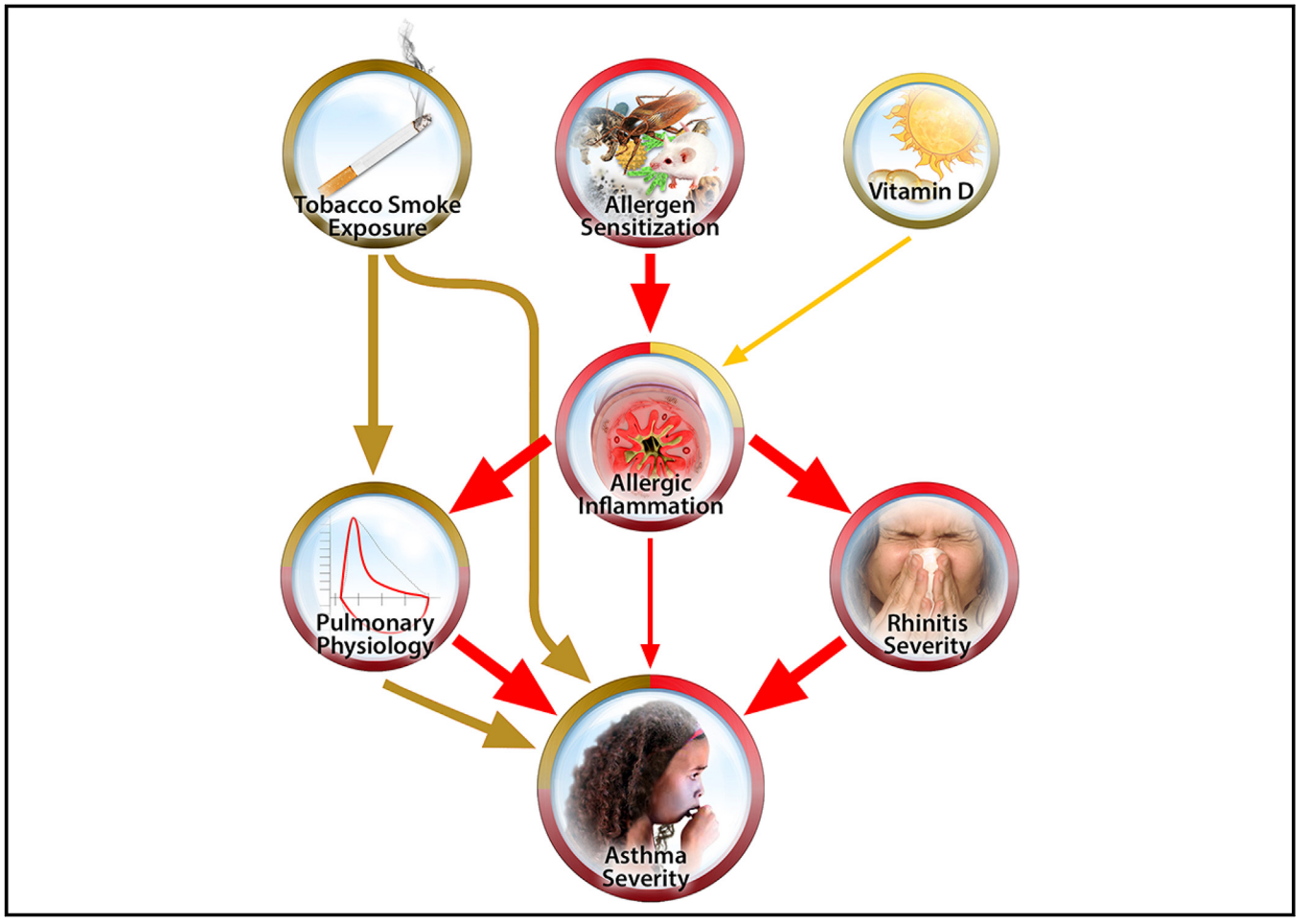
# Pathways through which asthma risk factors contribute to asthma severity in inner-city children

**Andrew H. Liu, MD,[a,b] Denise C. Babineau, PhD,[c] Rebecca Z. Krouse, MS,[c] Edward M. Zoratti, MD,[d] Jacqueline A. Pongracic, MD,[e] George T. O'Connor, MD, MS,[f] Robert A. Wood, MD,[g] Gurjit K. Khurana Hershey, MD, PhD,[h] Carolyn M. Kercsmar, MD,[h] Rebecca S. Gruchalla, MD, PhD,[i] Meyer Kattan, MD,[j] Stephen J. Teach, MD, MPH,[k] Melanie Makhija, MD,[e] Dinesh Pillai, MD,[k] Carin I. Lamm, MD,[j] James E. Gern, MD,[l] Steven M. Sigelman, RN, MHA,[m] Peter J. Gergen, MD, MPH,[m] Alkis Togias, MD,[m] Cynthia M. Visness, PhD,[c] and William W. Busse, MD[l]** *Denver and Aurora, Colo; Chapel Hill, NC; Detroit, Mich; Chicago, Ill; Boston, Mass; Baltimore, Md; Cincinnati, Ohio; Dallas, Tex; New York, NY; Washington, DC; Madison, Wis; and Bethesda, Md*

## GRAPHICAL ABSTRACT




From [a]National Jewish Health, Denver; [b]Children's Hospital Colorado and University of Colorado School of Medicine, Aurora; [c]the Rho Federal Systems Division, Chapel Hill; [d]the Henry Ford Health System, Detroit; [e]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago; [f]Boston University School of Medicine, Boston; [g]Johns Hopkins University School of Medicine, Baltimore; [h]Cincinnati Children's Hospital, Cincinnati; [i]the University of Texas Southwestern Medical Center, Dallas; [j]the College of Physicians and Surgeons, Columbia University, New York; [k]Children's National Health System and the George Washington University School of Medicine and Health Sciences, Washington; [l]the University of Wisconsin School of Medicine and Public Health, Madison; and [m]the National Institute of Allergy and Infectious Diseases, Bethesda.

**Background: Pathway analyses can be used to determine how host and environmental factors contribute to asthma severity.**
**Objective: To investigate pathways explaining asthma severity in inner-city children.**
**Methods: On the basis of medical evidence in the published literature, we developed a conceptual model to describe how 8 risk-factor domains (allergen sensitization, allergic inflammation, pulmonary physiology, stress, obesity, vitamin D, environmental tobacco smoke [ETS] exposure, and rhinitis severity) are linked to asthma severity. To estimate the relative magnitude and significance of hypothesized relationships among these domains and asthma severity, we applied a causal network analysis to test our model in an Inner-City Asthma Consortium study. Participants comprised 6- to 17-year-old children (n = 561) with asthma and rhinitis from 9 US inner cities who were evaluated every 2 months for 1 year. Asthma severity was measured by a longitudinal composite assessment of day and night symptoms, exacerbations, and controller usage.**
**Results: Our conceptual model explained 53.4% of the variance in asthma severity. An allergy pathway (linking allergen sensitization, allergic inflammation, pulmonary physiology, and rhinitis severity domains to asthma severity) and the ETS exposure pathway (linking ETS exposure and pulmonary physiology domains to asthma severity) exerted significant effects on asthma severity. Among the domains, pulmonary physiology and rhinitis severity had the largest significant standardized total effects on asthma severity (−0.51 and 0.48, respectively), followed by ETS exposure (0.30) and allergic inflammation (0.22). Although vitamin D had modest but significant indirect effects on asthma severity, its total effect was insignificant (0.01).**
**Conclusions: The standardized effect sizes generated by a causal network analysis quantify the relative contributions of different domains and can be used to prioritize interventions to address asthma severity. (J Allergy Clin Immunol 2016;138:1042-50.)**

***Key words:*** *Asthma, children, inner-city, allergy, sensitization, inflammation, lung function, pulmonary physiology, rhinitis, environmental tobacco smoke exposure*

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Inner-city children experience a high burden of asthma symptoms and morbidity despite guidelines-directed care.[1,2] The National Institutes of Health/National Institute of Allergy and Infectious Diseases sponsored the Inner-City Asthma Consortium Asthma Phenotypes in the Inner City (APIC) study to investigate how host and environmental factors contribute to asthma severity among children carefully monitored while prospectively receiving optimal, guidelines-based care. Results of the primary objectives of the APIC study are presented in the articles titled "Asthma Phenotypes in the Inner City: Distinguishing Characteristics of Difficult-to-Control Asthma in Children"[3] and "Asthma Phenotypes in Inner-City Children,"[4] which appear in this issue of the journal.

On the basis of clinical and mechanistic evidence in the published literature that we have detailed in this article's Online Repository at www.jacionline.org, we developed a conceptual model to describe how 8 risk-factor domains (allergen sensitization, allergic inflammation, pulmonary physiology, stress, obesity, vitamin D, environmental tobacco smoke [ETS] exposure, and rhinitis severity) are linked to asthma severity (Fig 1). This model allows us to conceptualize which domains have a direct influence on asthma severity and/or an indirect influence on asthma severity by acting through another domain(s). We then tested this conceptual model in the APIC cohort and data set using a causal network analysis, a quantitative approach that is commonly used to describe the effects of genomics, metabolomics, or biochemical pathway influences on disease phenotypes but, to our knowledge, has never been applied in the context of

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Corresponding author: Andrew H. Liu, MD, Children's Hospital Colorado, 13123 East 16th Ave, Box B395, Aurora CO 80045. E-mail: Andrew.liu@childrenscolorado.org.

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