Published in final edited form as:

Allergy. 2010 February ; 65(2): 256–263. doi:10.1111/j.1398-9995.2009.02159.x.

Risk Factors for Allergic Rhinitis in Costa Rican Children with Asthma

Supinda Bunyavanich, MD, M.Phil^{1,2,5}, Manuel E. Soto-Quiros, MD, PhD⁶, Lydiana Avila, MD⁶, Daniel Laskey, BS¹, Jody M. Senter, BS¹, and Juan C. Celedón, MD, Dr. PH^{1,3,4,5}

¹ Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

² Division of Rheumatology, Immunology, and Allergy, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

³ Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

⁴ Center for Genomic Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

⁵ Harvard Medical School, Boston, Massachusetts

⁶ Division of Pediatric Pulmonology, Hospital Nacional de Niños, San José, Costa Rica

Abstract

Background—Risk factors for allergic rhinitis (AR) in asthmatics are likely distinct from those for AR or asthma alone. We sought to identify clinical and environmental risk factors for AR in children with asthma.

Methods—We performed a cross-sectional study of 616 Costa Rican children aged 6–14 years with asthma. Candidate risk factors were drawn from questionnaire data, spirometry, methacholine challenge testing, skin testing, and serology. Two outcome measures, skin test reaction (STR)-positive AR and physician-diagnosed AR, were examined by logistic regression.

Results—STR-positive AR had high prevalence (80%) in Costa Rican children with asthma, and its independent risk factors were nasal symptoms after exposure to dust or mold, parental history of AR, older age at asthma onset, oral steroid use in the past year, eosinophilia, and positive IgEs to dust mite and cockroach. Physician-diagnosed AR had lower prevalence (27%), and its independent risk factors were nasal symptoms after pollen exposure, STR to tree pollens, a parental history of AR, inhaled steroid and short-acting β_2 agonist use in the past year, household mold/mildew, and fewer older siblings. A physician's diagnosis was only 29.5% sensitive for STR-positive AR.

Conclusions—Risk factors for AR in children with asthma depend on the definition of AR. Indoor allergens drive risk for STR-positive AR. Outdoor allergens and home environmental conditions are risk factors for physician-diagnosed AR. We propose that children with asthma in Costa Rica and other Latin American nations undergo limited skin testing or specific IgE measurements to reduce the current under-diagnosis of AR.

Keywords

allergic rhinitis; asthma; physician diagnosis; risk factor; skin test

INTRODUCTION

Asthma is the most common chronic disease of childhood and has extensive impact on child health and development (1). Allergic rhinitis (AR) contributes to asthma severity and increases risk for hospitalizations and emergency department visits in children with asthma (2,3). Treatment of comorbid AR may reduce the odds of asthma-related healthcare by up to 80% (4).

Based on their frequent coexistence and shared pathophysiologic features, asthma and AR are thought to result from inflammation of a continuous respiratory tract (5). Various mechanisms may account for AR in asthmatics, but it remains unclear why only some asthmatics develop AR (6). In studies using the same questionnaire-based protocol (International Study of Asthma and Allergies in Childhood), the prevalence of AR in asthmatics varies widely, from 4.1% in Turkey (7) and 5.1% in Nigeria (8) to 20.1% in Thailand (9) and 53–63% in the UK (10).

Risk factors for AR in asthmatics are likely distinct from those for AR or asthma alone, since not all asthmatics develop AR and not all with AR have asthma. Identification of risk factors for AR in asthmatics could facilitate its diagnosis and treatment, which could decrease asthma morbidity. The aim of this study was to identify clinical and environmental factors that determine risk for AR in children with asthma.

METHODS

Study Population

Participants included 616 children ages 6–14 years with asthma recruited between February 2001 and March 2006 as part of the Genetics of Asthma in Costa Rica study. This population is a genetic isolate of mixed Spanish and Amerindian descent with one of the world's highest rates of asthma (27.4% of children aged 6–7 years (11)). Questionnaires were sent to the parents of 13,125 schoolchildren enrolled in 113 schools in Costa Rica. Of the 7,282 children whose parents returned questionnaires, 2,714 had asthma (defined as physician-diagnosed asthma and ≥ 2 respiratory symptoms or recurrent asthma attacks in the past year). Of these 2,714 children, 616 (22.7%) had high probability of having ≥ 6 great-grandparents born in the Central Valley of Costa Rica (to ensure descent from the founder population), and were willing to participate with their parents. There were no significant differences in gender or grade in school between participants and non-participants. This study was approved by the Institutional Review Boards of the Hospital Nacional de Niños (San Jose, Costa Rica) and Brigham and Women's Hospital (Boston, MA).

Procedures

After obtaining written informed consent from the parents of participating children, the following procedures were implemented: a) administration of a questionnaire modified from one used by the Collaborative Study on the Genetics of Asthma (12). The questionnaire addressed general and respiratory health, family history, and environmental characteristics; b) spirometry; c) methacholine challenge testing; d) allergy skin testing; and e) blood sample collection for measurement of peripheral blood eosinophils, serum total IgE, and serum IgE levels to *Blattella germanica* and *Dermatophagoides pteronyssinus*.

Spirometry

Each subject performed baseline spirometry according to American Thoracic Society guidelines (13) using a Collins Survey Tach Spirometer (Warren Collins, Braintree, MA). Following baseline spirometry, subjects received 200µg of albuterol. Spirometry was repeated after 15 minutes.

Methacholine Challenge Testing

Using a modified Chatham Protocol (14), methacholine challenge testing was performed on subjects with baseline FEV1 $\geq$ 65% of predicted.

Skin Testing

Skin testing to *Dermatophagoides pteronyssinus*, *D. farinae*, mixed grasses, mixed trees, *Periplaneta americana*, *Blatella germanica*, cat hair, dog hair, *Alternaria tenuis*, histamine, and diluent was done on all subjects using extracts and lancets from ALK-Abelló (Round Rock, TX). Grass and tree mixes encompassed allergens relevant to Costa Rica's pollen seasons. A skin test was considered positive if the maximum wheal diameter exceeded the diluent wheal diameter by $\geq$ 3mm.

Serologic Testing

Serum total IgE and allergen-specific IgE levels to *B. germanica* and *D. pteronyssinus* were measured in duplicate using the UniCAP 250 system (Pharmacia & Upjohn, Kalamazoo, MI). Allergen-specific IgE levels were considered positive if $\geq$ 0.35 IU/ml. Peripheral blood eosinophils were counted by Coulter-Counter.

Outcome Definitions

Two definitions of AR were assessed. Both required current nasal symptoms, as evidenced by affirmative answers to both these questions: "Has [name] ever had hay fever or a runny or stuffy nose accompanied by sneezing and itching at a time when he/she did not have a cold or flu?" and "Has [name] had these symptoms in the last 12 months?" For the first definition of AR, a subject had to have current nasal symptoms and $\geq$ 1 positive skin test reaction (STR) to allergens. This definition, henceforth referred to as STR-positive AR, is consistent with Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 guidelines, which state that the diagnosis of AR is based on a concordance between allergic symptoms and diagnostic tests demonstrating allergen-specific IgE (15). In practice and clinical research, however, AR is typically defined using nasal symptoms and/or a physician's diagnosis (16). For our second definition of AR, henceforth referred to as physician-diagnosed AR, a subject had to have current nasal symptoms and a physician's diagnosis of AR. We chose to require nasal symptoms for physician-diagnosed AR because two participants carried a physician's diagnosis of AR without having any nasal symptoms. Analyses done with AR defined by physician diagnosis alone did not yield results significantly different from those using our definition for physician-diagnosed AR (data not shown).

Statistical Methods

Univariate relationships between AR and candidate risk factors were examined using Fisher's exact test for categorical variables, Mantel-Haenszel chi-square test for ordinal variables, and the two-sided t-test for continuous variables.

Stepwise logistic regression was used for the multivariate analyses. The initial models included known confounders and covariates associated with AR at $P \leq 0.20$ in the univariate analysis. Final models included age, gender, parental education (highest level attained by either parent) and variables that were either significantly associated with AR ($P < 0.05$), or

that changed the estimated odds ratios by $\geq 15\%$. The c-statistic and Hosmer-Lemeshow test were used to assess model fit. All analyses were done using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

The characteristics of children with and without AR, using either definition, are shown in Table 1. Of the 616 children with asthma, 492 (80%) had STR-positive AR. Compared to findings from questionnaire-based studies, this is among the highest reported rates of AR in asthmatics (17). The prevalence was lower (27%) for physician-diagnosed AR.

Among all children, the mean age was 9.0 years, 40% were female, and none were smokers. 36.5% of participating children used inhaled steroids. Using either definition of AR, there were no significant differences in prematurity, breast feeding history, intrauterine smoke exposure, or BMI between children with and without AR.

Risk Factors for AR

STR-positive AR: Nasal Symptoms and STR to ≥ 1 Allergen—The results of the univariate analyses of the relation between the variables of interest and STR-positive AR are shown in Tables 1 and 2. Compared to children without STR-positive AR, those with STR-positive AR were more likely to have been diagnosed with asthma at an older age, to have used oral steroids in the prior year, to have increased bronchodilator responsiveness and increased airway responsiveness, and to have a parent with AR. In addition, children with STR-positive AR were more likely to have nasal symptoms after exposure to any allergen and to have higher levels of eosinophils, total IgE, and specific IgE to cockroach and dust mite. Notably, home environmental exposures such as family size were not significantly different in children with and without STR-positive AR.

The results of the multivariate analysis of risk factors for STR-positive AR are shown in Table 2. In this analysis, having nasal symptoms after exposure to house dust or mold, parental history of AR, older age at asthma onset, oral steroid use in the prior year, increased eosinophils, a positive IgE to dust mite, and a positive IgE to cockroach were all independently associated with increased odds of STR-positive AR.

Given the strong effect of dust-mite-specific IgE on STR-positive AR (because of its strong correlation with STR to dust mite), secondary analyses were done to determine the relative importance of risk factors after excluding STR to dust mite from the analysis. In a model where AR was defined as nasal symptoms and STR to ≥ 1 allergen other than dust mite, a positive IgE to dust mite remained the strongest risk factor for AR. In that model (Table 3), nasal symptoms after exposure to dust, a positive IgE to cockroach, parental history of AR and eosinophilia continued to be significantly associated with STR-positive AR.

Physician-diagnosed AR: Nasal Symptoms and a Physician's Diagnosis of AR

—Tables 1 and 4 show the results of the univariate analyses of the relation between the variables of interest and physician-diagnosed AR. These analyses identified a few common risk factors with STR-positive AR, including nasal symptoms after certain exposures (pollens, dust, and mold), parental history of AR, and an elevated dust-mite-specific IgE. However, many risk factors were distinct. Compared to children without physician-diagnosed AR, those with physician-diagnosed AR were more likely to have at least one parent educated beyond high school, to have used inhaled steroids and short-acting β_2 agonist in the last year, to have fewer older siblings, to have STR to mixed tree and mixed grass pollens, and to have parental report of home mold/mildew. Children with physician-

diagnosed AR were less likely to share their bedroom with others than those without physician-diagnosed AR.

The results of the multivariate analysis of risk factors for physician-diagnosed AR are shown in Table 4. Nasal symptoms after exposure to pollens, STR to mixed tree pollens, parental history of AR, inhaled steroid and short-acting β_2 agonist use in the past year, and parental sighting of household mold/mildew were all associated with increased odds of physician-diagnosed AR. Conversely, having ≥ 3 older siblings was associated with a 60% reduction in the odds of physician-diagnosed AR.

DISCUSSION

Risk factors for atopic diseases have been insufficiently studied in Hispanics. This is the first large study of AR in Latin American children with asthma that incorporates questionnaire data and multiple objective measures of asthma and atopy.

The prevalence and risk factors for AR in children with asthma pivoted upon the definition of AR used. When AR was defined by nasal symptoms and STR, its prevalence in our cohort was 80%, and its main risk factors were driven by perennial allergens. When defined by nasal symptoms and a physician's diagnosis, AR had only 27% prevalence, with seasonal allergens and environmental exposures serving as major risk factors. Nasal symptoms and a physician's diagnosis had only 29.5% sensitivity and 82% specificity for STR-positive AR in this population. Further, asthmatic children with physician-diagnosed AR had distinct characteristics from those with STR-positive AR.

We were motivated to study AR in children with asthma because of the association between AR and asthma severity (2,3). Corroborating this, our univariate analyses demonstrated that compared to children without STR-positive AR, those with STR-positive AR had higher asthma severity as reflected by oral steroid use, higher bronchodilator response, and increased airway responsiveness. Oral steroid use remained an independent risk factor after multivariate adjustment. Use of inhaled steroid and short-acting β_2 agonist were independent risk factors for physician-diagnosed AR. A comparison of asthma severity measures associated with STR-positive AR to those associated with physician-diagnosed AR suggests worse asthma control in children without a formal physician's diagnosis of AR.

A parental history of AR increased risk for AR in our cohort of asthmatic children regardless of AR definition. This is consistent with a previous study of children with AR (unselected for asthma), that demonstrated three-fold higher odds of AR in childhood if one parent also had AR (18). In that study, however, parental asthma and parental eczema also increased the odds of AR to a lesser degree. In our study, parental history of AR— but not of asthma or eczema—increased risk for AR. Our findings and those of others (18–20) suggest that family histories of asthma, eczema, and AR should be considered as separate risk factors.

The hygiene hypothesis posits that early life environmental exposures modulate immunological maturation (21). Environmental conditions such as family size (21), sibship (22), and home exposures (23), have been studied as atopic risk factors. Consistent with these studies, lower birth order and home sightings of mold/mildew increased risk for physician-diagnosed AR in our study. However, our adjusted analyses demonstrated no association between home environmental exposures and STR-positive AR. The immunologic mechanisms for the hygiene hypothesis remain controversial (24). If the effect of early-life environmental exposures is to alter TH2 polarization, and ultimately allergen-specific IgE production, then one would expect associations with STR-positive AR.

We found that the odds of STR-positive AR increased with older age of asthma onset. 85% of the children had STR, suggesting that most had atopic asthma. Because sensitization to allergens increases with age (25), it makes sense that atopic asthma and STR-positive AR would increase with age. Our finding adds to the relationship between asthma, STR, and AR identified by Martinez et al, who observed higher rates of STR and rhinitis in persistent and late wheezers as compared to never wheezers (26). We did not observe an association between age of asthma onset and physician-diagnosed AR, likely because of misclassification of non-allergic rhinitis as AR by physicians. 13% of children with physician-diagnosed AR had no STR in our study.

AR has been more strongly associated with sensitization to outdoor allergens, and asthma with indoor allergens (27). The children in our study with physician-diagnosed AR had more symptoms and STR to pollens. In contrast, symptoms and IgE-mediated responses to indoor allergens were the main independent risk factors for STR-positive AR. In fact, dust mite-specific IgE drove risk for STR-positive AR, and outdoor allergens did not confer any independent risk. This difference highlights that physicians' diagnoses of AR are biased towards seasonal AR because of its intermittent and acute nature, despite a significant burden of disease caused by perennial allergens. In our study, 61% of children had perennial AR (nasal symptoms and STR to indoor allergens) without seasonal AR (nasal symptoms and STR to pollens). If a physician were to inquire only about seasonal symptoms, she would miss 58% of children with perennial AR. Thus, physicians should screen for chronic nasal symptoms that could indicate perennial AR. Because the existing literature on AR relies on physicians' diagnoses, our current understanding of the relative contributions of outdoor and indoor allergens to AR may discount the true impact of perennial indoor allergens, particularly in asthmatic children.

In this study, physicians did not diagnose over 70% of children with nasal symptoms and demonstrable allergen-specific IgE. The underdiagnosis of AR apart from asthma has been previously observed in other populations (28), including Hispanics in the United States Northeast (29). The underdiagnosis of AR in Costa Rica is unlikely to be due to healthcare access. Costa Ricans have universal healthcare (30), and reflecting this, 36.5% of children in our study used inhaled steroids, while only 6% of Latin American asthmatics overall (31) and 9–26% of severe asthmatics in Europe, North America, and Asia use inhaled steroids (32). Because treatment of AR in children with asthma may reduce the odds of asthma-related acute care by up to 80% (4), addressing the AR diagnostic and treatment gap is particularly compelling in children with asthma. We hope that this study will compel physicians to screen their asthmatic patients for naso-ocular symptoms.

Although a greater awareness of AR in children with asthma could partially improve the high rate of underdiagnosis that we observed, allergy skin testing could further aid in correctly identifying AR. Because skin testing can be limited by time and infrastructure, skin testing to one or a few of the most prevalent allergens in a given environment could be a solution. In our study, STR to just dust mite would capture 94% of children with any positive STR and 80% of children with nasal symptoms. If skin testing were not available, as is true in resource-limited settings, obtaining one allergen-specific IgE level could be an alternative. This would be less preferable than skin testing since the sensitivity of allergen-specific IgE as compared to skin testing varies widely (16). In our study, a positive IgE to dust mite would capture 87% of children with any STR and 78% of children with nasal symptoms. Having all children with asthma undergo limited skin testing or allergen-specific IgE measurement could reduce physician underdiagnosis of AR and identify children for whom AR therapy could reduce asthma morbidity.

Our study has three main limitations. First, as this was part of a larger study on asthma genetics, inclusion criteria required a high probability of descent from the founder population and a commitment from both parents to contribute blood samples. These criteria may have caused selection bias, although our analyses showed no significant difference in gender or grade in school between participants and non-participants, and study subjects demonstrated a wide range of asthma severity markers. Second, the cross-sectional design of this study precludes us from assessing these risk factors as prospective predictors of AR in children with asthma. Finally, some findings from this study may be specific to Costa Rican and Hispanic children, although other findings in this cohort have been generalizable to asthmatics overall (33,34). Our focus on Hispanic children with asthma brings attention to a demographic not frequently studied, despite high asthma prevalence in many Hispanic communities (35).

In summary, we have found that apart from a parental history of AR in this Costa Rican cohort, the clinical and environmental factors that determine risk for AR in children with asthma depend upon one's definition of AR. Outdoor seasonal allergens and home environmental conditions are key risk factors when AR is defined by nasal symptoms and a physician's diagnosis. Indoor perennial allergens drive risk for AR when it is defined by nasal symptoms and a positive skin test. However defined, AR is underdiagnosed in children with asthma in Costa Rica. Physicians should screen their asthmatic patients for both seasonal and perennial AR. We propose that children with asthma in non-industrialized nations in general and in Latin America in particular undergo limited skin testing or specific IgE measurements to the most common allergens in their environment to aid in the diagnosis of AR. The diagnosis and treatment of AR in children with asthma could significantly reduce asthma morbidity.

Acknowledgments

This work was supported by grants HL04370, HL066289, and T32 HL007427 from the U.S. National Institutes of Health.

References

1. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Washington DC: National Heart Lung and Blood Institute and National Asthma Education and Prevention Program; 2007. Report No.: 08–4051
2. Thomas M, Kocevar VS, Zhang Q, Yin DD, Price D. Asthma-related health care resource use among asthmatic children with and without concomitant allergic rhinitis. *Pediatrics*. 2005; 115(1): 129–34. [PubMed: 15629992]
3. Sazonov Kocevar V, Thomas J 3rd, Jonsson L, Valovirta E, Kristensen F, Yin DD, et al. Association between allergic rhinitis and hospital resource use among asthmatic children in Norway. *Allergy*. 2005; 60(3):338–42. [PubMed: 15679719]
4. Corren J, Manning BE, Thompson SF, Hennessy S, Strom BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. *J Allergy Clin Immunol*. 2004; 113(3):415–9. [PubMed: 15007339]
5. Dixon AE. Rhinosinusitis and asthma: the missing link. *Curr Opin Pulm Med*. 2009; 15(1):19–24. [PubMed: 19077701]
6. Jani AL, Hamilos DL. Current thinking on the relationship between rhinosinusitis and asthma. *J Asthma*. 2005; 42(1):1–7. [PubMed: 15801321]
7. Kuyucu S, Saraclar Y, Tuncer A, Geyik PO, Adalioglu G, Akpinarli A, et al. Epidemiologic characteristics of rhinitis in Turkish children: the International Study of Asthma and Allergies in Childhood (ISAAC) phase 2. *Pediatr Allergy Immunol*. 2006; 17(4):269–77. [PubMed: 16771780]
8. Falade A, Olawuyi JF, Osinusi K, Onadeko BO. Prevalence and severity of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema in 6- to 7-year-old Nigerian primary school children:

- the international study of asthma and allergies in childhood. *Medical Principles and Practice*. 2004; 13(1):20–25. [PubMed: 14657614]
9. Uthaisangsook S. Prevalence of asthma, rhinitis, and eczema in the university population of Phitsanulok, Thailand. *Asian Pac J Allergy Immunol*. 2007; 25(2–3):127–32. [PubMed: 18035799]
 10. Shamssain MH, Shamsian N. Prevalence and severity of asthma, rhinitis, and atopic eczema in 13- to 14-year-old schoolchildren from the northeast of England. *Ann Allergy Asthma Immunol*. 2001; 86(4):428–32. [PubMed: 11345287]
 11. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2007; 62(9):758–66. [PubMed: 17504817]
 12. Blumenthal MN, Banks-Schlegel S, Bleecker ER, Marsh DG, Ober C. Collaborative studies on the genetics of asthma--National Heart, Lung and Blood Institute. *Clin Exp Allergy*. 1995; 25 (Suppl 2):29–32. [PubMed: 8590337]
 13. American Thoracic Society. Standardization of Spirometry, 1994 Update. *Am J Respir Crit Care Med*. 1995; 152(3):1107–36. [PubMed: 7663792]
 14. Chatham M, Bleecker ER, Norman P, Smith PL, Mason P. A screening test for airways reactivity. An abbreviated methacholine inhalation challenge. *Chest*. 1982; 82(1):15–8. [PubMed: 7083928]
 15. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008; 63(S86):8–160. [PubMed: 18331513]
 16. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol*. 2008; 122(2 Suppl):S1–84. [PubMed: 18662584]
 17. Cruz AA, Popov T, Pawankar R, Annesi-Maesano I, Fokkens W, Kemp J, et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy*. 2007; 62 (Suppl 84):1–41. [PubMed: 17924930]
 18. Dold S, Wjst M, von Mutius E, Reitmeir P, Stiepel E. Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. *Arch Dis Child*. 1992; 67(8):1018–22. [PubMed: 1520004]
 19. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med*. 1998; 158(1):176–81. [PubMed: 9655726]
 20. Bjerg A, Hedman L, Perzanowski MS, Platts-Mills T, Lundback B, Ronmark E. Family history of asthma and atopy: in-depth analyses of the impact on asthma and wheeze in 7- to 8-year-old children. *Pediatrics*. 2007; 120(4):741–8. [PubMed: 17908760]
 21. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989; 299(6710):1259–60. [PubMed: 2513902]
 22. Matheson MC, Walters EH, Simpson JA, Wharton CL, Ponsonby AL, Johns DP, et al. Relevance of the hygiene hypothesis to early vs. late onset allergic rhinitis. *Clin Exp Allergy*. 2009; 39(3): 370–8. [PubMed: 19187325]
 23. Ibargoyen-Roteta N, Aguinaga-Ontoso I, Fernandez-Benitez M, Marin-Fernandez B, Guillen-Grima F, Serrano-Monzo I, et al. Role of the home environment in rhinoconjunctivitis and eczema in schoolchildren in Pamplona, Spain. *J Investig Allergol Clin Immunol*. 2007; 17(3):137–44.
 24. Romagnani S. Coming back to a missing immune deviation as the main explanatory mechanism for the hygiene hypothesis. *J Allergy Clin Immunol*. 2007; 119(6):1511–3. [PubMed: 17556059]
 25. Rhodes HL, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med*. 2002; 165(2):176–80. [PubMed: 11790650]
 26. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med*. 1995; 332(3):133–8. [PubMed: 7800004]
 27. Schoefer Y, Schafer T, Meisinger C, Wichmann HE, Heinrich J. Predictivity of allergic sensitization (RAST) for the onset of allergic diseases in adults. *Allergy*. 2008; 63(1):81–6. [PubMed: 18053017]

28. Gruchalla RS, Gan V, Roy L, Bokovoy J, McDermott S, Lawrence G, et al. Results of an inner-city school-based asthma and allergy screening pilot study: a combined approach using written questionnaires and step testing. *Ann Allergy Asthma Immunol.* 2003; 90(5):491–9. [PubMed: 12775130]
29. Celedon JC, Sredl D, Weiss ST, Pisarski M, Wakefield D, Cloutier M. Ethnicity and skin test reactivity to aeroallergens among asthmatic children in Connecticut. *Chest.* 2004; 125(1):85–92. [PubMed: 14718425]
30. Unger JP, De Paepe P, Buitron R, Soors W. Costa Rica: achievements of a heterodox health policy. *Am J Public Health.* 2008; 98(4):636–43. [PubMed: 17901439]
31. Neffen H, Fritscher C, Schacht FC, Levy G, Chiarella P, Soriano JB, et al. Asthma control in Latin America: the Asthma Insights and Reality in Latin America (AIRLA) survey. *Rev Panam Salud Publica.* 2005; 17(3):191–7. [PubMed: 15826399]
32. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol.* 2004; 114(1):40–7. [PubMed: 15241342]
33. Hersh CP, Raby BA, Soto-Quiros ME, Murphy AJ, Avila L, Lasky-Su J, et al. Comprehensive testing of positionally cloned asthma genes in two populations. *Am J Respir Crit Care Med.* 2007; 176(9):849–57. [PubMed: 17702965]
34. Hunninghake GM, Soto-Quiros ME, Avila L, Su J, Murphy A, Demeo DL, et al. Polymorphisms in IL13, total IgE, eosinophilia, and asthma exacerbations in childhood. *J Allergy Clin Immunol.* 2007; 120(1):84–90. [PubMed: 17561245]
35. Hunninghake GM, Weiss ST, Celedon JC. Asthma in Hispanics. *Am J Respir Crit Care Med.* 2006; 173(2):143–63. [PubMed: 16210666]

Table 1

Participant Characteristics

	STR-positive AR		Physician-diagnosed AR	
	No AR (n = 124)	AR (n = 492)	No AR (n = 449)	AR (n = 167)
Baseline Characteristics				
Female	50 (40.3%)	196 (39.8%)	173 (38.5%)	73 (43.7%)
Age – years	8.9 (8.6–9.3)	9.1 (8.9–9.2)	9.0 (8.8–9.2)	9.2 (8.9–9.4)
Parental Education				
Less than High School	63 (50.8%)	243 (49.4%)	243 (54.1%)	63 (37.7%) ^{***}
High School Only	24 (19.4%)	119 (24.2%)	100 (22.3%)	43 (25.7%)
More than High School	37 (29.8%)	130 (26.4%)	106 (23.6%)	61 (36.5%) ^{**}
Symptom Triggers				
House dust	88 (71.0%)	446 (90.7%) ^{***}	378 (84.2%)	156 (93.4%) ^{**}
Mold	64 (51.6%)	388 (78.9%) ^{***}	317 (70.6%)	135 (80.8%) [*]
Pollens	34 (27.4%)	208 (42.3%) ^{**}	158 (35.2%)	84 (50.3%) ^{***}
Cats	7 (5.7%)	64 (13.0%) [*]	50 (11.1%)	21 (12.6%)
Dogs	12 (9.7%)	96 (19.5%) [*]	74 (16.5%)	34 (20.4%)
Asthma and Atopic History				
Age at Asthma Onset – years	2.0 (1.6–2.4)	2.6 (2.4–2.9) ^{**}	2.5 (2.3–2.7)	2.5 (2.1–2.8)
Inhaled steroids in last year	37 (29.8%)	188 (38.2%)	139 (31%)	86 (51.5%) ^{***}
Short-acting β_2 agonist in last year	95 (76.6%)	397 (80.7%)	346 (77.1%)	146 (87.4%) ^{**}
Oral steroid in last year	86 (69.4%)	408 (82.9%) ^{**}	356 (79.3%)	138 (82.6%)
History of eczema or rash	62 (50%)	283 (57.5%)	243 (54.1%)	102 (61.1%)
Family History				
Parent with asthma	60 (48.4%)	234 (47.6%)	218 (48.6%)	76 (45.5%)
Parent with allergic rhinitis	43 (35.0%)	237 (48.2%) [*]	182 (40.6%)	98 (58.7%) ^{***}
Parent with eczema	12 (9.7%)	47 (9.6%)	41 (9.1%)	18 (10.8%)
Home Environment				
Number of people in the house	5.0 (4.7–5.2)	5.0 (4.9–5.1)	5.0 (4.9–5.2)	4.9 (4.7–5.1)
Shared bedroom	91 (73.4%)	342 (69.5%)	326 (72.6%)	107 (64.1%) [*]
Number of older siblings	1.2 (1.0–1.5)	1.2 (1.1–1.3)	1.3 (1.2–1.4)	1.0 (0.8–1.1) [*]
History of day care	3 (2.4%)	12 (2.4%)	13 (2.9%)	2 (1.2%)
Cat at home	18 (14.5%)	34 (6.9%) [*]	44 (9.8%)	8 (4.8%)
Dog at home	59 (47.6%)	250 (50.8%)	233 (51.9%)	76 (45.5%)
Signs of mold/mildew	71 (57.3%)	311 (63.2%)	267 (59.5%)	115 (68.9%) [*]
Airway Responsiveness				
Bronchodilator response – ml [#]	57 (37–78)	98 (85–111) ^{**}	85 (72–97)	103 (77–129)
AHR to methacholine $\leq 8.58\mu\text{mol}^\wedge$	85 (75.2%)	388 (87.8%) ^{**}	345 (85.0%)	128 (85.9%)
Laboratory Findings				

	STR-positive AR		Physician-diagnosed AR	
	No AR (n = 124)	AR (n = 492)	No AR (n = 449)	AR (n = 167)
Peripheral blood eosinophil count	345 (290–401)	657 (620–695) ***	594 (554–634)	596 (534–658)
Total IgE – ng/ml	262 (173–351)	808 (727–888) ***	679 (601–758)	747 (602–891)
Specific IgE to Cockroach – IU/ml	0.5 (0.1–0.8)	1.6 (1.2–2.1) ***	1.4 (1.0–1.9)	1.2 (0.8–1.7)
Specific IgE to Dust Mite – IU/ml	7.9 (3.6–12.2)	41.2 (37.6–44.7) ***	31.6 (28.0–35.1)	42.3 (36.1–48.6) **
Skin Test Reactivity~				
<i>Alternaria tenuis</i>	2 (1.6%)	30 (6.1%)	20 (4.5%)	12 (7.2%)
<i>Blatella germanica</i>	20 (16.4%)	280 (56.9%) ***	223 (49.8%)	77 (46.4%)
<i>Periplaneta Americana</i>	17 (13.9%)	289 (58.7%) ***	217 (48.4%)	89 (53.6%)
<i>Dermatophagoides farinae</i>	27 (22.1%)	431 (87.6%) ***	328 (73.2%)	130 (78.3%)
<i>Dermatophagoides pteronyssinus</i>	23 (18.9%)	457 (92.9%) ***	342 (76.3%)	138 (83.1%)
Cat	2 (1.6%)	71 (14.4%) ***	57 (12.7%)	16 (9.6%)
Dog	1 (0.8%)	55 (11.2%) ***	36 (8.0%)	20 (12.1%)
Mixed grasses	3 (2.5%)	50 (10.2%) *	32 (7.1%)	21 (12.7%) *
Mixed trees	4 (3.3%)	75 (15.2%) ***	46 (10.3%)	33 (19.9%) **

Values are presented as number (percentage) or mean (95% confidence interval)

Difference between subjects with and without AR on univariate analysis at

* p<0.05,

** p<0.005,

*** p<0.0005

Bronchodilator not given to 20 subjects,

^ Methacholine challenge test not done on 61 subjects,

~ Skin test not done on 2 subjects

Table 2

Risk factors for STR-positive Allergic Rhinitis in Children with Asthma

	Unadjusted		Adjusted*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Symptom Trigger				
House Dust	4.0 (2.4–6.5)	<0.0001	3.0 (1.4–6.5)	0.004
Mold	3.5 (2.3–5.3)	<0.0001	3.5 (1.9–6.4)	<0.0001
Family History				
Parent with Allergic Rhinitis	1.7 (1.1–2.6)	0.009	2.9 (1.6–5.4)	0.0005
Asthma and Atopic History				
Age of Asthma Onset -- years				
< 2 years old	1.0		1.0	
2–5 years old	1.8 (1.2–2.8)	0.010	1.5 (0.8–2.9)	0.18
≥ 5 years old	2.8 (1.5–5.4)	0.001	2.8 (1.2–6.7)	0.02
Oral steroid in last year	2.1 (1.4–3.4)	0.002	2.0 (1.0–3.8)	0.03
Laboratory Findings				
Peripheral blood eosinophil count > 500	6.0 (3.8–9.6)	<0.0001	3.1 (1.7–5.9)	0.0004
Positive IgE to Cockroach	5.0 (2.9–8.4)	<0.0001	2.1 (1.0–4.3)	0.048
Positive IgE to Dust Mite	26.2 (15.8–43.3)	<0.0001	17.2 (9.0–32.6)	<0.0001

* Values adjusted for age, gender, parental education, and other variables in the model.

Table 3

Risk factors for Allergic Rhinitis Defined as Nasal Symptoms and Any STR Except Dust Mite

	Unadjusted		Adjusted*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Symptom Trigger				
House Dust	2.3 (1.4–3.7)	0.0006	2.1 (1.2–3.6)	0.009
Family History				
Parent with Allergic Rhinitis	1.5 (1.1–2.1)	0.01	1.8 (1.2–2.6)	0.004
Laboratory Findings				
Peripheral blood eosinophil count > 500	3.0 (2.2–4.3)	<0.0001	2.0 (1.4–3.0)	0.0005
Positive IgE to Cockroach	4.6 (3.2–6.7)	<0.0001	3.2 (2.1–4.9)	<0.0001
Positive IgE to Dust Mite	6.6 (4.4–10.0)	<0.0001	3.4 (2.1–5.4)	<0.0001

* Values adjusted for age, gender, parental education, and other variables in the model.

Table 4

Risk factors for Physician-diagnosed Allergic Rhinitis in Children with Asthma

	Unadjusted		Adjusted*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Symptom Trigger				
Pollens	1.9 (1.3–2.7)	0.0008	1.9 (1.2–2.8)	0.002
Family History				
Parent with Allergic Rhinitis	2.1 (1.4–3.0)	<0.0001	1.9 (1.3–2.8)	0.002
Asthma and Atopic History				
Inhaled steroid in last year	2.4 (1.6–3.4)	<0.0001	2.4 (1.6–3.5)	<0.0001
Short-acting β_2 agonist in last year	2.1 (1.2–3.4)	0.005	1.9 (1.1–3.3)	0.03
Home Environment				
Number of older siblings				
None	1.0		1.0	
1 or 2	0.7 (0.5–1.0)	0.07	0.9 (0.6–1.3)	0.45
≥ 3	0.4 (0.2–0.7)	0.004	0.4 (0.2–0.8)	0.008
Signs of mold/mildew	1.5 (1.0–2.2)	0.04	1.6 (1.1–2.5)	0.02
Skin Test Reactivity				
Mixed trees	2.2 (1.3–3.5)	0.003	1.8 (1.1–3.0)	0.04

* Values adjusted for age, gender, parental education, and other variables in the model.