Pathways through which Asthma Risk Factors Contribute to Asthma Severity in Inner-City Children

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Background Supporting the Conceptual Model of Asthma Severity

Based on clinical and mechanistic evidence in the published literature and consensus among investigators, a conceptual model was developed to hypothetically describe how 8 risk factor domains of allergen sensitization, allergic inflammation, pulmonary physiology, stress, obesity, Vitamin D, environmental tobacco smoke (ETS) exposure and rhinitis severity are linked to asthma severity (Figure 1). The basis for constructing this model and its pathways are discussed in the following sections.

Allergy Pathway

Ample evidence links allergic sensitization and IgE to allergic inflammation, pulmonary physiology and asthma severity, especially in children. In a birth cohort study of BHR in New Zealand children, serum total IgE measured at age 11 years was associated with asthma and highly correlated with methacholine BHR in asthmatic and non-asthmatic children.[1] Even more so, in the same cohort, a multivariable analysis demonstrated a stronger correlation of the number of positive allergy skin tests to cat, dog, mite and Aspergillus determined at age 13 years with BHR, as well as airflow limitation by FEV_1/FVC and FEV_1 (% predicted).[2] In the Childhood Asthma Management Program (CAMP) study and the Severe Asthma Research Program (SARP), asthma phenotypes with greater disease severity manifest with more exacerbations, greater lung dysfunction (i.e., airflow limitation, methacholine BHR and bronchodilator responsiveness), higher levels of total serum IgE, peripheral blood eosinophils, FeNO, and greater number of allergen sensitizations.[3,4] The severe asthma phenotype in children is consistent with a severe 'Th2-high' phenotype in adults, with IL-13-induced epithelial gene expression (e.g., periostin), allergic inflammation (i.e., BAL and blood eosinophilia, higher total serum IgE), greater lung dysfunction (i.e., BHR, BD response), and exacerbation risk.[5]

Asthma severity and exacerbations are associated with allergen sensitization and exposure to indoor allergens: house dust mite,[6] cockroach,[7] rodents,[8-13] molds,[14-18] and pets.[6,14] Sensitization to dust mite, dog and/or cat, especially when combined with high levels of home exposure, is also associated with asthma persistence and lower lung function through childhood.[19,20] A recent update review on indoor exposures affecting asthma exacerbations of a 2000 Institute of Medicine report (*Clearing the Air: Asthma and Indoor Air Exposures*) [21,22] found sufficient evidence for causal relationships or associations between common indoor allergens (mite, cat, cockroach, mold, dog) and asthma exacerbations in allergen-sensitized individuals. Allergen sensitization to common foods has also been linked to asthma severity and exacerbations.[23,24]

The Inner City Asthma Study (ICAS) study revealed that 94% of the cohort of inner city children with moderate to severe asthma were sensitized to at least one perennial inhalant allergen, of which 50% were sensitized to 3 or more, and had a high frequency of home exposures to dampness/mold (45%), cockroach (58%), rodents (39%), and furry pets (28%).[25] For inner-city children with asthma, their schools can also be a significant source of allergen exposure that worsens their asthma. High levels of mouse[26,27] and mold[28,29] allergens in inner-city schools have been associated with increased asthma symptom days in sensitized children. Inner-City asthma studies have also shown that therapeutically blocking IgE-mediated responses with omalizumab reduced asthma exacerbations and improved asthma symptoms and control [30,31]. Since most inner-city children with moderate to severe asthma are sensitized to multiple indoor allergens, with exposure at home and/or school being common, the allergy pathway may be particularly relevant to this study.

Allergic sensitization is linked to allergic inflammation. IgE antibodies to inhalant allergens are essential mediators of allergen-driven inflammation in asthma. In children with asthma, the number of positive inhalant allergen prick skin tests and total serum IgE levels correlated with

sputum eosinophils[32] and FeNO.[33,34] In cat, dog, or mite sensitized asthmatics, specific allergen exposure is associated with increased FeNO.[6,35]

Allergic inflammatory markers are correlated with airway inflammation and each other. Sputum eosinophilia correlates with FeNO and peripheral blood eosinophilia,[32] and FeNO correlates with peripheral blood eosinophilia.[33]

Allergic inflammation is associated with pulmonary physiology. Sputum eosinophilia and FeNO are correlated with greater BHR, bronchodilator reversibility, and airflow limitation.[32,33,36]

Allergic inflammation is also linked to asthma severity. Sputum eosinophilia is associated with asthma exacerbations, beta-agonist rescue use, and frequency of nocturnal symptoms.[32] Elevated FeNO level is an indicator of greater asthma severity and poor control (i.e., beta-agonist use, day- and night-time symptoms, spirometry).[37,38]

Allergic rhinitis can affect asthma severity. Allergic rhinitis is reported in 85 – 95% of allergic asthmatics, and clinical rhinitis severity is associated with asthma severity.[39] Nasal obstruction due to rhinitis could reduce or bypass the usual nasal functions of warming, humidifying, and filtering respirable air, thereby reducing these common asthma triggers. *Allergic inflammation and other provocative stimuli in the nose can also affect asthma severity directly and indirectly via pulmonary physiology.* In patients with allergic rhinitis and asthma, nasal allergen challenge induced nasal and lower airways eosinophilia, methacholine BHR, and late-phase airflow limitation.[39-41] Similarly, in patients with rhinitis and asthma, nasal inhalation of cold air or mucosal application of methacholine increased lower airways resistance.[42,43] In some studies, treatment of allergic rhinitis with intranasal corticosteroids improved FEV_1, bronchial hyperreactivity, asthma symptom scores, and rescue medication use.[44] Also, treating allergic

rhinitis with nasal corticosteroids and antihistamines reduces the risk for asthma-related ER visits and hospitalizations.[45]

Pulmonary physiology is linked to asthma severity. Spirometric measures of airflow are frequently used as an objective marker of asthma severity in guidelines-based care.[46,47] Persistent airway obstruction (e.g., low FEV_1/FVC) has been shown to develop in a subgroup of children with asthma and is associated with disease severity and morbidity.[36,48-50] In the CAMP study, airflow limitation (pre-BD FEV_1 % predicted) was associated with subsequent asthma symptoms and exacerbation risk,[51] and bronchial hyperreactivity to methacholine correlated with airflow limitation, asthma symptoms, and clinical severity.[52] Cluster analysis studies to distinguish childhood asthma phenotypes have associated greater allergy, allergic inflammation and lung dysfunction with more clinically severe disease.[3,4]

Environmental Tobacco Smoke (ETS) Pathway

ETS exposure can affect asthma severity directly and through its effects on allergic inflammation and pulmonary physiology. A recent Cochrane-based meta-analysis of ETS exposure and asthma severity in children[53] and an update of a 2000 Institute of Medicine report[21,22] demonstrated an increased risk and suggestive evidence of associations between ETS exposure and reduced lung function (FEV_1/FVC ratio), wheezing symptoms, and ED visits and hospitalizations for asthma. In the Severe Asthma Research Program, children and adults with ETS exposure had lower lung function, greater bronchodilator response, and greater risk of severe exacerbations.[54] In urban children with inner-city demographic features (57% African American, 76% Medicaid), detectable serum and salivary cotinine (i.e., biomarkers for ETS exposure) were common in children hospitalized for asthma, and were also associated with subsequent hospital re-admission.[55] ETS exposure has also been shown to be negatively associated with FeNO levels in allergic asthmatic children and normal subjects.[56-58] The ETS

pathway may be particularly relevant to explaining asthma severity because most (48-75%) inner-city children with asthma reside in households with smokers, have detectable tobacco smoke exposure in their homes, or have elevated urine cotinine levels indicating ETS exposure.[25,59-62]

Vitamin D Pathway

Vitamin D could affect asthma severity through its effects on allergic inflammation and pulmonary physiology. Vitamin D could decrease asthma severity by enhancing corticosteroid responses that could effectively reduce airway inflammation.[63] In adults with asthma, reduced vitamin D levels were associated with impaired lung function, increased BHR, and reduced *in vitro* corticosteroid responsiveness.[64] In the CAMP study, children who received daily corticosteroid had less improvement in FEV_1 if they were vitamin D deficient (total 25-hydroxyvitamin D<20 ng/mL) versus insufficient (<30 ng/mL) or sufficient.[65] Vitamin D might also mitigate the risk of asthma exacerbations by the induction of innate anti-microbial and anti-inflammatory responses, although specific mechanisms are less clear.[66] In the CAMP study, vitamin D insufficiency was associated with being African American and having an increased risk of asthma hospitalization or ER visits.[67] In children with asthma in Costa Rica and Puerto Rico, vitamin D insufficiency was associated with increased peripheral blood eosinophils, lower FEV_1/FVC, increased methacholine BHR, and a history of exacerbations.[68,69] However, in a nationalized study of inner city adolescents with asthma, vitamin D levels were not associated with asthma symptoms, control, exacerbations, lung function, or FeNO.[70] A recent systematic review and meta-analysis of vitamin D supplementation clinical trials in children with asthma suggested a statistically significant reduction in exacerbation risk in treated versus controls (relative risk 0.41, 5-95% confidence interval 0.27-0.63), without adequate evidence to draw conclusions about other outcomes.[71] Considering that Black urban children in Washington D.C. with asthma had a much higher prevalence of vitamin D insufficiency and deficiency when

compared with their matched non-asthmatic controls,[72] inner-city children with asthma may be particularly susceptible to concerns related to vitamin D insufficiency, supporting the relevance of this vitamin D pathway in our study.

Stress Pathway

Psychosocial stress can affect asthma severity directly and through its effects on allergic inflammation and pulmonary physiology. The stressors associated with inner-city living can influence adverse asthma outcomes in a number of ways. In inner-city children and adolescents, violence and severely negative or stressful life events were associated with increased day and night symptoms of asthma and exacerbation/hospitalization risk.[73-75] Caretaker-perceived stress also mediated the effects of violence or severely negative life events on asthma symptoms and attacks.[73,76]

Psychosocial stress has been associated with allergic inflammation. Asthmatic children living in lower SES had higher chronic stress and perceived threat, which was associated with higher IL-5 and IL-13 production in PMA/ionomycin-stimulated PBMC, and peripheral blood eosinophilia.[77] In children with asthma, stress-induced increases in FeNO were more pronounced in those living in lower SES.[78] A prolonged stressor, the final exam period in asthmatic college students, enhanced sputum eosinophilia and a shift towards a Th2 mRNA profile following allergen challenge.[79] In other social science experiments, social and arithmetic stressors were associated with increased FeNO in patients with and without asthma.[80,81]

Psychosocial stress and intense emotions can also increase airflow limitation. With intense anger or fear, children with asthma had declines in FEV_1 that improved with relaxation.[82] In response to emotional or psychological stressors, airways resistance measured by impulse oscillometry increased, such that 22% of children with asthma had a greater than 20%

increase.[83,84] Considering the high levels of perceived stress and stressful events associated with inner city living, this stress pathway seems relevant to this APIC cohort study.

Obesity Pathway

Obesity has been linked to asthma severity, both directly and via pulmonary physiology. Among inner-city asthmatic subjects in the ICAC ACE Study, the prevalence of obesity (BMI > 95th percentile BMI-for-age reference values) was 34% in boys and 37% in girls.[85]. This study also found that higher BMI correlated with more frequent asthma symptoms, lower ACT scores, and the occurrence of exacerbations among females but not males. Others have reported that obese asthmatic children are more likely to have asthma exacerbations and other clinical markers of severe disease[86] are less responsive to corticosteroid (ICS) than their non-obese counterparts.[87,88] In the CAMP study, children who became obese developed significant airflow limitation, as measured by FEV_1/FVC.[89] Obese asthmatic adults in a randomized, controlled weight loss program for 3 months, had a mean weight loss of 16.5 kg and significant improvement in bronchial hyperreactivity to methacholine, FEV_1, and asthma control, without improvements in the control group.[90] In black and Latino children and adolescents with asthma, obesity was associated with bronchodilator unresponsiveness, and obese, bronchodilator-unresponsive children reported more wheezing, night awakening, and higher-level controller usage.[91] Residents of low-income, inner-city communities in the US have a high prevalence of obesity.[92] Because our APIC cohort is largely comprised of black and Latino children, the obesity pathway may be particularly relevant to this study.

REFERENCES

1. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. The New England journal of medicine 1991;325:1067-71.
2. Burrows B, Sears MR, Flannery EM, Herbison GP, Holdaway MD, Silva PA. Relation of the course of bronchial responsiveness from age 9 to age 15 to allergy. American journal of respiratory and critical care medicine 1995;152:1302-8.
3. Howrylak JA, Fuhlbrigge AL, Strunk RC, et al. Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. J Allergy Clin Immunol 2014;133:1289-300, 300 e1-12.
4. Fitzpatrick AM, Teague WG, Meyers DA, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. J Allergy Clin Immunol 2011;127:382-9 e1-13.
5. Woodruff PG, Modrek B, Choy DF, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. American journal of respiratory and critical care medicine 2009;180:388-95.
6. Langley SJ, Goldthorpe S, Craven M, Morris J, Woodcock A, Custovic A. Exposure and sensitization to indoor allergens: association with lung function, bronchial reactivity, and exhaled nitric oxide measures in asthma. J Allergy Clin Immunol 2003;112:362-8.
7. Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. The New England journal of medicine 1997;336:1356-63.
8. Phipatanakul W, Eggleston PA, Wright EC, Wood RA. Mouse allergen. I. The prevalence of mouse allergen in inner-city homes. The National Cooperative Inner-City Asthma Study. J Allergy Clin Immunol 2000;106:1070-4.

9. Phipatanakul W, Eggleston PA, Wright EC, Wood RA, National Coooperative Inner-City Asthma S. Mouse allergen. II. The relationship of mouse allergen exposure to mouse sensitization and asthma morbidity in inner-city children with asthma. J Allergy Clin Immunol 2000;106:1075-80.
10. Pongracic JA, Visness CM, Gruchalla RS, Evans R, 3rd, Mitchell HE. Effect of mouse allergen and rodent environmental intervention on asthma in inner-city children. Ann Allergy Asthma Immunol 2008;101:35-41.
11. Torjusen EN, Diette GB, Breysse PN, Curtin-Brosnan J, Aloe C, Matsui EC. Dose-response relationships between mouse allergen exposure and asthma morbidity among urban children and adolescents. Indoor air 2013;23:268-74.
12. Ahluwalia SK, Peng RD, Breysse PN, et al. Mouse allergen is the major allergen of public health relevance in Baltimore City. J Allergy Clin Immunol 2013;132:830-5 e1-2.
13. Perry T, Matsui E, Merriman B, Duong T, Eggleston P. The prevalence of rat allergen in inner-city homes and its relationship to sensitization and asthma morbidity. J Allergy Clin Immunol 2003;112:346-52.
14. Nelson HS, Szefler SJ, Jacobs J, Huss K, Shapiro G, Sternberg AL. The relationships among environmental allergen sensitization, allergen exposure, pulmonary function, and bronchial hyperresponsiveness in the Childhood Asthma Management Program. J Allergy Clin Immunol 1999;104:775-85.
15. O'Connor G T, Walter M, Mitchell H, et al. Airborne fungi in the homes of children with asthma in low-income urban communities: The Inner-City Asthma Study. J Allergy Clin Immunol 2004;114:599-606.
16. Pongracic JA, O'Connor GT, Muilenberg ML, et al. Differential effects of outdoor versus indoor fungal spores on asthma morbidity in inner-city children. J Allergy Clin Immunol 2010;125:593-9.

17. Sharpe RA, Bearman N, Thornton CR, Husk K, Osborne NJ. Indoor fungal diversity and asthma: a meta-analysis and systematic review of risk factors. J Allergy Clin Immunol 2015;135:110-22.
18. Vicencio AG, Santiago MT, Tsirilakis K, et al. Fungal sensitization in childhood persistent asthma is associated with disease severity. Pediatr Pulmonol 2014;49:8-14.
19. Illi S, von Mutius E, Lau S, et al. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. Lancet 2006;368:763-70.
20. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. The New England journal of medicine 2003;349:1414-22.
21. Institute of Medicine (U.S.). Committee on the Assessment of Asthma and Indoor Air. Clearing the air : asthma and indoor air exposures. Washington, D.C.: National Academy Press; 2000.
22. Kanchongkittiphon W, Mendell MJ, Gaffin JM, Wang G, Phipatanakul W. Indoor environmental exposures and exacerbation of asthma: an update to the 2000 review by the Institute of Medicine. Environmental health perspectives 2015;123:6-20.
23. Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2010;126:798-806 e13.
24. Wang J, Visness CM, Sampson HA. Food allergen sensitization in inner-city children with asthma. J Allergy Clin Immunol 2005;115:1076-80.
25. Crain EF, Walter M, O'Connor GT, et al. Home and allergic characteristics of children with asthma in seven U.S. urban communities and design of an environmental intervention: the Inner-City Asthma Study. Environmental health perspectives 2002;110:939-45.

26. Permaul P, Petty C, Sheehan W, et al. Mouse Allergen Exposure in Urban Schools and its Effect on Childhood Asthma Morbidity. J Allergy and Clin Immunol 2013;131:AB 141.
27. Sheehan WJ, Rangsithienchai PA, Muilenberg ML, et al. Mouse allergens in urban elementary schools and homes of children with asthma. Ann Allergy Asthma Immunol 2009;102:125-30.
28. Baxi S, Petty C, Fu C, et al. Classroom Fungal Spore Exposure and Asthma Morbidity in Inner-City School Children. J Aller Clin Immunol 2013;131:AB 54.
29. Baxi S, Sheehan WJ, Permaul P, et al. Airborne Fungus Diversity and Concentrations in Inner City Elementary Schools Ped Aller Immunol 2013;24:697-703.
30. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. The New England journal of medicine 2011;364:1005-15.
31. Teach SJ, Gergen PJ, Szefler SJ, et al. Seasonal risk factors for asthma exacerbations among inner-city children. J Allergy Clin Immunol 2015;135:1465-73 e5.
32. Covar RA, Spahn JD, Martin RJ, et al. Safety and application of induced sputum analysis in childhood asthma. J Allergy Clin Immunol 2004;114:575-82.
33. Strunk RC, Szefler SJ, Phillips BR, et al. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. J Allergy Clin Immunol 2003;112:883-92.
34. Spanier AJ, Hornung R, Lierl M, Lanphear BP. Environmental exposures and exhaled nitric oxide in children with asthma. J Pediatr 2006;149:220-6.
35. Simpson A, Custovic A, Pipis S, Adisesh A, Faragher B, Woodcock A. Exhaled nitric oxide, sensitization, and exposure to allergens in patients with asthma who are not taking inhaled steroids. American journal of respiratory and critical care medicine 1999;160:45-9.

36. Szefler SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. Lancet 2008;372:1065-72.
37. Meyts I, Proesmans M, De Boeck K. Exhaled nitric oxide corresponds with office evaluation of asthma control. Pediatr Pulmonol 2003;36:283-9.
38. Delgado-Corcoran C, Kissoon N, Murphy SP, Duckworth LJ. Exhaled nitric oxide reflects asthma severity and asthma control. Pediatr Crit Care Med 2004;5:48-52.
39. Togias A. Rhinitis and asthma: evidence for respiratory system integration. J Allergy Clin Immunol 2003;111:1171-83; quiz 84.
40. Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. J Allergy Clin Immunol 2001;107:469-76.
41. Corren J, Adinoff AD, Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. J Allergy Clin Immunol 1992;89:611-8.
42. Nolte D, Berger D. On vagal bronchoconstriction in asthmatic patients by nasal irritation. Eur J Respir Dis Suppl 1983;128 (Pt 1):110-5.
43. Littell NT, Carlisle CC, Millman RP, Braman SS. Changes in airway resistance following nasal provocation. Am Rev Respir Dis 1990;141:580-3.
44. Lohia S, Schlosser RJ, Soler ZM. Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis. Allergy 2013;68:569-79.
45. 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;113:415-9.
46. National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.

http://www.nhlbi.nih.gov/guidelines/asthma/: U.S. Department of Health and Human Services; 2007.

47. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. . 2015. (Accessed October 10, 2015, 2015, at http://www.ginasthma.org.)

48. Covar RA, Spahn JD, Murphy JR, Szefler SJ, Childhood Asthma Management Program Research G. Progression of asthma measured by lung function in the childhood asthma management program. American journal of respiratory and critical care medicine 2004;170:234-41.

49. Horak E, Lanigan A, Roberts M, et al. Longitudinal study of childhood wheezy bronchitis and asthma: outcome at age 42. BMJ 2003;326:422-3.

50. Oswald H, Phelan PD, Lanigan A, et al. Childhood asthma and lung function in mid-adult life. Pediatr Pulmonol 1997;23:14-20.

51. Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD, Group CR. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. Pediatrics 2006;118:e347-55.

52. Weiss ST, Van Natta ML, Zeiger RS. Relationship between increased airway responsiveness and asthma severity in the childhood asthma management program. American journal of respiratory and critical care medicine 2000;162:50-6.

53. Wang Z, May SM, Charoenlap S, et al. Effects of secondhand smoke exposure on asthma morbidity and health care utilization in children: a systematic review and meta-analysis. Ann Allergy Asthma Immunol 2015;115:396-401 e2.

54. Comhair SA, Gaston BM, Ricci KS, et al. Detrimental effects of environmental tobacco smoke in relation to asthma severity. PloS one 2011;6:e18574.

55. Howrylak JA, Spanier AJ, Huang B, et al. Cotinine in children admitted for asthma and readmission. Pediatrics 2014;133:e355-62.
56. Laoudi Y, Nikasinovic L, Sahraoui F, Grimfeld A, Momas I, Just J. Passive smoking is a major determinant of exhaled nitric oxide levels in allergic asthmatic children. Allergy 2010;65:491-7.
57. Yates DH, Breen H, Thomas PS. Passive smoke inhalation decreases exhaled nitric oxide in normal subjects. American journal of respiratory and critical care medicine 2001;164:1043-6.
58. Kharitonov SA, Robbins RA, Yates D, Keatings V, Barnes PJ. Acute and chronic effects of cigarette smoking on exhaled nitric oxide. American journal of respiratory and critical care medicine 1995;152:609-12.
59. Halterman JS, Borrelli B, Tremblay P, et al. Screening for environmental tobacco smoke exposure among inner-city children with asthma. Pediatrics 2008;122:1277-83.
60. Kattan M, Mitchell H, Eggleston P, et al. Characteristics of inner-city children with asthma: the National Cooperative Inner-City Asthma Study. Pediatr Pulmonol 1997;24:253-62.
61. Kumar R, Curtis LM, Khiani S, et al. A community-based study of tobacco smoke exposure among inner-city children with asthma in Chicago. J Allergy Clin Immunol 2008;122:754-9 e1.
62. Matsui EC, Hansel NN, Aloe C, et al. Indoor pollutant exposures modify the effect of airborne endotoxin on asthma in urban children. American journal of respiratory and critical care medicine 2013;188:1210-5.
63. Goleva E, Searing DA, Jackson LP, Richers BN, Leung DY. Steroid requirements and immune associations with vitamin D are stronger in children than adults with asthma. J Allergy Clin Immunol 2012;129:1243-51.

64. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. American journal of respiratory and critical care medicine 2010;181:699-704.
65. Wu AC, Tantisira K, Li L, et al. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. American journal of respiratory and critical care medicine 2012;186:508-13.
66. Paul G, Brehm JM, Alcorn JF, Holguin F, Aujla SJ, Celedon JC. Vitamin D and asthma. American journal of respiratory and critical care medicine 2012;185:124-32.
67. Brehm JM, Schuemann B, Fuhlbrigge AL, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. J Allergy Clin Immunol 2010;126:52-8 e5.
68. Brehm JM, Acosta-Perez E, Klei L, et al. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. American journal of respiratory and critical care medicine 2012;186:140-6.
69. Brehm JM, Celedon JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. American journal of respiratory and critical care medicine 2009;179:765-71.
70. Gergen PJ, Teach SJ, Mitchell HE, et al. Lack of a relation between serum 25-hydroxyvitamin D concentrations and asthma in adolescents. Am J Clin Nutr 2013;97:1228-34.
71. Pojsupap S, Iliriani K, Sampaio TZ, et al. Efficacy of high-dose vitamin D in pediatric asthma: a systematic review and meta-analysis. The Journal of asthma : official journal of the Association for the Care of Asthma 2015;52:382-90.
72. Freishtat RJ, Iqbal SF, Pillai DK, et al. High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. J Pediatr 2010;156:948-52.

73. Wright RJ, Mitchell H, Visness CM, et al. Community violence and asthma morbidity: the Inner-City Asthma Study. Am J Public Health 2004;94:625-32.
74. Wright RJ, Steinbach SF. Violence: an unrecognized environmental exposure that may contribute to greater asthma morbidity in high risk inner-city populations. Environmental health perspectives 2001;109:1085-9.
75. Sandberg S, Jarvenpaa S, Penttinen A, Paton JY, McCann DC. Asthma exacerbations in children immediately following stressful life events: a Cox's hierarchical regression. Thorax 2004;59:1046-51.
76. Sandberg S, Paton JY, Ahola S, et al. The role of acute and chronic stress in asthma attacks in children. Lancet 2000;356:982-7.
77. Chen E, Hanson MD, Paterson LQ, Griffin MJ, Walker HA, Miller GE. Socioeconomic status and inflammatory processes in childhood asthma: the role of psychological stress. J Allergy Clin Immunol 2006;117:1014-20.
78. Chen E, Strunk RC, Bacharier LB, Chan M, Miller GE. Socioeconomic status associated with exhaled nitric oxide responses to acute stress in children with asthma. Brain Behav Immun 2010;24:444-50.
79. Liu LY, Coe CL, Swenson CA, Kelly EA, Kita H, Busse WW. School examinations enhance airway inflammation to antigen challenge. American journal of respiratory and critical care medicine 2002;165:1062-7.
80. Ritz T, Ayala ES, Trueba AF, Vance CD, Auchus RJ. Acute stress-induced increases in exhaled nitric oxide in asthma and their association with endogenous cortisol. American journal of respiratory and critical care medicine 2011;183:26-30.
81. Ritz T, Trueba AF, Simon E, Auchus RJ. Increases in exhaled nitric oxide after acute stress: association with measures of negative affect and depressive mood. Psychosom Med 2014;76:716-25.

82. Tal A, Miklich DR. Emotionally induced decreases in pulmonary flow rates in asthmatic children. Psychosom Med 1976;38:190-200.
83. Ritz T, Kullowatz A, Goldman MD, et al. Airway response to emotional stimuli in asthma: the role of the cholinergic pathway. Journal of applied physiology 2010;108:1542-9.
84. McQuaid EL, Fritz GK, Nassau JH, Lilly MK, Mansell A, Klein RB. Stress and airway resistance in children with asthma. J Psychosom Res 2000;49:239-45.
85. Kattan M, Kumar R, Bloomberg GR, et al. Asthma control, adiposity, and adipokines among inner-city adolescents. J Allergy Clin Immunol 2010;125:584-92.
86. Black MH, Zhou H, Takayanagi M, Jacobsen SJ, Koebnick C. Increased asthma risk and asthma-related health care complications associated with childhood obesity. Am J Epidemiol 2013;178:1120-8.
87. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. Respir Med 2007;101:2240-7.
88. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. Eur Respir J 2006;27:495-503.
89. Strunk RC, Colvin R, Bacharier LB, et al. Airway Obstruction Worsens in Young Adults with Asthma Who Become Obese. J Allergy Clin Immunol Pract 2015;3:765-71 e2.
90. Pakhale S, Baron J, Dent R, Vandemheen K, Aaron SD. Effects of weight loss on airway responsiveness in obese adults with asthma: does weight loss lead to reversibility of asthma? Chest 2015;147:1582-90.
91. McGarry ME, Castellanos E, Thakur N, et al. Obesity and bronchodilator response in black and Hispanic children and adolescents with asthma. Chest 2015;147:1591-8.
92. Kumanyika SK. Obesity in minority populations: an epidemiologic assessment. Obes Res 1994;2:166-82.

454 93. Pongracic JA, Krouse RZ, Babineau DC, et al. Asthma Phenotypes in the Inner City:
455 Distinguishing Characteristics of Difficult-to-Control Asthma in Children. J Aller Clin
456 Immunol Submitted simultaneously.

457 **TABLE E1**. Characterization of study participants by demographics and observed variables in
458 each domain. Summary statistics include mean (standard deviation) <minimum; maximum> for
459 normally distributed continuous variables, median [25th percentile; 75th percentile] <minimum;
460 maximum> for non-normally distributed continuous variables and frequency (percentage) for
461 categorical variables.
462

Characteristic	Summary Measure	N
Demographics		
Male	324 (57.75%)	561
Race[1]:		561
Black (non-Hispanic)	361 (64.35%)	
Hispanic	160 (28.52%)	
Other/Mixed	31 (5.53%)	
White (non-Hispanic)	9 (1.60%)	
Age at Screening (years)	10.80 (3.02) <6.00;17.00>	561
Income<$15,000[2]	308 (55.10%)	559
Obesity		
BMI z-score at Screening	0.98 (1.18) <-4.18;3.01>	561
BMI percentile at Screening[2]	85.84 (55.67, 97.66) <0.00, 99.87>	561
Vitamin D		
Total 25-hydroxyvitamin D at V0 (ng/mL)	19.31 (7.39) <2.50;50.29>	561
Environmental tobacco smoke exposure		
Number of smokers in the home at Screening:		561
0	329 (58.65%)	
1	171 (30.48%)	
>1	61 (10.87%)	
Urine cotinine at Screening (ng/mL)[3]		553
0 = 0-10	92 (16.64%)	
1 = 10-30	325 (58.77%)	
2 = 30-100	89 (16.09%)	
3 = 100-200	16 (2.89%)	
4 = 200-500	18 (3.25%)	
5 = 500-1000	7 (1.27%)	
6 = >1000	6 (1.08%)	
Stress		

Characteristic	Summary Measure	N
Caretaker Perceived Stress Scale at V0	14.93 (7.49) <0.00;36.00>	561
Rhinitis severity		
Mean of rhinitis medication score[4] between V0 and V6	10.33 (4.82) <0.00;15.00>	561
Variance of rhinitis medication score[4] between V0 and V6	14.68 (15.22) <0.00;64.29>	561
Mean of rhinitis symptom score[5] between V0 and V6	6.45 (3.75) <0.00;19.86>	561
Variance of rhinitis symptom score[5] between V0 and V6	17.91 (15.63) <0.00;113.30>	561
Allergic inflammation		
Blood eosinophil count at V0 (cells/mm3)[6]	300.00 [177.75, 500.00] <0.00;1700.00>	556
FeNO at V0 (ppb)[6]	19.50 [11.85;37.48] <2.50;162.48>	520
FeNO at V6 (ppb)[6]	24.00 [13.00;45.00] <3.15;300.00>	519
Pulmonary physiology		
Bronchodilator response at V6	10.26 (11.48) <-32.40;86.40>	518
Mean of FEV_1 (% predicted) between V0 and V6	93.68 (14.37) <56.03;145.90>	561
Variance of FEV_1 (% predicted) between V0 and V6	83.24 (97.97) <1.28;668.86>	561
Mean of FEV_1/FVC (x100) between V0 and V6	79.26 (8.10) <49.63;96.31>	560
Variance of FEV_1/FVC (x100) between V0 and V6	24.97 (32.32) <0.44;335.56>	559
Allergen sensitization		
Total serum IgE at V0 (kU/L)[6]	291.00 [92.0;840.00] <1.00;5001.00>	557
Number of allergen sensitizations[7] (panel of 22) at Screening	9.01 (6.24) <0.00;21.00>	561
Sensitized to molds[8] at V0	292 (52.05%)	561
Sensitized to dust mites[9] at V0	337 (60.1%)	561
Sensitized to roaches[10] at V0	323 (57.6%)	561
Sensitized to rodents[11] at V0	241 (43.0%)	561
Sensitized to pets[12] at V0	371 (66.1%)	561
Sensitized to pollen/peanut[13] at V0	406 (72.4%)	561
Sensitized to foods[14] at V0	172 (30.8%)	558
Asthma severity		

Characteristic	Summary Measure	N
ACT/cACT[15] at V6:		535
Well Controlled	434 (81.1%)	
Not Well Controlled	91 (17.0%)	
Very Poorly Controlled	10 (1.87%)	
Mean of controller treatment step between V0 and V6	3.14 (1.93) <0.00;6.00>	561
Variance of controller treatment step between V0 and V6	0.96 (0.89) <0.00;5.24>	561
Mean of CASI component - Day symptoms & albuterol use[16] between V0 and V6	0.30 (0.35) <0.00;2.00>	561
Variance of CASI component - Day symptoms & albuterol use[16] between V0 and V6	0.41 (0.56) <0.00;2.57>	561
Mean of CASI component - Night symptoms & albuterol use[17] between V0 and V6	0.27 (0.39) <0.00;2.00>	561
Variance of CASI component - Night symptoms & albuterol use[17] between V0 and V6	0.42 (0.61) <0.00;2.70>	561
Mean of CASI component - Exacerbations[18] between V0 and V6	0.30 (0.50) <0.00;4.00>	561
Variance of CASI component - Exacerbations[18] between V0 and V6	0.76 (1.44) <0.00;10.29>	561

1. Race is dichotomous (black vs. other) in the structural equation model.
2. Not included in the structural equation model.
3. Analyzed as a continuous variable in the structural equation model.
4. Rhinitis medication score is set to 0 for no medications, 5 for antihistamines only, 10 for nasal steroids only, and 15 for antihistamines and nasal steroids.
5. Rhinitis symptom score is based on the Modified Rhinitis Symptom Utility Index.[93]
6. Variable is log10 transformed in the structural equation model.
7. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: *Alternaria tenuis* (skin prick test) or *Alternaria alternata* (specific IgE), *Aspergillus fumigatus* (both skin prick test and specific IgE), *Cladosporium herbarum* (specific IgE only), *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, German cockroach, American cockroach, mouse, rat, cat, dog, oak, pecan, birch, maple, Eastern 8 tree mix, ragweed mix (giant/short; skin prick test) or short ragweed (specific Ige), timothy grass, Kentucky Blue/June, Orchard and Timothy (K-O-T) grass mix, peanut, egg and milk.
8. Sensitization is based on a positive prick skin test and/or positive specific IgE to at least one of the following allergens: *Alternaria tenuis* (skin prick test) or *Alternaria alternata* (specific IgE), *Aspergillus fumigatus*, and *Cladosporium herbarum*.
9. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*.
10. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: German cockroach and American cockroach.
11. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: mouse and rat.
12. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: cat and dog.
13. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: oak, pecan, birch, maple, Eastern 8 tree mix, ragweed, timothy grass, Kentucky Blue/June, Orchard and Timothy (K-O-T) grass mix, and peanut.
14. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: egg and milk.
15. ACT is categorized as very poorly controlled (≤15), not well controlled (≥16 & ≤19), and well controlled (≥20). cACT is categorized as very poorly controlled (≤12), not well controlled (≥13 & ≤19), and well controlled (≥20).

16. Composite Asthma Severity Index (CASI) component – Day symptoms includes measures of day asthma symptoms and albuterol use in the last 2 weeks (scoring range between 0 and 3).
17. CASI component – Night symptoms includes measures of night asthma symptoms and albuterol use in the last 2 weeks (scoring range between 0 and 3).
18. CASI component – Exacerbations includes hospitalizations and/or oral corticosteroid bursts in the last 2 months.

TABLE E2. Effect of age, sex and race on each domain. The direct effect of age is the adjusted standard deviation (SD) (± standard error (SE)) increase in each domain for every one SD increase in age while the direct effect of sex or race is the adjusted standard deviation (SD) (± standard error (SE)) increase in each domain comparing males to females or black and non-black respectively.

Domain	Standardized Direct Effect of Age	Standardized Direct Effect of Sex	Standardized Direct Effect of Race
Allergen Sensitization	0.097±0.045 (p=0.033)	0.136±0.045 (p=0.002)	0.077±0.045 (p=0.085)
Allergic Inflammation	0.187±0.059 (p=0.002)	0.136±0.051 (p=0.008)	-0.089±0.055 (p=0.106)
Pulmonary Physiology	-0.261±0.060 (p<0.001)	-0.005±0.056 (p=0.933)	0.128±0.057 (p=0.025)
ETS Exposure	0.222±0.067 (p=0.001)	-0.121±0.068 (p=0.075)	0.205±0.070 (p=0.003)
Vitamin D	-0.286±0.036 (p<0.001)	0.163±0.040 (p<0.001)	-0.16±0.039 (p<0.001)
Stress	-0.033±0.043 (p=0.435)	-0.002±0.042 (p=0.96)	-0.002±0.044 (p=0.96)
Obesity	BMI z-score adjusts for age and sex already so association not included.	BMI z-score adjusts for age and sex already so association not included.	0.023±0.043 (p=0.588)
Rhinitis Severity	-0.018±0.053 (p=0.74)	-0.171±0.052 (p=0.001)	0.144±0.049 (p=0.003)
Asthma Severity	-0.043±0.06 (p=0.472)	-0.036±0.05 (p=0.477)	-0.108±0.052 (p=0.039)

TABLE E3. Indirect effects of Allergen Sensitization on Asthma Severity. Estimates (± standard error) are interpreted as the standard deviation (SD) increase in Asthma Severity for every one SD increase in Allergen Sensitization, via the intermediate or intermediate pathway. All estimates are adjusted for age, sex and race.

Independent Domain	Intermediate or Intermediate Pathway	Standardized Indirect Effect	Standardized Total Indirect Effect
Allergen Sensitization	Allergic Inflammation	-0.16±0.06 (p=0.01)	0.18±0.05 (p<0.001)
	Allergic Inflammation → Pulmonary Physiology	0.19±0.04 (p<0.001)	
	Allergic Inflammation → Rhinitis Severity	0.16±0.03 (p<0.001)	
	Allergic Inflammation → Rhinitis Severity → Pulmonary Physiology	-0.01±0.01 (p=0.35)	

TABLE E4. Mediated effects of domains on Asthma Severity. The direct effect is the adjusted standard deviation (SD) (± standard error (SE)) increase in Asthma Severity for every one SD increase in the independent domain. The indirect effect is the SD (± SE) increase in Asthma Severity for every one SD increase in independent domain, via the mediator or mediating pathway. The total effect is the SD (± SE) increase in Asthma Severity for every one SD increase in the independent domain. All estimates are adjusted for age, sex and race.

Independent Domain	Mediator or Mediating Pathway	Standardized Direct Effect	Standardized Indirect Effect	Standardized Total Effect	Evidence of Mediation
Allergic Inflammation	Pulmonary Physiology	-0.20±0.08 (p=0.01)	0.24±0.05 (p<0.001)	0.22±0.06 (p<0.001)	Yes
	Rhinitis Severity		0.20±0.04 (p<0.001)		Yes
	Rhinitis Severity → Pulmonary Physiology		-0.01±0.01 (p=0.35)		No
Environmental Tobacco Smoke	Allergic Inflammation	0.17±0.08 (p=0.03)	0.02±0.02 (p=0.41)	0.30±0.08 (p<0.001)	No
	Pulmonary Physiology		0.14±0.04 (p<0.001)		Yes
	Allergic Inflammation → Pulmonary Physiology		-0.02±0.02 (p=0.40)		No
	Allergic Inflammation → Rhinitis Severity		-0.02±0.02 (p=0.40)		No
	Allergic Inflammation → Rhinitis Severity → Pulmonary Physiology		0.001±0.002 (p=0.51)		No
Vitamin D	Allergic Inflammation	0.01±0.05 (p=0.82)	0.03±0.02 (p=0.08)	0.01±0.05 (p=0.89)	No
	Pulmonary Physiology		0.03±0.02 (p=0.24)		No
	Allergic Inflammation → Pulmonary Physiology		-0.04±0.02 (p=0.03)		No
	Allergic Inflammation → Rhinitis Severity		-0.03±0.01 (p=0.04)		No
	Allergic Inflammation → Rhinitis Severity → Pulmonary Physiology		0.002±0.002 (p=0.39)		No
Stress	Allergic Inflammation	0.06±0.05 (p=0.22)	-0.01±0.01 (p=0.24)	0.08±0.05 (p=0.12)	No
	Pulmonary Physiology		0.003±0.03 (p=0.90)		No
	Allergic Inflammation → Pulmonary Physiology		0.02±0.01 (p=0.21)		No
	Allergic Inflammation → Rhinitis Severity		0.01±0.01 (p=0.20)		No
	Allergic Inflammation → Rhinitis Severity → Pulmonary Physiology		-0.001±0.001 (p=0.44)		No
Obesity	Pulmonary Physiology	0.06±0.04 (p=0.11)	-0.01±0.02 (p=0.76)	0.06±0.04 (p=0.18)	No
Rhinitis Severity	Pulmonary Physiology	0.52±0.06 (p<0.001)	-0.03±0.04 (p=0.34)	0.48±0.06 (p<0.001)	No

TABLE E5. Frequency and percentage of groups based on urine cotinine at Screening stratified by number of smokers in the home ($p<0.001$ based on Pearson chi-squared test).

Number of smokers in the home	Urine cotinine at Screening (ng/mL)			
	0-10	**10-30**	**>30**	**Total**
0	65 (20.1%)	214 (66.0%)	45 (13.9%)	324
1	22 (13.1%)	86 (51.2%)	60 (35.7%)	168
≥1	5 (8.2%)	25 (41.0%)	31 (50.8%)	61
Total	92	325	136	553