used for the development of the prediction model.

Informed written consent was obtained from the parents or guardians of each participating child. The study was performed within the framework of an institutional collaboration between the Institute of Tropical Medicine (ITM) in Antwerp, Belgium, the National Institute for Hygiene, Epidemiology and Microbiology (INHEM), and the Pedro Kuri Institute (IPK) of Tropical Medicine in Havana, Cuba. Approval was obtained from the ethics committees of these institutes.

### Asthma Outcome

At baseline and in 2007 a parent or guardian of each child was interviewed using the standard Spanish version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [20]. Asthma was defined as an affirmative answer to the second ISAAC core asthma question on current wheeze ("Has your child had wheezing or whistling in the chest in the last 12 months?") [21].

### Potential Predictors

Potential predictors of asthma, based on previous literature, were assessed in 2003 and 2004. Antibiotic use during the child's first year of life, furry pet ownership inside the house during the child's first year of life, smoking by the mother during the child's early life (pregnancy and/or first year of life), current smoking inside the child's home, preschool day-care attendance, low birth weight (<2500 g), premature birth (<37 weeks of gestational age), crowding (>2 persons/bedroom), sibship ( $\geq 1$  siblings), area of residence (rural vs urban), municipality (SJM vs Fomento), educational level of the mother (<high school vs  $\geq$ high school), monthly household income ( $\leq 250$  pesos ( $\approx 7$  euro)/mo vs >250 pesos/mo), breastfeeding for at least 6 months, infection with soil-transmitted helminths (STHs, ie, *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm), and infection with protozoa were considered as potential environmental predictors. Potential genetic and host factors, ie, age (continuous), sex, allergic sensitization (atopy), and a family history of atopic diseases (in mother, father and/or sibling) as proxy for genetic predisposition, were also taken into account. Apart from infection and allergic sensitization, information on the predictors was collected by means of a structured parental questionnaire.

One fresh stool sample was collected from each child and used for one direct smear and two 25-mg Kato-Katz examinations [22], with recording of all parasites detected. Infection with STHs was defined as the presence of STH eggs detected by either of the methods. Protozoa infection was defined as the presence of any protozoa cysts and/or trophozoites by direct smear.

Skin prick testing for allergic sensitization was performed using extracts of 7 allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat dander, mixed tree, mixed grass, *Alternaria alternata*, and cockroach) produced by ALK. Histamine (10 mg/mL) was used as a positive control and allergen diluent as a negative control. The extracts and controls were placed on the volar side of the left forearm using separate ALK lancets. Skin response was measured after 15 minutes; a wheal of 3 mm or larger in the absence of significant reactivity to the diluent control and a positive reaction to histamine was considered a positive reaction. Allergic sensitization was defined as a positive reaction to at least 1 of the 7 allergens applied.

### Statistical Analysis

For the development of the prediction model we followed the guidelines of Harrell [23], Royston et al [24], and Altman et al [25], ie, backward regression, with assessment of

model performance and validation. Performance and validation are important to determine to which extent a model reflects reality and how it will perform in other populations.

To avoid bias due to missing values that could result from a complete case analysis, multiple imputation was applied to account for the missing values [26]. This resulted in 5 multiple imputed data sets. Univariate logistic regression analyses were conducted to assess the relationship of each potential predictor with the outcome measure separately ( $P < .05$ ). Subsequently, all potential predictors were entered into a multivariable logistic regression model. To obtain the final model the prognostic variables were selected taking into account all 5 imputed data sets, ie, by applying Rubin's Rules [27] in combination with backward regression analysis. For the selection of variables a  $P$  value of less than .15 was used. We chose this less strict  $P$  value as using a value of .05 can lead to selection bias and optimism as a result of overfitting, meaning that the model would be too closely adapted to the data [24].

The prognostic accuracy of the models was estimated by their model-fit (calibration) using the Hosmer-Lemeshow (H-L) test statistic and the explained variation ( $R^2$ ). The discriminative ability of the model, ie, the probability of distinguishing between asthma-positive and -negative children, was estimated by assessing the area under the receiver operating characteristic curve (AUC) with 0.5 indicating a model with no discriminating power and 1.0 a perfectly discriminating model. The final model was internally validated by bootstrapping techniques. We used 200 bootstrap samples. Optimism in regression coefficients due to overfitting was estimated by the calibration slope of the observed proportions plotted against the predicted probabilities, with a slope of 1.0 indicating no optimism by overfitting. Accuracy measures were estimated in each imputed dataset and subsequently averaged (except for the H-L test statistic). SPSS Statistics 17.0 for Windows (SPSS Inc.) was used for all analyses except for the model validation, which was performed with R version 2.10 (R Foundation for Statistical Computing) [28].

## Results

The 1042 children from the baseline study population were aged 4 to 14 years (mean, 8.6 years), consisted of 531 boys (51.0%) and 511 girls (49.0%); 492 children (47.2%) lived in a rural area, and 550 (52.8%) in an urban area. The monthly family income was 250 pesos/mo or less in 558 children (54.0%), and for 551 children (53.2%) the mother had an educational level of less than high school. Of the 1036 children who provided stool samples, 101 (9.7%) were positive for *T trichiura*, 60 (5.8%) for *A lumbricooides*, 100 (9.7%) for hookworm, and 462 (44.6%) for protozoa infection.

In 2007, 890 (85.4%) children of the selected cohort were traced. The main reason for loss to follow-up was that they had moved outside the study area. This population was then aged 7 to 17 years (mean, 11.4 years), and consisted of 456 boys (51.2%) and 434 girls (48.8%). The response rate to the questionnaires was 90.0% ( $n=801$ ). Asthma was reported in 31 children (3.9%). Table 1 shows the characteristics of the study

Table 1. Characteristics of the Study Population With and Without Asthma<sup>a</sup>

	Asthma (n=31)	No Asthma (n=770)
Age, median (IQR), y	9 (2)	8 (3)
Female sex	19 (61.3)	378 (49.1)
Municipality (Fomento)	20 (64.5)	627 (81.4)
Area of residence (urban)	20 (64.5)	429 (55.7)
Education of mother ( $\geq$ grade 12)	15 (48.4)	366 (47.9)
Income ( $>250$ peso/mo)	15 (48.4)	362 (47.4)
<i>Trichuris trichiura</i> infection	3 (9.7)	67 (8.7)
<i>Ascaris lumbricooides</i> infection	3 (9.7)	32 (4.2)
Hookworm infection	2 (6.5)	76 (9.9)
Any protozoa infection	13 (41.9)	353 (46.0)
Low birth weight	7 (22.6)	71 (9.3)
Premature birth	3 (9.7)	47 (6.1)
Breastfeeding ( $\geq 6$ mo)	10 (32.3)	383 (49.9)
Antibiotics use during child's first year of life	20 (64.5)	329 (43.2)
Family history of atopic diseases	20 (64.5)	303 (39.5)
Mother smoked during child's early life	6 (19.4)	99 (12.9)
Current smoking inside child's house	19 (61.3)	364 (47.3)
Furry pet ownership inside the house during child's first year of life	14 (45.2)	417 (54.3)
Preschool day-care attendance	6 (19.4)	133 (17.3)
Crowding ( $>2$ persons/bedroom)	8 (25.8)	221 (28.9)
Sibship ( $\geq 1$ siblings)	26 (83.9)	643 (82.3)
Allergic sensitization	11 (35.5)	141 (18.3)

<sup>a</sup> Values are extracted from the complete, nonimputed cases ( $n=801$ ) and are expressed as number (%) of patients, unless otherwise specified; asthma was assessed in 2007 and the characteristics in 2003/2004.

population according to asthma outcome. In children with asthma, low birth weight, antibiotic use in their first year of life, a family history of atopic disease, and allergic sensitization were more prevalent than in those without.

From the 1042 children at baseline complete data on asthma status in 2007 were available for 801 children (76.9%). Missing data in individual predictors from 2003/2004 ranged from 0% to 1.4%. Children with missing data on asthma status significantly differed from those with complete data regarding age, municipality, area of residence, and infection status. For this reason, multiple imputation was applied to account for missing values. Thus our results pertain to the imputed dataset, including all 1042 children.

### Univariate and Multivariable Analysis

Antibiotic use in the child's first year of life, a family history of atopic diseases, and municipality were univariate predictors of the development of asthma (Table 2).

In the multivariable logistic regression analysis, antibiotic use in the child's first year of life, a family history of atopic diseases, allergic sensitization, and municipality were predictors of the development of asthma (Table 3). The H-L test statistic was not significant in any of the imputed datasets, indicating that the overall model fit was good. The model explained 8.0% of the variation in the outcome, and

Table 2. Univariate Associations of Possible Predictors With Asthma

	Odds Ratio (95%CI)	P Value
Age	1.01 (0.87-1.18)	.877
Female sex	1.14 (0.59-2.19)	.686
Municipality (Fomento)	0.38 (0.18-0.81)	.16
Area of residence (urban)	1.16 (0.60-2.26)	.65
Education mother ( $\geq$ grade 12)	0.95 (0.46-1.95)	.886
Income ( $>$ 250 peso/month)	0.98 (0.47-2.03)	.954
<i>Trichuris trichiura</i> infection	1.13 (0.37-3.46)	.819
<i>Ascaris lumbricoides</i> infection	1.83 (0.68-4.95)	.227
Hookworm infection	0.74 (0.24-2.31)	.62
Any protozoa infection	0.81 (0.45-1.44)	.465
Low birth weight	1.67 (0.66-4.25)	.271
Premature birth	1.04 (0.35-3.13)	.94
Breast feeding ( $\geq$ 6 mo)	0.62 (0.26-1.47)	.256
Antibiotics use during child's first years of life	1.92 (1.03-3.56)	.41
Family history of atopic diseases	2.12 (1.13-3.99)	.21
Mother smoked during child's early life	1.40 (0.56-3.45)	.455
Current smoking inside child's house	1.27 (0.58-2.76)	.531
Furry pet ownership inside the house during child's first year of life	0.80 (0.37-1.71)	.541
Preschool day-care attendance	0.89 (0.39-2.00)	.769
Crowding ( $>$ 2 persons/bedroom)	1.07 (0.53-2.16)	.851
Sibship ( $\geq$ 1 siblings)	1.16 (0.55-2.46)	.7
Allergic sensitization	1.40 (0.74-2.67)	.3

<sup>a</sup> Values extracted from imputed cases (n=1042); asthma was assessed in 2007 and the characteristics in 2003/2004.

Table 3. Multivariable Prediction model for Asthma

	Odds Ratio (95%CI)	P Value
Antibiotics use during child's first year of life	1.66 (0.89-3.11)	.108
Allergic sensitization	1.83 (0.94-3.55)	.075
Family history of atopic diseases	2.19 (1.19-4.04)	.013
Municipality (Fomento)	0.34 (0.15-0.74)	.009

<sup>a</sup> Values extracted from imputed cases (n=1042); asthma was assessed in 2007 and the characteristics in 2003/2004.

the AUC of the model was 0.69 (95%CI, 0.60-0.78). After internal validation the R<sup>2</sup> reduced to 6.3% and the AUC to 0.67. The calibration slope was 0.92 indicating little optimism or overfitting of the regression coefficients.

## Discussion

To date, few studies have considered multiple risk factors in prediction models and those that have been performed in populations from affluent countries. We studied the contribution of a set of environmental and other common risk factors to asthma development in a population of Cuban

schoolchildren in a 3-year follow-up study. We found that antibiotic use during the child's first year of life, municipality, a family history of atopic diseases, and allergic sensitization were the most important predictors for the development of childhood asthma in Cuba. Poverty-related factors, such as low income and education, and parasitic infections, did not have any effect. The performance of the prognostic model was moderate.

Some limitations should be remarked on. The ISAAC questionnaire is a well-established, widely used and validated questionnaire for the measurement of asthma in childhood populations [20]. Nevertheless, some information and recall bias may have occurred using this or other questionnaires in the study. Although a low incidence of asthma is normal in school-aged children [29,30], this limited the power of our study. Therefore, we cannot rule out that we missed some weaker predictors. We are aware that the use of retrospective data to assess most predictors weakens our findings to some extent. Prospective longitudinal data recorded in real time and before the outcome of interest would be preferable, but they were not available. Nevertheless, our study provided a unique opportunity to explore, for an important childhood disease, many common predictors simultaneously in a developing country using a prediction model. We were not able to validate the model in an external dataset, which would have been the best approach. However, with our internal validation, we were able to obtain a realistic indication about how the model would perform in other populations. The rule of thumb in logistic models to consider at least 10 events per predictor variable (EPV) was not met in our model. However, Vittinghoff and McCulloch [31] elegantly showed in a large simulation study that this rule can be relaxed and that with less than 10 EPV only little bias in coefficient estimates can be expected. Furthermore, our model validation by bootstrapping, a recommended method in models with less than 10 EPV [31], showed little bias of our estimates. Finally, although we used multiple imputation to account for missing values, we cannot totally exclude bias due to loss to follow-up.

To our knowledge only 2 other prediction models for asthma development have been developed as suggested by Harrell [23], Royston et al [24], and Altman et al [25], namely those by Balemans et al [13] and Caudri et al [14]. Both studies concerned Dutch populations and had a clinical focus, which influenced the predictors investigated. Nevertheless, like us, they also addressed some genetic, host, and environmental predictors.

The role of genetic predisposition and allergic sensitization in asthma development is well known [3] and was confirmed by our study and the Dutch studies [13,14]. Childhood asthma is more common in boys, as reflected by the study of Caudri et al [14], while in adolescence this trend reverses and asthma becomes more common in females, as shown by Balemans et al [13]. This time-dependent effect of sex on asthma may explain why sex was not a predictor in our study as our Cuban study population consisted of both children and adolescents.

Among the environmental predictors that were considered in all 3 studies, ie, sibship, breastfeeding, infection, smoking, birth weight, day-care attendance, pet ownership, and antibiotic use, we found only the last factor to be of importance.

Antibiotic use has been positively associated with asthma although the mechanism involved is not clear. It has been suggested that antibiotics could influence the immune system by changing the bowel flora and as such cause asthma [3]. Furthermore, they could be a proxy for the number of early-life (viral) infections [3]. Some of these infections, such as viral respiratory tract infections, are generally associated with increased asthma risk [3,32]. Respiratory tract infections increase asthma risk and were identified as predictors of asthma by Balemans et al [13] and Caudri et al [14]. Passive smoking exposure is in general associated with an increased risk of asthma [3], but this was only confirmed by Balemans et al and not by Caudri et al or by our study. Apart from differences in study populations, the inconsistencies in study results may also be due to differences in asthma definitions, the age of assessing predictors and outcome, and the time between measurements.

Poverty-related factors, such as low income and education, and parasitic infections, did not have a significant effect on the development of asthma in Cuban children. So far the association between socioeconomic status and asthma prevalence has been inconclusive [3]. Based on the hygiene hypothesis, an inverse association is generally assumed between STHs and asthma [33], although helminth-specific effects have been reported recently [34]. However, our prediction model suggests that STH infections do not play an important role in the development of asthma in Cuban schoolchildren. This may be due to the relatively low prevalence of STH infections in these children or to the timing of infection assessment, as infections occurring during infancy appear to be more important than those occurring later in childhood [35].

Studies assessing risk factors concurrently have been performed in developing countries [36-38], but not according to the approach of Harrell [23], Royston et al [24], or Altman et al [25]. In line with our study, these studies suggest that a family history of atopic diseases and allergic sensitization are predictors of asthma development [36,37]. Environmental factors found included smoking exposure [36], education [36, 38], breastfeeding [38], siblings [38], and day-care attendance [37]. Typical poverty-related factors were not studied.

To date, all the prediction models for asthma, including ours, have shown only moderate performance. While a large range of common risk factors have been assessed, they still appear to be insufficient to explain the development of a multifactorial disease such as asthma. Other (environmental) factors would appear to be of importance. For example, concurrently with the rise of asthma in the last decades, diets have changed considerably, particularly in westernized countries [5]. Air pollution has been positively associated with asthma, and people in urban areas, where air pollution is greater, tend to have more asthma than those in rural areas [4]. Climate, by means of temperature and humidity, for example, and subsequently climate change can also influence pollution and pollen levels in the air and consequently induce asthma [4]. Municipality, an independent predictor in our study, could be a proxy for the above factors, but also for other unidentified environmental factors.

In conclusion, the role of genetic predisposition and allergic sensitization in asthma development in a nonaffluent country was confirmed by our study. Antibiotic use during early life

was the only important environmental predictor for asthma development in Cuban schoolchildren. Poverty-related factors, such as low income and education, and parasitic infections, do not seem to have an effect. More prediction models should be developed, taking into account additional environmental factors, to identify important predictors that can be targeted for prevention and control of asthma in affluent as well as nonaffluent countries.

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## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Previous Presentation

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