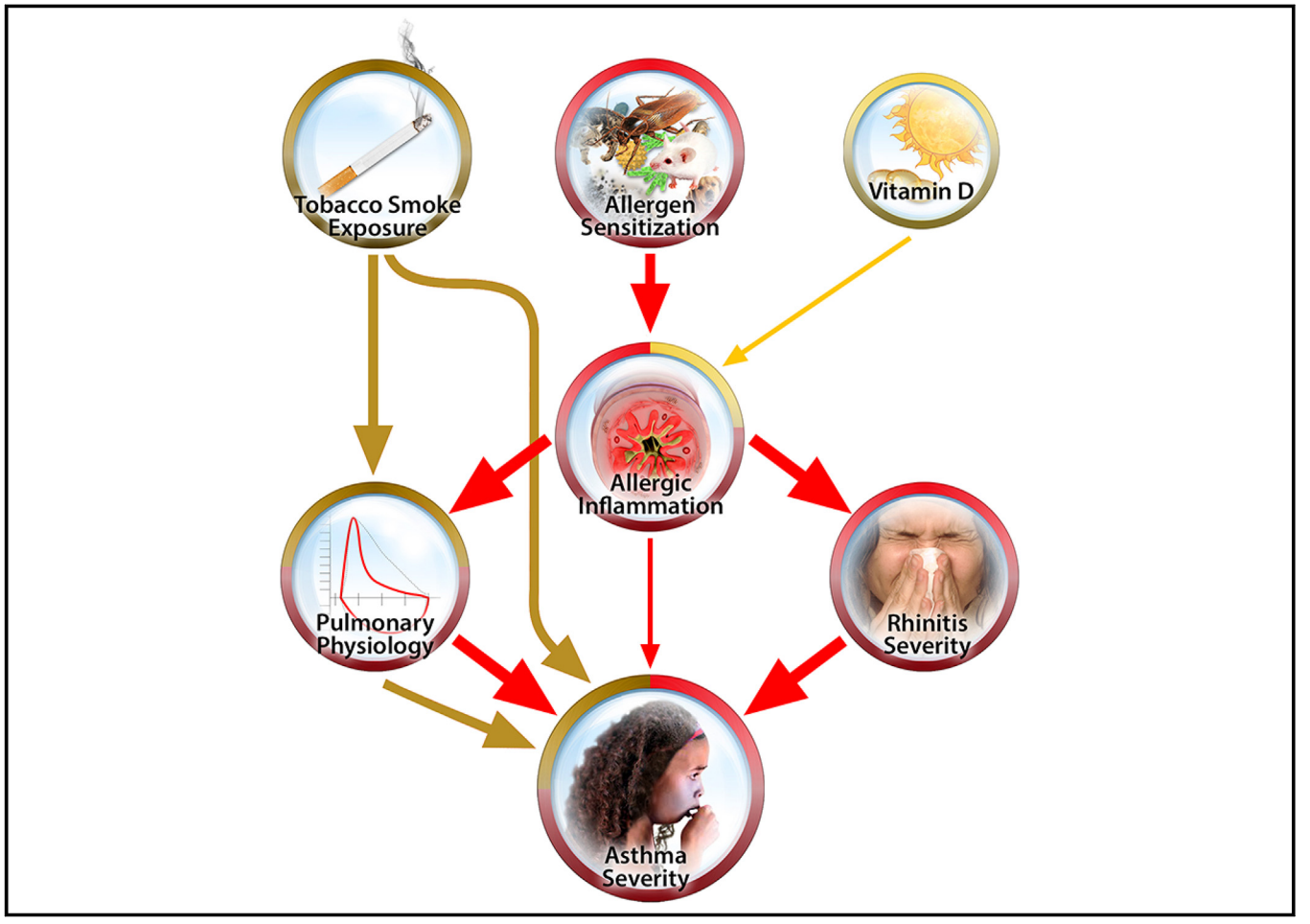
Pathways through which asthma risk factors contribute to asthma severity in inner-city children

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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 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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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 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- to17-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 3[5] 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 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 (FEV_1 [% predicted] and FEV_1/forced vital capacity) at V0 to V6, which were summarized using the mean and variance across the visits, as well as the FEV_1 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/mm^3) 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 models[20] 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

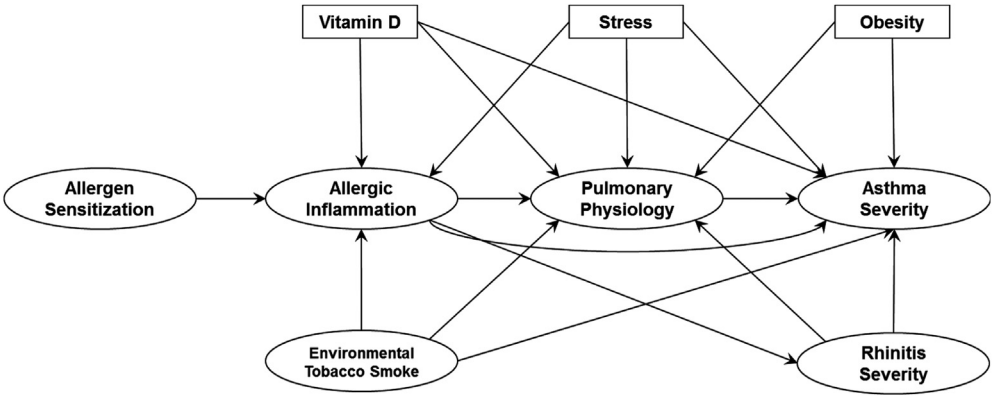


FIG 1. Conceptual model of asthma severity. This model was generated in advance of any analyses based on observations derived from the medical literature and became the test object of this study. Oval boxes indicate domains defined by multiple observed variables, whereas rectangles indicate domains defined 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 $\pm$ 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 $\pm$ 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 $\pm$ 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 $\pm$ 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 $\log_{10}$ 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;

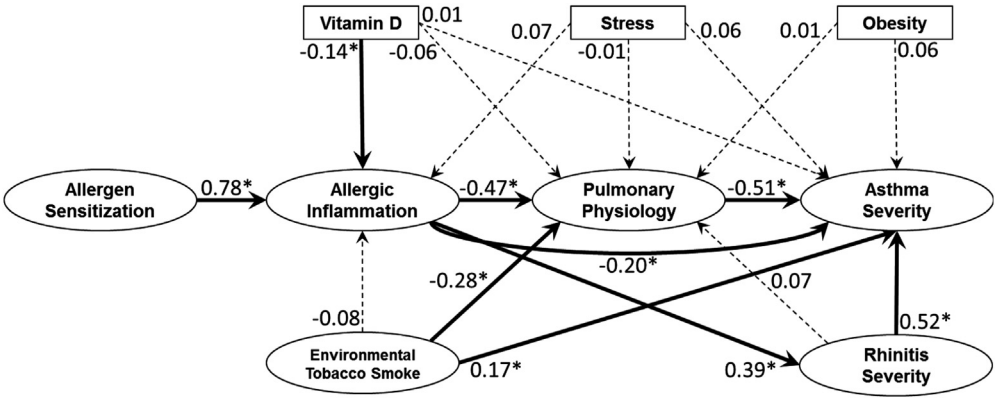


FIG 2. Direct and indirect effects of all pathways. Estimates are standardized direct effects that are interpreted as the SD increase in the dependent domain for every 1-SD increase in the independent domain. Estimates with associated *P* values that are less than .05 are denoted by asterisk and solid 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.

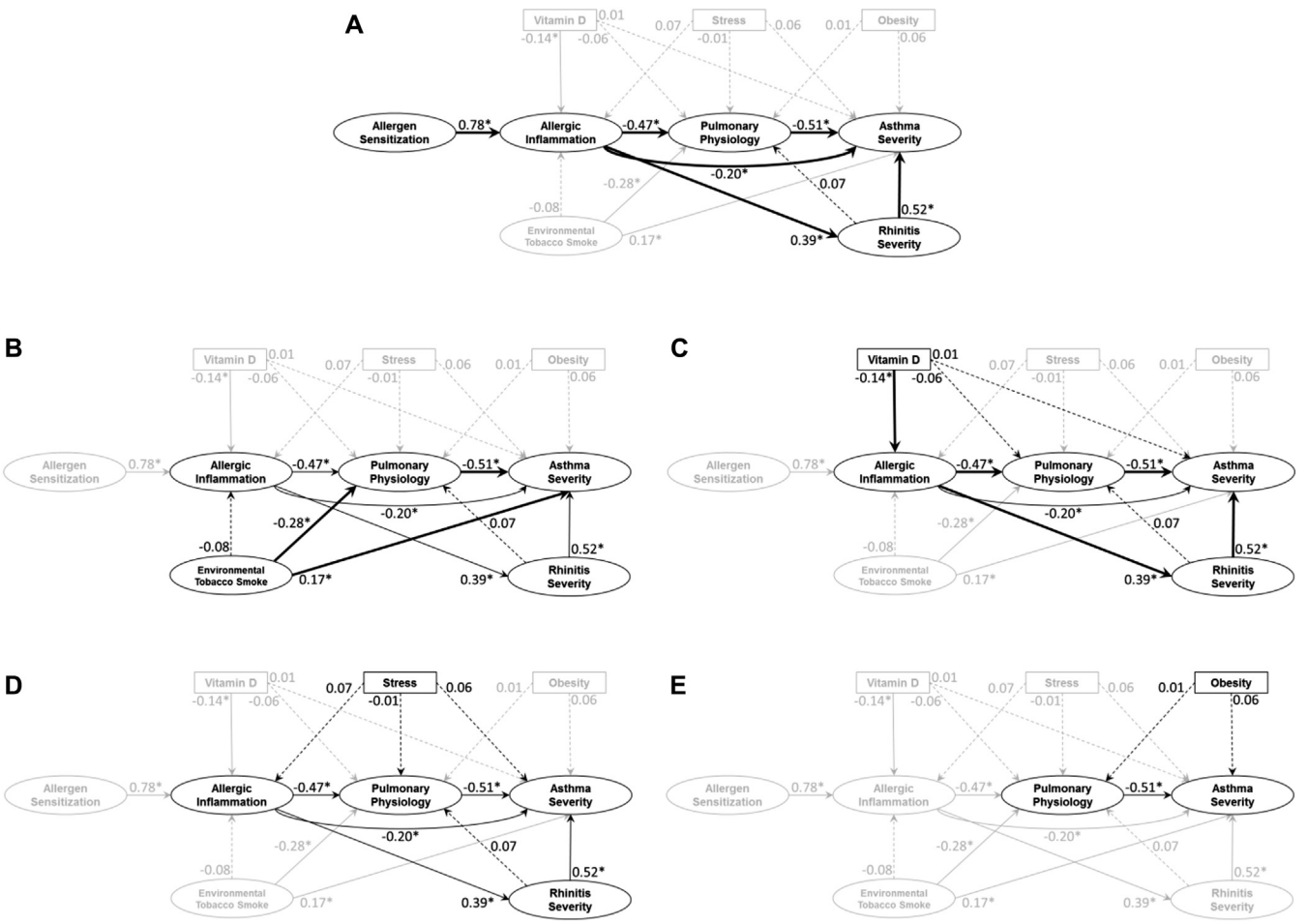


FIG 3. Pathways to asthma severity. **A,** Allergy pathway. **B,** ETS pathway. **C,** Vitamin D pathway. **D,** Stress pathway. **E,** Obesity pathway. Estimates are standardized direct effects that are interpreted as the SD increase in the dependent domain for every 1-SD increase in the independent 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 FEV_1 (% predicted), higher mean FEV_1/forced vital capacity, lower variance of FEV_1/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.

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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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