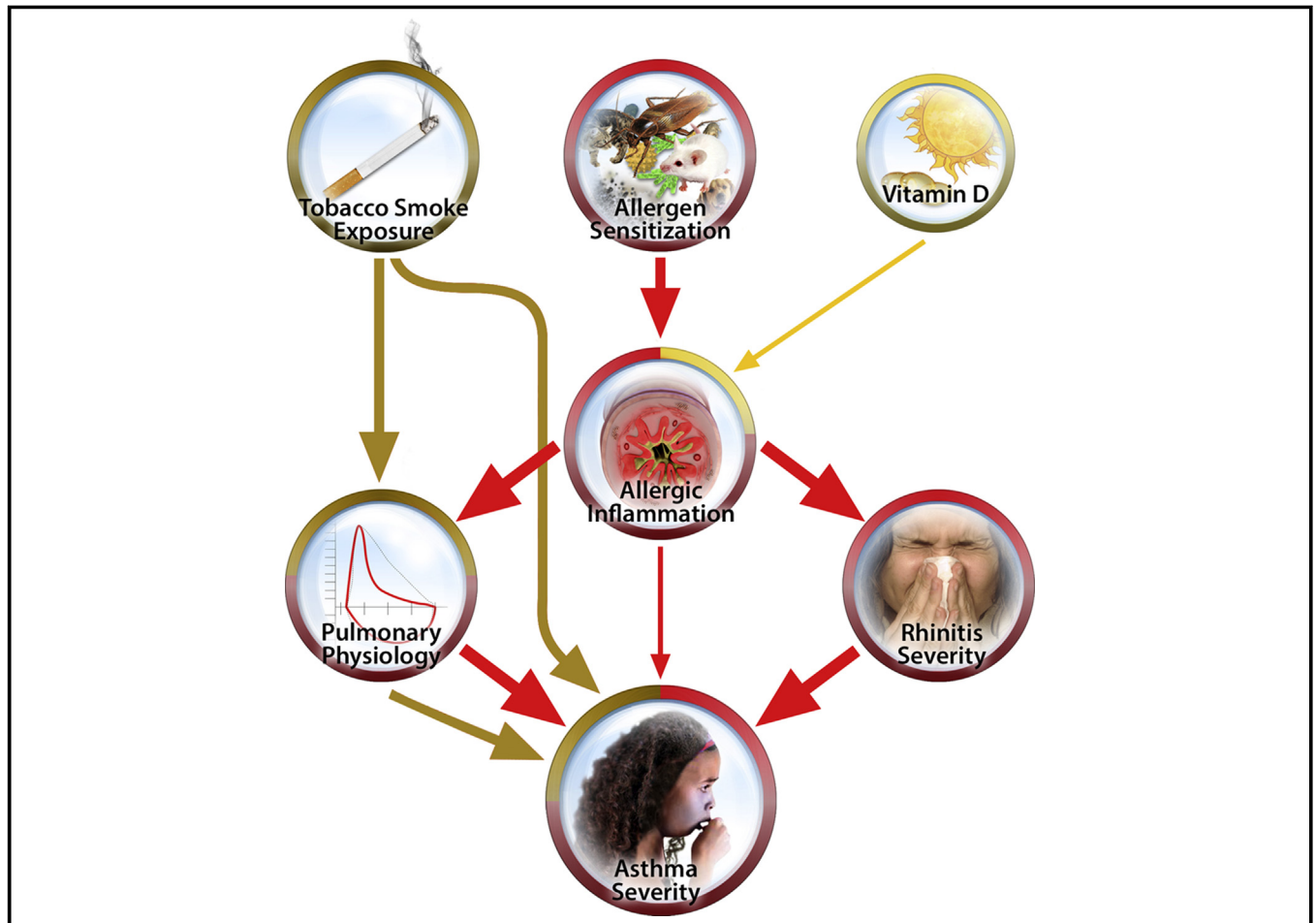


Pathways through which asthma risk factors contribute to asthma severity in inner-city children



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GRAPHICAL ABSTRACT



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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](http://www.jacionline.org) 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

This project has been funded in whole or in part with federal funds from the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Department of Health and Human Services (under contract nos. HHSN272200900052C and HHSN272201000052I, and 1UM1AI114271-01). Additional support was provided by the National Center for Research Resources (NCRR), and the National Center for Advancing Translational Sciences (NCATS), NIH (under grant nos. NCRR/NIH UL1TR000451, UL1RR025780, UL1TR000075 and NCATS/NIH UL1TR000154, UL1TR001082, UL1TR000077-04, UL1TR000040, UL1TR000150, and UL1TR001105). GlaxoSmithKline (GSK) provided Ventolin, Flovent, Advair, and Flonase under a clinical trial agreement with NIH NIAID; GSK did not have a role in the development or approval of the protocol, conduct of the trial, data analysis, manuscript preparation, or the decision to submit the manuscript for publication.

Disclosure of potential conflict of interest: A. H. Liu has received a grant from the National Institutes of Health, is a member of the Data Monitoring Committee for an asthma study for GlaxoSmithKline (GSK), and has received payment for lectures from Merck. D. C. Babineau, R. Z. Krouse, and C. M. Visness have received grants from the National Institutes of Health (NIH)-National Institute of Allergy and Infectious Diseases (NIAID). E. M. Zoratti, G. K. K. Hershey, M. Makhija, D. Pillai, C. I. Lamm, and S. M. Sigelman have received grants from the NIH. J. A. Pongracic has received travel support and a subcontract from the University of Wisconsin; has received writing assistance, medicines, equipment, or administrative support from GSK; and has received study drugs for other studies from GSK, Teva, Merck, Boehringer-Ingelheim, and Genentech/Novartis. G. T. O’Connor has received grants from the NIH and has consultant arrangements with AstraZeneca. R. A. Wood has received grants from the NIH, DBV, and Aimmune; has consultant arrangements with Sanofi and Stallergenes; is employed by Johns Hopkins University; and has received royalties from Up To Date. C. M. Kerckmar has received a grant from the NIH and was the chair of the Data Safety Monitoring Board on GSK-funded, Food and Drug Administration–mandated trial

evaluating the safety of inhaled corticosteroid + long-acting beta-agonist versus inhaled corticosteroid alone in children (ClinicalTrials.gov Identifier: NCT01462344). R. S. Gruchalla is employed by the Center for Biologics Evaluation and Research and has consultant arrangements with the Massachusetts Medical Society. M. Kattan has received a grant from the NIH-NIAID and is on the advisory board for Novartis Pharma. S. J. Teach has received grants from the NIH-NIAID, Novartis, Patient-Centered Outcomes Research Institute, Fight for Children Foundation, EJF Philanthropies, and the NIH-National Heart, Lung, and Blood Institute; has consultant arrangements with Novartis; and has received royalties from Up To Date. J. E. Gern has received grants from the NIH and GSK; has consultant arrangements with GSK, Genentech, Amgen, Novartis, Janssen, and Regeneron; has received payment for the development of educational presentations from Boehringer-Ingelheim; and has stock/stock options in 3V BioSciences. W. W. Busse has received a grant from the NIH-NIAID; has received partial study funding and provision of study drug and placebo from Novartis; is a member of the Data Safety Monitoring Boards for Boston Scientific and Circassia; is a member of the Study Oversight Committee for ICON; and has consultant arrangements with Novartis, GSK, Genentech, Roche, Pfizer, Merck, Boehringer-Ingelheim, Sanofi, AstraZeneca, Teva, Tekeda, Aerocrine, and 3M. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication November 20, 2015; revised May 24, 2016; accepted for publication June 3, 2016.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2016.06.060>

Abbreviations used

APIC: Asthma Phenotypes in the Inner City
 BMI: Body mass index
 ETS: Environmental tobacco smoke

explaining asthma severity. Understanding the relative contributions of these risk factors to asthma severity in inner-city children, via direct and/or indirect pathways, can provide a basis for further investigations into linking mechanisms while also guiding personalized asthma management and population health policy.

METHODS**Conceptual model of risk factors contributing to asthma severity**

A conceptual model was developed to hypothetically describe how 8 risk-factor domains of allergen sensitization, allergic inflammation, pulmonary physiology, stress, obesity, vitamin D, ETS exposure, and rhinitis severity are linked to asthma severity in children (Fig 1). These domains were based on variables ascertained on at least the large majority of APIC study participants, and justified by clinical and mechanistic evidence in the published literature. The literature review substantiating the links of this model is described in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org.

Study participants

All study participants included in this investigation were in the National Institute of Allergy and Infectious Diseases–sponsored Inner-City Asthma Consortium APIC study. Details of the APIC cohort are reported in this issue of the journal in Pongracic et al.³ Briefly, APIC included 6- to 17-year-old children with a broad spectrum of asthma residing in low-income census tracts in 9 US cities (Baltimore, Md; Boston, Mass; Chicago, Ill; Cincinnati, Ohio; Dallas, Tex; Denver, Colo; Detroit, Mich; New York, NY; and Washington, DC). For inclusion, study participants had to have a diagnosis of asthma by a physician and demonstrate adequate adherence to study-prescribed daily asthma controller therapies. The protocol was approved by institutional review boards from each participating center, and written informed consent was obtained by the legal guardians of participating children.

Study and assessments

APIC participants received a comprehensive assessment at screening and had their asthma and rhinitis managed on the basis of National Asthma Education and Prevention Program Expert Panel Report 3⁵ and the Allergic Rhinitis and its Impact on Asthma^{6,7} guidelines-derived treatment algorithms. Clinical assessment and medication adjustments occurred every 2 months for 1 year, denoted by V0, V1, V2, V3, V4, V5, and V6, as described in Pongracic et al.³ All medications (except montelukast) were provided free of charge to the study participants.

The variables used to define the domains of asthma severity and its risk factors are presented in Table I. The asthma severity, rhinitis severity, allergen sensitization, allergic inflammation, pulmonary physiology, and ETS exposure domains were composed of multiple variables, whereas vitamin D, stress, and obesity domains were composed of single variables (Table I; see Table E1 in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org). The asthma severity domain was composed of 4 Composite Asthma Severity Index components (day symptoms and albuterol use, night symptoms and albuterol use, daily controller treatment step level, and exacerbations) measured at V0 to V6 and summarized using the mean and variance across all visits,¹³ as well as by the Asthma Control Test/Childhood Asthma Control Test categories (well controlled, not well controlled, very poorly controlled) at V6.^{8–12} The rhinitis severity domain included the mean and variance of both a symptom score and a medication use score across the visits. The allergen sensitization domain was composed of total serum IgE level, the number of allergen

sensitizations, and determination of allergen sensitization to molds, dust mites, cockroaches, rodents, pets, pollen/peanut, and foods as described.³ The allergic inflammation domain included fractional exhaled nitric oxide and blood eosinophil counts. The pulmonary physiology domain was composed of spirometry measures (FEV₁ [% predicted] and FEV₁/forced vital capacity) at V0 to V6, which were summarized using the mean and variance across the visits, as well as the FEV₁ bronchodilator response at V6. The ETS exposure domain was composed of the number of smokers in the home and urine cotinine, as measured by NicAlert test strips (Nymox Pharmaceutical Corp, Hasbrouck Heights, NJ).

Total serum IgE and allergen-specific IgE levels (ImmunoCAP; Phadia, Uppsala Sweden) to a panel of 20 allergens (17 common inhalant allergens and egg, milk, and peanut) were measured from blood drawn at V0. Prick skin testing was performed at screening for 12 common indoor and outdoor allergens. *Allergen sensitization* was defined by a wheal size of 3 mm or larger than that achieved with the saline control on prick skin testing or specific IgE level of 0.35 kUA/L or more. A total of 22 allergen sensitizations were assessed and grouped in clusters (described in Pongracic et al).³ The blood sample at V0 was also used to measure blood eosinophil count (cells/mm³) and serum vitamin D concentration, determined by serum total 25-hydroxyvitamin D using HPLC.

Spirometry was performed at every asthma/rhinitis management visit, and bronchodilator reversibility was performed at V6. Acceptability was determined by American Thoracic Society/European Respiratory Society guidelines.¹⁴ For children younger than 8 years, American Thoracic Society Preschool Guidelines were used.¹⁵ Fractional exhaled nitric oxide was measured at V0 and V6 using the NIOX MINO device (Aerocrine, Stockholm, Sweden).

Obesity was determined at screening by body mass index (BMI) *z* score based on Centers for Disease Control and Prevention guidelines.¹⁶ Stress was measured in the caretaker at V0 using the 10-item Perceived Stress Scale.¹⁷ ETS exposure was assessed at screening by the number of smokers in the home, and urine cotinine was measured using NicAlert test strips (Nymox Pharmaceutical Corp). The NicAlert test semi-quantitatively tests for cotinine using levels, which correspond to concentration ranges. Levels 0 to 2 (<100 ng/mL) indicate a nonuser of tobacco products and levels 3 to 6 (>100 ng/mL) indicate a user of tobacco products. The lower limit of detection is 10 ng/mL or level 1.¹⁸ Compared with LC-MS/MS, NicAlert test strips have 91% specificity, 92% sensitivity, 94% positive predictive value, and 88% negative predictive value.¹⁹

Statistical methods

To test our conceptual model of asthma severity in Fig 1, a causal network analysis was implemented using structural equation models²⁰ to simultaneously perform (1) a confirmatory factor analysis of each domain in Table I to estimate the relationship between the domain of interest and each observed variable used to measure the domain and (2) a series of regression models to estimate the standardized direct effect of each independent domain on a dependent domain (represented by arrows in Fig 1). To interpret the estimated effects from this model, note that (1) increases in the domains of asthma severity, allergen sensitization, allergic inflammation, rhinitis severity, ETS exposure, and obesity are interpreted as poorer outcomes, whereas increases in the domains of pulmonary physiology and vitamin D are interpreted as better outcomes and (2) a positive direct effect is interpreted as the SD increase in the dependent domain for every 1-SD increase in the independent domain, whereas a negative (or inverse) direct effect is interpreted as the SD decrease in the dependent domain for every 1-SD increase in the independent domain. To account for potential confounding from demographic variables, all estimates were adjusted for age at screening, sex, and race. All models were fit using Mplus Version 7.3.²¹

In cases in which our conceptual model indicated that the association between the independent and dependent domains could be mediated by another domain, we tested for mediated effects using the approach of Baron and Kenny,²² which splits the estimated total effect of the independent domain on the dependent domain into a sum of 2 parts: (1) the indirect effect of the independent domain on the dependent domain acting through a mediating domain or pathway and (2) the direct effect of the independent domain on the dependent domain, adjusting for the effect of any other domains that are

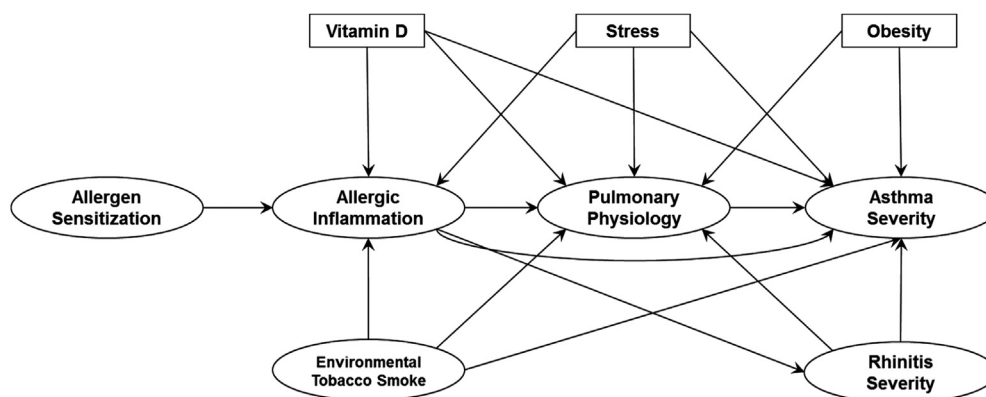


FIG 1. Conceptual model of asthma severity. This model was generated in advance of any analyses based on observations derived from the medical literature and became the test object of this study. Oval boxes indicate domains defined by multiple observed variables, whereas rectangles indicate domains defined by one observed variable only. An arrow connecting 2 domains represents the direction of the hypothesized relationship between the 2 domains.

hypothesized to be associated with the dependent domain. Evidence of mediation was found if the following 3 effects were statistically significant at the .05 significance level: (1) the total effect of the independent domain on the dependent domain; (2) the direct effect of the independent domain on the mediating domain or pathway; and (3) the direct effect of the mediating domain or pathway on the dependent domain. In cases in which our conceptual model indicated only an indirect effect between distal domains (and so no test of mediation could be conducted), only the indirect effect between the domains was estimated.

Because controller treatment step level is partially determined by measures of pulmonary physiology, a sensitivity analysis was performed in which asthma severity was redefined by removing the mean and variance of controller treatment step level between V0 and V6.

RESULTS

Participant characteristics

To ensure adequate longitudinal data on clinical asthma severity and rhinitis severity, of 717 APIC participants enrolled, 98 participants (13.7%) were excluded because they did not complete at least 4 of the 6 Evaluation and Management visits, and 40 additional participants (5.6%) were excluded because they did not have rhinitis. Participants without rhinitis were excluded because rhinitis severity, a domain in our hypothetical model of asthma severity, was not measured. An additional 18 study participants (2.5%) were excluded because of missing race classification, Caretaker Perceived Stress Scale at V0, BMI *z* score at screening, or total 25-hydroxyvitamin D at V0. This resulted in an analytic sample size of 561 participants (78.2% of the APIC cohort). Characteristics of the 561 participants are reported in Table E1. Overall, the median age at screening was 10.8 years, 57.8% were male, and 64.4% self-identified as non-Hispanic black while 28.5% self-identified as Hispanic. In addition, 55.1% were from households with an annual income of less than \$15,000.

Domains

Standardized estimates of the effect of each domain on each of the observed variables comprising each domain are shown in Fig E1, A-F, in this article's Online Repository at www.jacionline.org. All variables were significantly associated with their respective domains except for 1 variable in asthma severity (variability in controller treatment step across V0-V6).

Pathways

Fig 2 provides standardized estimates of the direct effects of each independent domain on each dependent domain for all pathways in our conceptual model using the APIC data; significant indirect effects are also indicated by the thick arrows. To address potential confounding arising from demographic covariates, all estimates were adjusted for age, sex, and race. Table E2 in this article's Online Repository at www.jacionline.org provides standardized estimates of the effects of age, sex, and race on each domain. This model accounted for 53.4% of the variation in asthma severity. Root mean square error of approximation, a commonly used measure of how well a structural equation model fits the observed data, was 0.063 (90% CI, 0.060-0.067), indicating an adequate fit.²³ Interpretation of these results by pathways is discussed in the following sections.

Allergy pathway

Fig 3, A, highlights the pathways to asthma severity through allergen sensitization, allergic inflammation, pulmonary physiology, and rhinitis severity. Our results showed the following:

- Allergen sensitization was positively associated with allergic inflammation. Specifically, for every 1-SD increase in allergen sensitization, allergic inflammation increased by 0.78 SDs (direct effect, 0.78 ± 0.04 ; $P < .001$). On comparing this standardized estimate to all others, we found that this association is the strongest one detected.
- Allergic inflammation was inversely associated with pulmonary physiology (direct effect, -0.47 ± 0.05 ; $P < .001$) and positively associated with rhinitis severity (direct effect, 0.39 ± 0.06 ; $P < .001$).
- Pulmonary physiology was inversely associated with asthma severity (direct effect, -0.51 ± 0.06 ; $P < .001$).
- Rhinitis severity was positively associated with asthma severity (direct effect, 0.52 ± 0.06 ; $P < .001$).

Analysis of indirect effects within the allergy pathway domains on asthma severity showed that allergen sensitization was positively associated with asthma severity via allergic inflammation, pulmonary physiology, and rhinitis severity such that the standardized total effect was 0.18 ± 0.05 ($P < .001$; see Table E3

TABLE I. Observed variables used to measure each domain

Domain	Observed variables
Asthma severity	Mean and variance of CASI component— Day symptoms and albuterol use* between V0 and V6 Mean and variance of CASI component— Night symptoms and albuterol score† between V0 and V6 Mean and variance of CASI component— Exacerbations‡ between V0 and V6 Mean and variance of controller treatment step between V0 and V6 ACT/cACT at V6 (categorized§)
Rhinitis severity	Mean and variance of rhinitis symptom score between V0 and V6 Mean and variance of rhinitis medication score¶ between V0 and V6
Allergen sensitization**	Total serum IgE level# at V0 Number of allergic sensitizations (panel of 22)†† at V0 Sensitized to molds‡‡ at V0 Sensitized to dust mites§§ at V0 Sensitized to roaches at V0 Sensitized to rodents¶¶ at V0 Sensitized to pets## at V0 Sensitized to pollen/peanut*** at V0 Sensitized to foods††† at V0
Allergic inflammation	Blood eosinophil count# at V0 Fractional exhaled nitric oxide# at V0 and V6
Pulmonary physiology	Bronchodilator response at V6 Mean and variance of FEV ₁ (% predicted) between V0 and V6 Mean and variance of FEV ₁ /FVC between V0 and V6
ETS exposure	Number of smokers in the home at screening (categorized‡‡‡) NicAlert result§§§ at screening
Vitamin D	Total 25-hydroxyvitamin D at V0
Stress	Caretaker Perceived Stress Scale score at V0
Obesity	BMI z score at screening

ACT, Asthma Control Test; cACT, Childhood Asthma Control Test; CASI, Composite Asthma Severity Index.

*CASI component—Day symptoms include measures of day asthma symptoms and albuterol use in the last 2 wk (scoring range between 0 and 3).

†CASI component—Night symptoms include measures of night asthma symptoms and albuterol use in the last 2 wk (scoring range between 0 and 3).

‡CASI component—Exacerbations include hospitalizations and/or oral corticosteroid bursts in the last 2 mo.

§ACT is categorized as very poorly controlled (≤ 15), not well controlled (≥ 16 and ≤ 19), and well controlled (≥ 20).^{5,8-10} cACT is categorized as very poorly controlled (≤ 12), not well controlled (≥ 13 and ≤ 19), and well controlled (≥ 20).^{11,12}

||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.

¶Rhinitis symptom score is based on the Modified Rhinitis Symptom Utility Index.³

#Variable is log₁₀ transformed in the structural equation model.

**Positive skin prick test result and/or a positive specific IgE.

††*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.

‡‡*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* and *Dermatophagoides pteronyssinus*.

|||German cockroach and American cockroach.

¶¶Mouse and rat.

##Cat and dog.

***Oak, pecan, birch, maple, Eastern 8 tree mix, ragweed, timothy grass, K-O-T grass mix, and peanut.

†††Egg and milk.

‡‡‡Number of smokers in the home is categorized as 0, 1, and >1 .

§§§Analyzed as a continuous variable in the structural equation model.

in this article's Online Repository at www.jacionline.org). Although allergic inflammation was inversely associated with asthma severity (direct effect, -0.20 ± 0.08 ; $P = .01$), the total effect of allergic inflammation on asthma severity was positive (0.22 ± 0.06 ; $P < .001$; see Table E4 in this article's Online Repository at www.jacionline.org) because the effect of allergic inflammation on asthma severity was mediated by pulmonary physiology and rhinitis severity (Table E4).

The ETS pathway

Fig 3, B, highlights the pathways from ETS exposure to asthma severity. Our results showed that ETS exposure was inversely associated with pulmonary physiology (direct effect,

-0.28 ± 0.07 ; $P < .001$) and positively associated with asthma severity (direct effect, 0.17 ± 0.08 ; $P = .03$). In addition, the total effect of ETS exposure on asthma severity was mediated by pulmonary physiology (Table E4). There was no evidence of an indirect effect of ETS exposure on asthma severity via allergic inflammation.

Vitamin D pathway

Fig 3, C, highlights the pathways from vitamin D to asthma severity. Our results showed that vitamin D was inversely associated with allergic inflammation (direct effect, -0.14 ± 0.06 ; $P = .02$), but not directly associated with pulmonary physiology (-0.06 ± 0.05 ; $P = .23$) or asthma severity (0.01 ± 0.05 ;

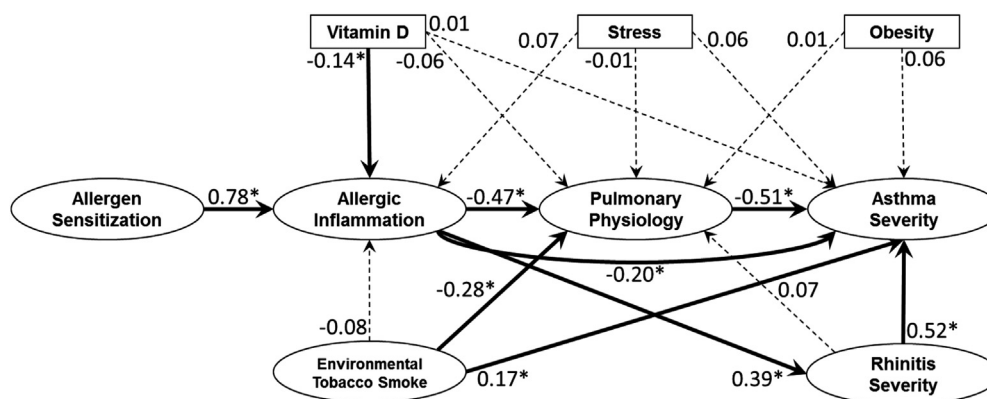


FIG 2. Direct and indirect effects of all pathways. Estimates are standardized direct effects that are interpreted as the SD increase in the dependent domain for every 1-SD increase in the independent domain. Estimates with associated *P* values that are less than .05 are denoted by asterisk and solid lines. Thick lines further denote statistically significant pathways by tests of indirect effects and mediation. Statistically insignificant estimates are denoted by dashed lines. All estimates are adjusted for age, sex, and race.

P = .82). Mediation analyses (Table E4) revealed modest indirect associations between vitamin D and asthma severity via allergic inflammation and pulmonary physiology (-0.04 ± 0.02 ; *P* = .03), and through allergic inflammation and rhinitis severity (-0.03 ± 0.01 ; *P* = .04). However, the total effect of vitamin D on asthma severity was insignificant (0.01 ± 0.05 ; *P* = .89).

Stress pathway

Fig 3, D, highlights the pathways from stress to asthma severity. Our results showed that stress was not directly associated with allergic inflammation (0.07 ± 0.05 ; *P* = .19), pulmonary physiology (-0.01 ± 0.05 ; *P* = .90), or asthma severity (0.06 ± 0.05 ; *P* = .22), nor were there significant indirect or total effects on asthma severity (Table E4).

Obesity pathway

Fig 3, E, highlights the pathways from obesity to asthma severity. Our results showed that obesity was not directly associated with pulmonary physiology (0.01 ± 0.05 ; *P* = .77) or asthma severity (0.06 ± 0.04 ; *P* = .11), nor were there significant indirect or total effects on asthma severity (Table E4). Although previous literature in the inner city has suggested that the effect of obesity on asthma control was significant in females but not in males,²⁴ a similar effect was not seen in national data.²⁵ Because this effect was not consistent within the literature, we tested whether the direct effect of obesity on asthma severity differed by sex by including an interaction between sex and obesity. However, our results showed no evidence that the effect of obesity on asthma severity differed by sex (*P* = .42) and so we did not account for this effect in our final model.

Sensitivity analysis

Because the controller treatment step at each visit was partially determined by measures included in the pulmonary physiology domain, a sensitivity analysis that redefined asthma severity without the mean and variance of controller treatment step across V0 and V6 was performed and showed similar results (results not shown).

DISCUSSION

We sought to integrate host and environmental factors known to influence asthma severity into pathways so that we can focus on important pathophysiologic aspects of the disease and target interventions for improvement of asthma management. To our knowledge, this is the first study to develop and test a pathways construct of asthma severity and determine the relative contributions of these factors and their pathways using a structural equation modeling approach. We had the benefit of applying this analytical approach to a large cohort of children with asthma living in 9 geographically distributed US inner cities, which was designed to define phenotypic characteristics of asthma. The APIC study differed from most asthma phenotypes studies in that it included prospective, standardized guidelines-based asthma and rhinitis management aimed at achieving optimal control of both lower and nasal airways disease activity. The APIC study also included participants with a wide range of asthma severity (ie, not limited to children with severe asthma), allowing for wide ranges of all outcomes of interest in our model.^{3,4} Characterizations of asthma and rhinitis severity were based on conventional composite assessments of day and night symptoms, exacerbations, and controller usage.^{5-7,26} Altogether, this pathways construct accounted for 53.4% of the observed variance in asthma severity in this study, a remarkable effect considering the complexity of this condition.

Our model supported the concept that multiple pathways contribute significantly to asthma severity and, importantly, that allergen sensitization is perhaps the originating domain in this pathophysiologic chain. On the basis of the model, we can conclude the following:

Allergy acts through more than 1 pathway to exert its effect on asthma severity. Our analysis verified sequential links to asthma severity, from allergen sensitization to allergic inflammation, and subsequently through pulmonary physiology or through rhinitis severity to asthma severity. This implies that conventional management does not adequately mitigate the effects of allergen sensitization on downstream airways inflammation, obstruction, and dysfunction. We can infer that more focus should be directed to interventions to suppress the allergy pathway to ameliorate asthma above and beyond the improvement achieved by current guidelines-based care.

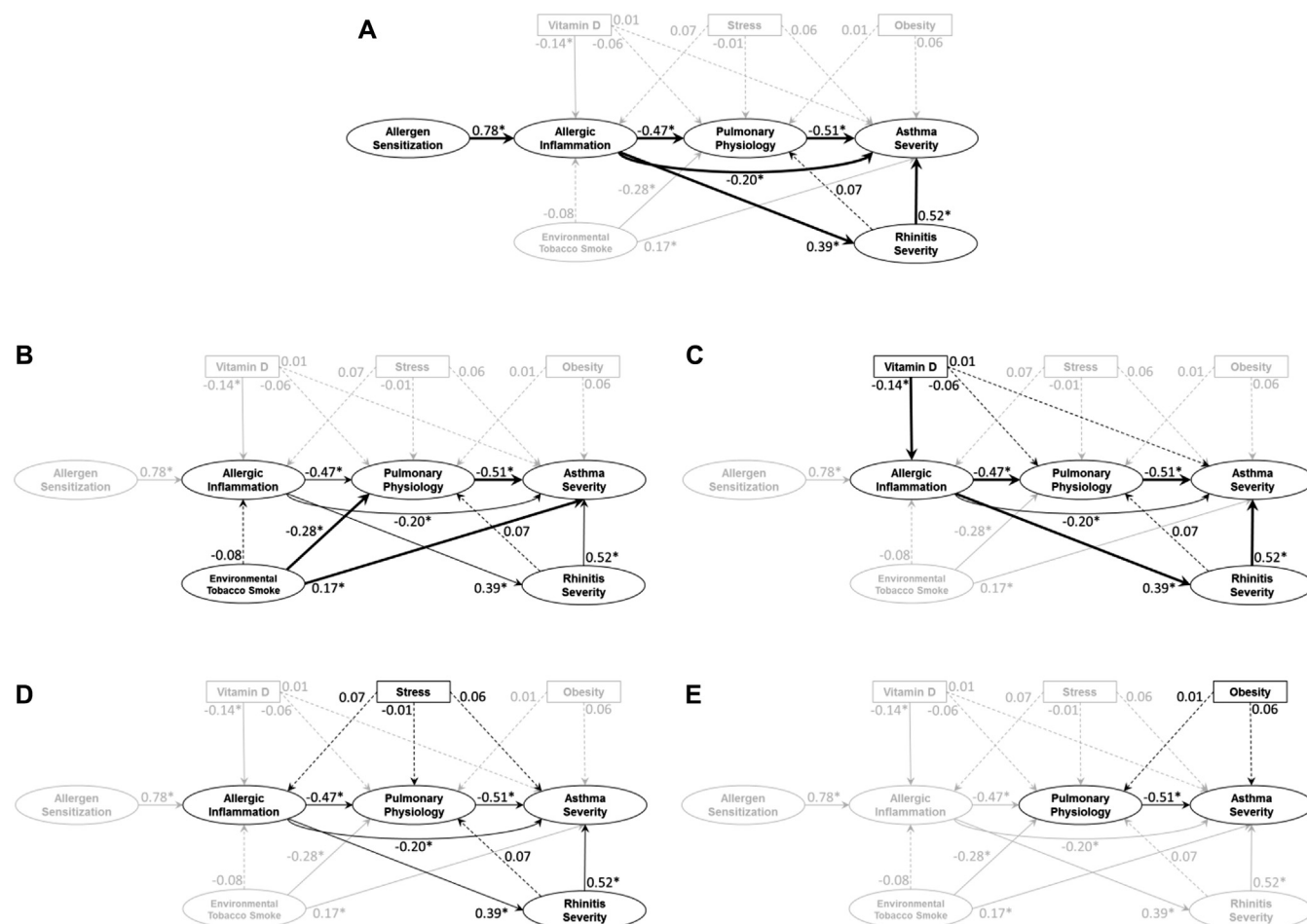


FIG 3. Pathways to asthma severity. **A**, Allergy pathway. **B**, ETS pathway. **C**, Vitamin D pathway. **D**, Stress pathway. **E**, Obesity pathway. Estimates are standardized direct effects that are interpreted as the SD increase in the dependent domain for every 1-SD increase in the independent domain. Estimates with associated *P* values that are less than .05 are denoted by asterisk and solid lines. Thick lines further denote statistically significant pathways by tests of indirect effects and mediation. Statistically insignificant estimates are denoted by dashed lines. All estimates are adjusted for age, sex, and race.

ETS exposure exerts significant direct and indirect (via pulmonary physiology) effects on asthma severity. There are significant direct and indirect effects of ETS exposure on asthma severity. ETS exposure was based on 2 semi-quantitative measures: number of smokers in the home by self-report and urine cotinine (a nicotine metabolite) by NicAlert test strips as an indicator of any ETS exposure. Studies using both measures have ranged from finding a high correlation between them, whereas other studies have found substantial discordance, with health effects being associated with one measure or the other, leading some investigators to conclude that both measures are useful and relevant when investigating the impact of ETS exposure on respiratory disease in children.²⁷ Accordingly, ETS exposure assessments for this study included both and have been compared in [Table E5](#) in this article's Online Repository at www.jacionline.org. We found a significant association between self-reported smokers in the home and urine cotinine levels ($P < .001$); however, urine cotinine was detectable in 80% of study participants reporting no tobacco smokers in the home. This reiterates the importance of both assessments as well as of measures to reduce

ETS exposure to improve asthma in the context of guidelines-based care.

Rhinitis severity had a remarkably strong direct effect on asthma severity. This supports the relevance of the “one airway” concept of disease (“from nostrils to alveoli”) for rhinitis in asthma^{6,28} and represents an important observation for investigators and clinicians who are studying and aiming to optimize asthma control. It is interesting that rhinitis severity does not directly impact pulmonary physiology, as some of the proposed mechanisms of the nose-lung interaction would predict.²⁸ The effect may be driven by the physiologic consequences of oral breathing, which is quite common in children in the presence of rhinitis. By losing the filtering and other air-conditioning capacity of the nasal passages, the lower airways may be rendered more susceptible to environmental stimuli, including allergens, irritants, and infectious agents.

Other pathways contributed less to asthma severity. Although vitamin D had modest but significant indirect effects on asthma severity mediated by allergic inflammation, pulmonary physiology, and rhinitis severity, the direct and total effects of vitamin

D on asthma severity were both insignificant. We also tested multiple pathways from stress to asthma severity and found them to be insignificant. Similarly, obesity was not significantly associated with asthma severity, nor was the effect of obesity on asthma severity modified by sex (data not shown). The lack of evidence regarding the effect of these domains on asthma severity does not mean that these are insignificant factors and might have been limited by our choice of variable(s) used to represent these domains or the conceptual model itself. For example, our choice of Caretaker Perceived Stress Scale is a standard measure often used and recommended to assess the effect of stress on asthma.^{17,29} Although other aspects of psychosocial stress not measured by this scale might have greater effects on asthma severity, they were not obtained in APIC. As well, our study sample consisted primarily of black or Hispanic children with higher BMIs. Consequently, our inability to detect significant effects of BMI on asthma severity may be due to a sample that is not representative of other study populations where this type of effect has been detected.

An important element of this analysis is that we can report standardized total, as well as direct and indirect, effects of each domain on asthma severity. On comparing the standardized total effect sizes on asthma severity (Table E4), we found that pulmonary physiology and rhinitis severity had the largest standardized total effect sizes (-0.51 and 0.48 , respectively, $P < .001$), followed by ETS exposure (0.30 , $P < .001$) and allergic inflammation (0.22 , $P < .001$). We were also able to determine whether some domains were significant mediators of the effects of others. Indeed, as we had hypothesized in constructing the model, the APIC data set confirmed an indirect effect of allergen sensitization on asthma severity via allergic inflammation, which then branched out into effects on pulmonary physiology and rhinitis severity; and the ETS effect on asthma severity is partially mediated through pulmonary physiology.

This investigation has limitations. Because this is an observational study, the direct, indirect, and total effects are estimates of statistical association rather than causation or clinical relevance. Exclusion of 18 participants with missing covariate data could also limit the generalizability of these findings. Compared with included participants, excluded participants had lower rhinitis symptom scores, lower variance of FEV₁ (% predicted), higher mean FEV₁/forced vital capacity, lower variance of FEV₁/forced vital capacity, and lower Composite Asthma Severity Index night symptoms and albuterol use. Their influence on the results is limited because they represent only 18 of 579 (3.1%) participants in our study. The domains, and the observed variables used to measure each domain, could be missing potentially important host and environmental factors such as other relevant environmental exposures and aspects of diet/nutrition. For example, cockroach allergen sensitization with high levels of exposure has been shown to have greater effects than sensitization alone on asthma severity in inner-city children,³⁰ so including allergen exposure in this model could have strengthened the allergy pathway. Because allergen measurements in house dust samples were obtained in only a subset of APIC participants, we did not include allergen exposure in this model. Some of our variables may lack adequate precision, validity, and/or domain representation to observe significant or strong pathway associations. For example, the stress domain is represented by the 10-question Caretaker Perceived Stress Scale score, which was recommended

in the National Institutes of Health/Agency for Healthcare Research and Quality-sponsored Asthma Outcomes Workshop Expert Report as a brief, well-validated, and simply administered measure of global stress.²⁹ However, the Caretaker Perceived Stress Scale does not necessarily capture other psychosocial mediators of asthma outcomes that are common in inner-city living and have been linked to asthma severity, such as violence and severely negative life events.³¹⁻³⁴ Some potential associations were not tested (eg, stress affecting asthma severity via BMI and/or ETS exposure) and could be explored in future work. Family history of asthma was not included in our conceptual model because, to our knowledge, family history of asthma has not been associated with asthma severity as it has been with asthma prevalence. We recognize that clear evidence of the genetic contribution to asthma severity exists, such as the association of the CDHR3 gene locus to severe asthma exacerbations in young children.³⁵ Another potential limitation of this study is its conduct in children with asthma living in US inner cities; extrapolation to children living in other locales and/or to adults would benefit from validation in those populations.

In conclusion, our causal network analysis is a rigorous investigative approach to develop and test a literature-based model of essential factors underlying asthma severity. This approach provides standardized effect sizes that are useful comparators of the relative contributions of different domains and can be used as a basis for prioritizing interventions to improve disease severity and management. With our complete model explaining more than half of the variability in asthma severity, the strong contributors are high priority targets for improving asthma outcomes in addition to standard care: allergen sensitization, allergic inflammation, ETS exposure, pulmonary physiology, and rhinitis severity. These findings demonstrate the usefulness of causal network analysis in formulating a blueprint for pathway-targeted interventional studies to improve future guidelines-directed care.

We are grateful to the APIC study participants and their families who gave of themselves to be our investigational partners; our study staff personnel who are dedicated to our inner-city asthma mission and clinical research excellence; and Christine Sorkness and Patrick Heinritz in the Inner-City Asthma Consortium Administrative Center (Madison, Wis) and Samuel Arbes, Michelle Walter, and Herman Mitchell at Rho, Inc, for their leadership, commitment to excellence despite all the challenges, and their legacies in inner-city asthma research.

Clinical implications: In children with asthma and rhinitis, allergen sensitization, allergic inflammation, pulmonary physiology, ETS exposure, and rhinitis severity are related through specific pathways to asthma severity.

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

Online Repository

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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 FEV₁/FVC and FEV₁ (% 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 eosinophils³² 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 FEV₁, 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 FEV₁/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 FEV₁ % 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 children⁵³ 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 (FEV₁/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 FEV₁ 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 FEV₁/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 FEV₁ 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 disease⁸⁶ 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 FEV₁/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, FEV₁, 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.

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

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) ($\pm$ 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) ($\pm$ 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 $\pm$ 0.045 (p=0.033)	0.136 $\pm$ 0.045 (p=0.002)	0.077 $\pm$ 0.045 (p=0.085)
Allergic Inflammation	0.187 $\pm$ 0.059 (p=0.002)	0.136 $\pm$ 0.051 (p=0.008)	-0.089 $\pm$ 0.055 (p=0.106)
Pulmonary Physiology	-0.261 $\pm$ 0.060 (p<0.001)	-0.005 $\pm$ 0.056 (p=0.933)	0.128 $\pm$ 0.057 (p=0.025)
ETS Exposure	0.222 $\pm$ 0.067 (p=0.001)	-0.121 $\pm$ 0.068 (p=0.075)	0.205 $\pm$ 0.070 (p=0.003)
Vitamin D	-0.286 $\pm$ 0.036 (p<0.001)	0.163 $\pm$ 0.040 (p<0.001)	-0.16 $\pm$ 0.039 (p<0.001)
Stress	-0.033 $\pm$ 0.043 (p=0.435)	-0.002 $\pm$ 0.042 (p=0.96)	-0.002 $\pm$ 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 $\pm$ 0.043 (p=0.588)
Rhinitis Severity	-0.018 $\pm$ 0.053 (p=0.74)	-0.171 $\pm$ 0.052 (p=0.001)	0.144 $\pm$ 0.049 (p=0.003)
Asthma Severity	-0.043 $\pm$ 0.06 (p=0.472)	-0.036 $\pm$ 0.05 (p=0.477)	-0.108 $\pm$ 0.052 (p=0.039)

TABLE E3. Indirect effects of Allergen Sensitization on Asthma Severity. Estimates ($\pm$ 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 $\pm$ 0.06 (p=0.01)	0.18 $\pm$ 0.05 (p<0.001)
	Allergic Inflammation → Pulmonary Physiology	0.19 $\pm$ 0.04 (p<0.001)	
	Allergic Inflammation → Rhinitis Severity	0.16 $\pm$ 0.03 (p<0.001)	
	Allergic Inflammation → Rhinitis Severity → Pulmonary Physiology	-0.01 $\pm$ 0.01 (p=0.35)	

TABLE E4. Mediated effects of domains on Asthma Severity. The direct effect is the adjusted standard deviation (SD) ($\pm$ standard error (SE)) increase in Asthma Severity for every one SD increase in the independent domain. The indirect effect is the SD ($\pm$ 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 ($\pm$ 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 $\pm$ 0.08 (p=0.01)	0.24 $\pm$ 0.05 (p<0.001)	0.22 $\pm$ 0.06 (p<0.001)	Yes
	Rhinitis Severity		0.20 $\pm$ 0.04 (p<0.001)		Yes
	Rhinitis Severity → Pulmonary Physiology		-0.01 $\pm$ 0.01 (p=0.35)		No
Environmental Tobacco Smoke	Allergic Inflammation	0.17 $\pm$ 0.08 (p=0.03)	0.02 $\pm$ 0.02 (p=0.41)	0.30 $\pm$ 0.08 (p<0.001)	No
	Pulmonary Physiology		0.14 $\pm$ 0.04 (p<0.001)		Yes
	Allergic Inflammation → Pulmonary Physiology		-0.02 $\pm$ 0.02 (p=0.40)		No
	Allergic Inflammation → Rhinitis Severity		-0.02 $\pm$ 0.02 (p=0.40)		No
	Allergic Inflammation → Rhinitis Severity → Pulmonary Physiology		0.001 $\pm$ 0.002 (p=0.51)		No
Vitamin D	Allergic Inflammation	0.01 $\pm$ 0.05 (p=0.82)	0.03 $\pm$ 0.02 (p=0.08)	0.01 $\pm$ 0.05 (p=0.89)	No
	Pulmonary Physiology		0.03 $\pm$ 0.02 (p=0.24)		No
	Allergic Inflammation → Pulmonary Physiology		-0.04 $\pm$ 0.02 (p=0.03)		No
	Allergic Inflammation → Rhinitis Severity		-0.03 $\pm$ 0.01 (p=0.04)		No
	Allergic Inflammation → Rhinitis Severity → Pulmonary Physiology		0.002 $\pm$ 0.002 (p=0.39)		No
Stress	Allergic Inflammation	0.06 $\pm$ 0.05 (p=0.22)	-0.01 $\pm$ 0.01 (p=0.24)	0.08 $\pm$ 0.05 (p=0.12)	No
	Pulmonary Physiology		0.003 $\pm$ 0.03 (p=0.90)		No
	Allergic Inflammation → Pulmonary Physiology		0.02 $\pm$ 0.01 (p=0.21)		No
	Allergic Inflammation → Rhinitis Severity		0.01 $\pm$ 0.01 (p=0.20)		No
	Allergic Inflammation → Rhinitis Severity → Pulmonary Physiology		-0.001 $\pm$ 0.001 (p=0.44)		No
Obesity	Pulmonary Physiology	0.06 $\pm$ 0.04 (p=0.11)	-0.01 $\pm$ 0.02 (p=0.76)	0.06 $\pm$ 0.04 (p=0.18)	No
Rhinitis Severity	Pulmonary Physiology	0.52 $\pm$ 0.06 (p<0.001)	-0.03 $\pm$ 0.04 (p=0.34)	0.48 $\pm$ 0.06 (p<0.001)	No

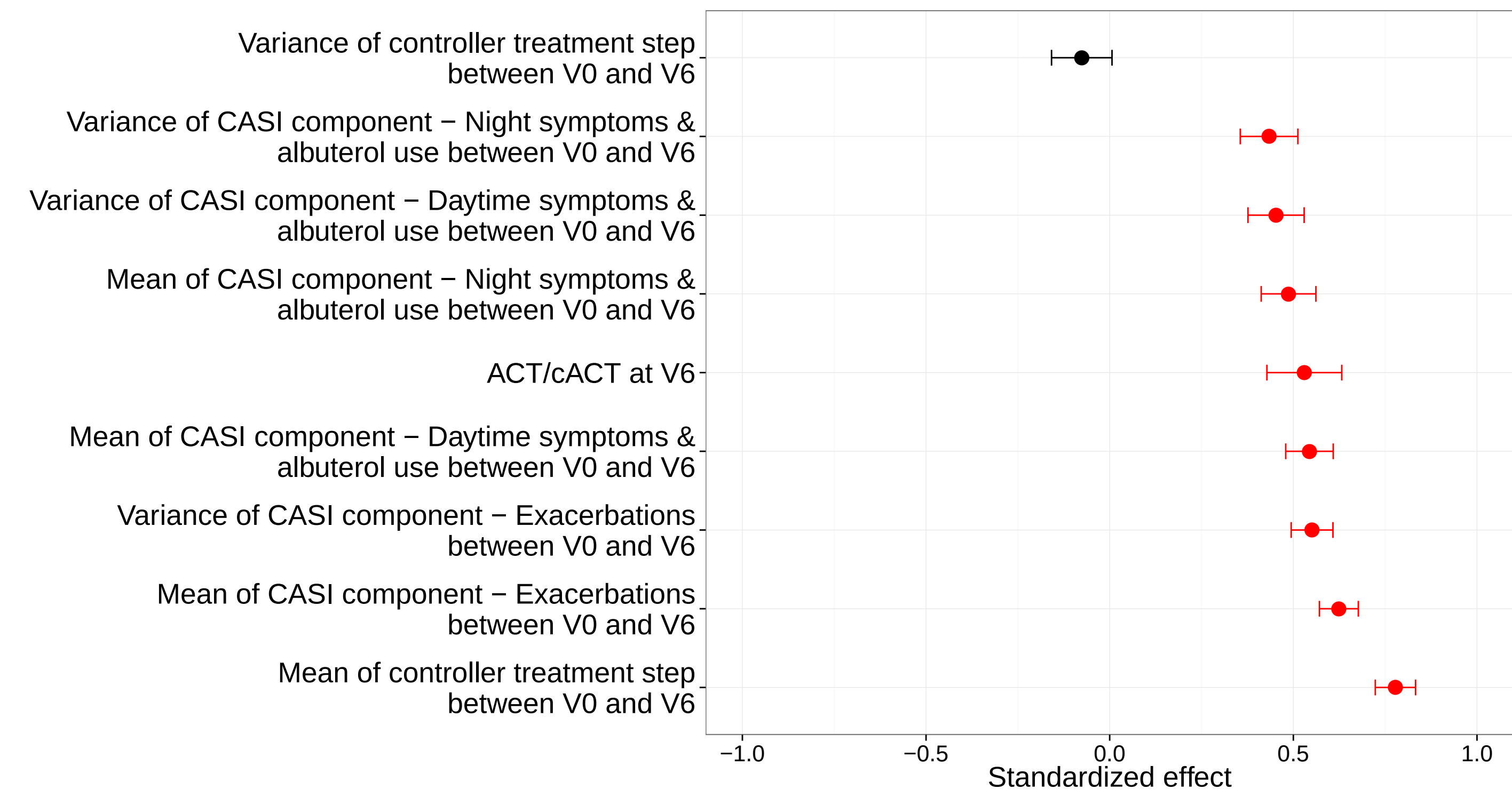
526 **TABLE E5.** Frequency and percentage of groups based on urine cotinine at Screening
527 stratified by number of smokers in the home (p<0.001 based on Pearson chi-squared test).
528

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

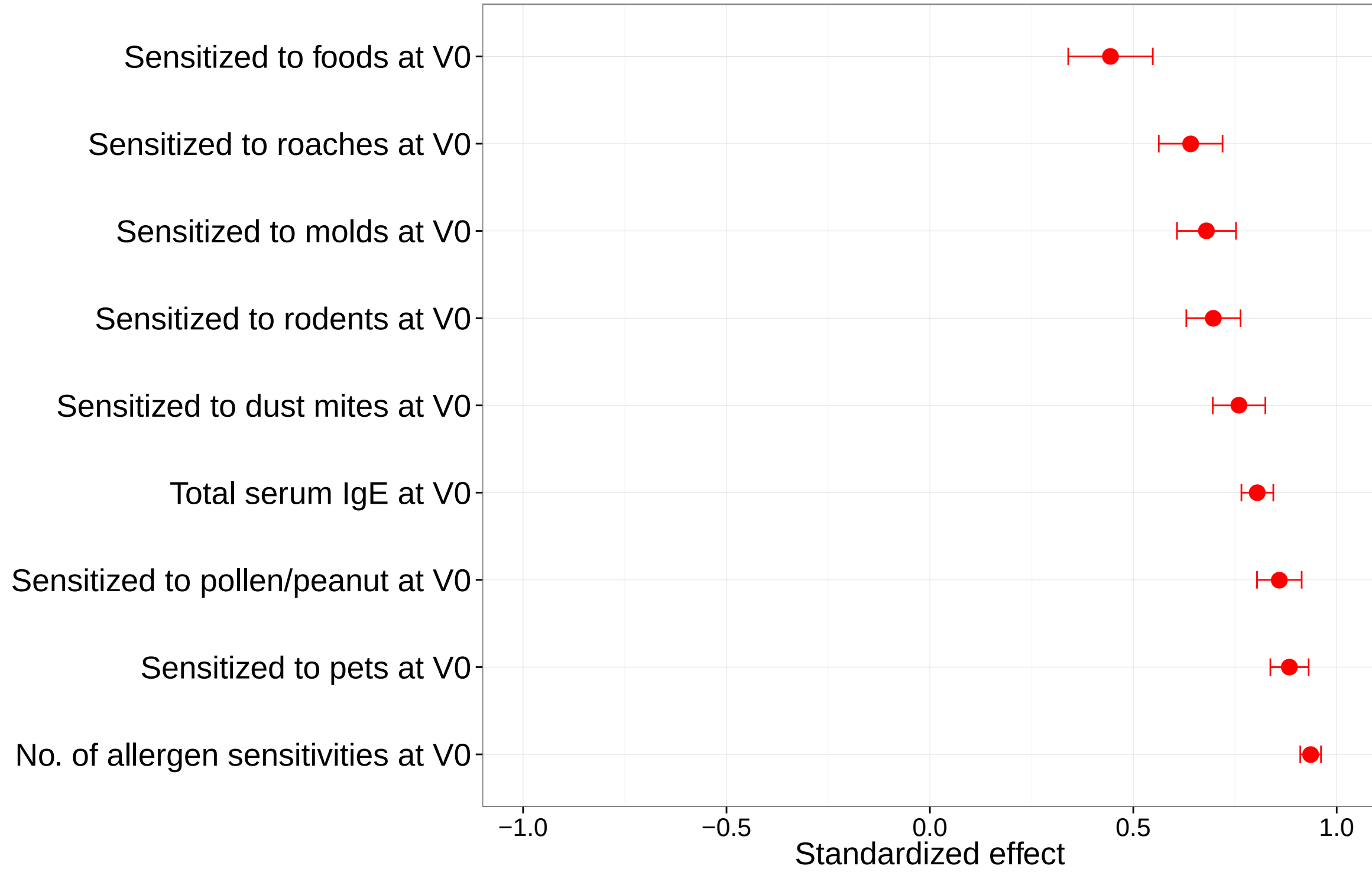
529

FIGURE E1A-F. Standardized effects of each domain on observed variables: (A) Asthma Severity, (B) Allergen Sensitization, (C) Allergic Inflammation, (D) Pulmonary Physiology, (E) Rhinitis Severity and (F) ETS exposure. For a continuous variable, solid circles denote the standardized regression coefficient obtained from a linear regression model. For a categorical variable, solid circles denote the standardized regression coefficient obtained from a probit regression model. Whiskers denote 95% confidence interval. Based on a significance level of 0.05, effects that are statistically significant are denoted in red while effects that are not statistically significant are denoted in black. All estimates are adjusted for age, sex and race.

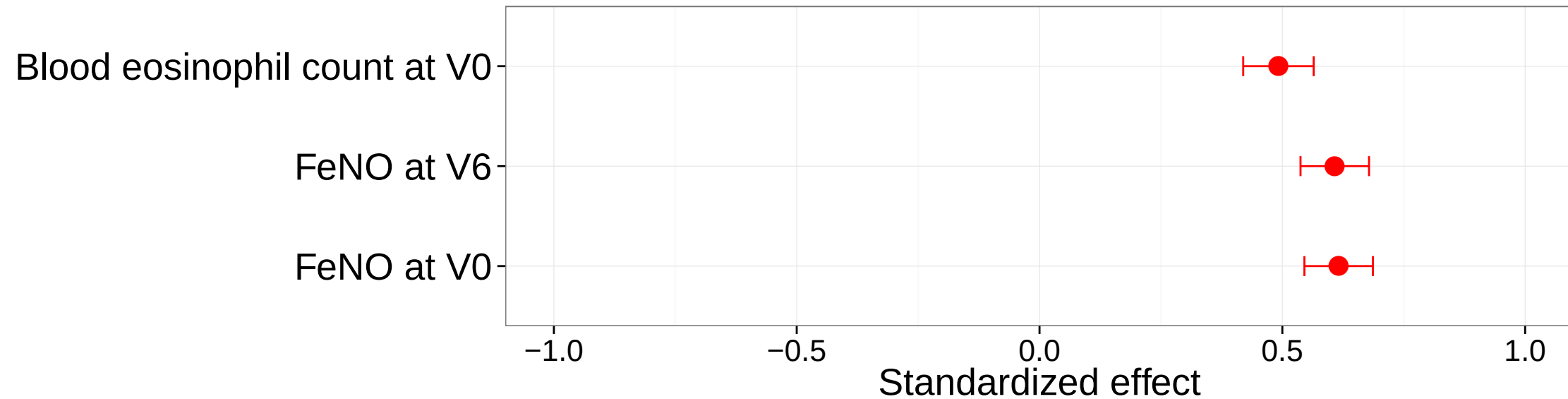
A. Standardized effect of Asthma Severity on observed variables.



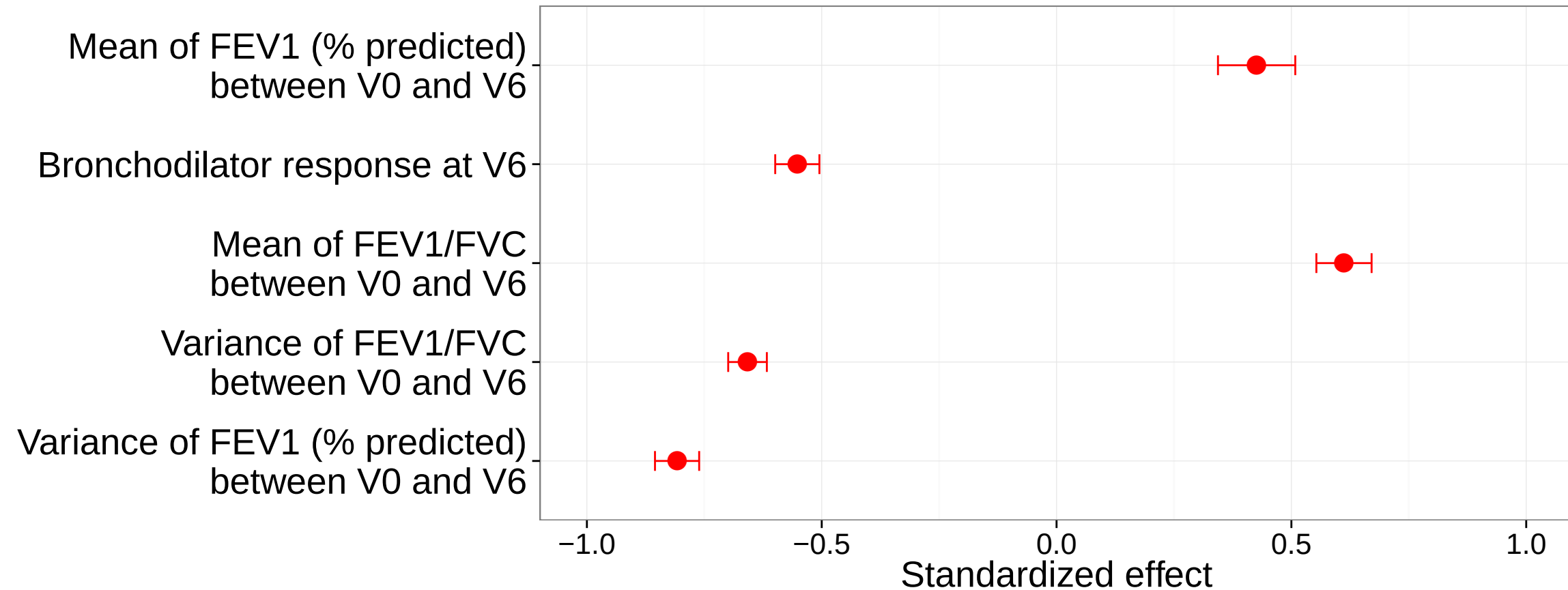
B. Standardized effect of Allergen Sensitization on observed variables.



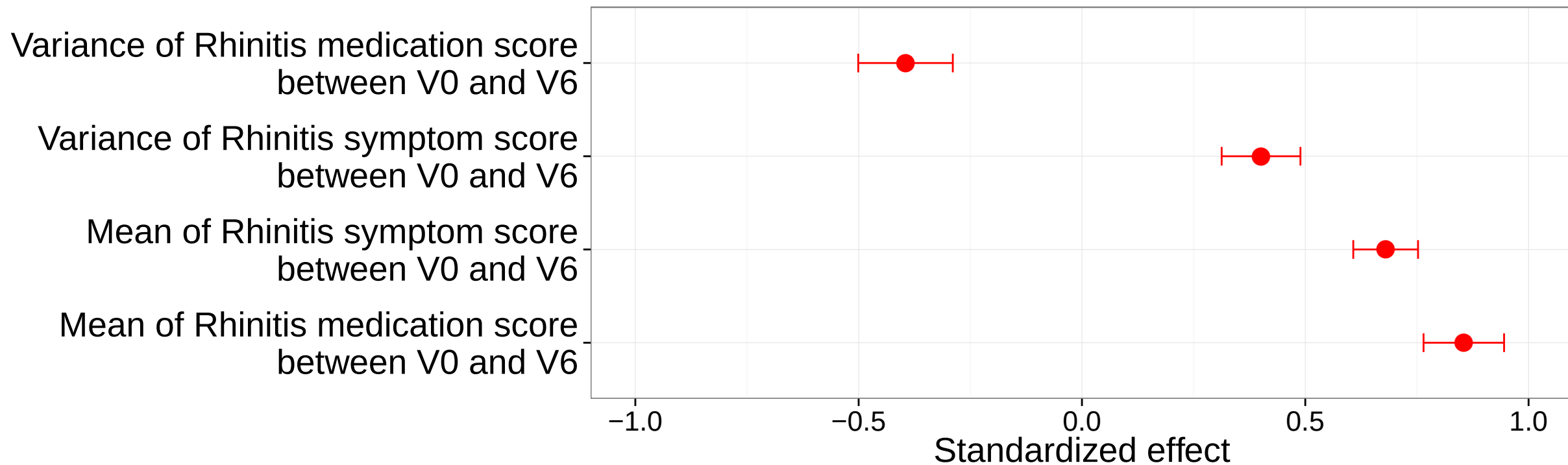
C. Standardized effect of Allergic Inflammation on observed variables.



D. Standardized effect of Pulmonary Physiology on observed variables.



E. Standardized effect of Rhinitis Severity on observed variables.



F. Standardized effect of ETS Exposure on observed variables.

