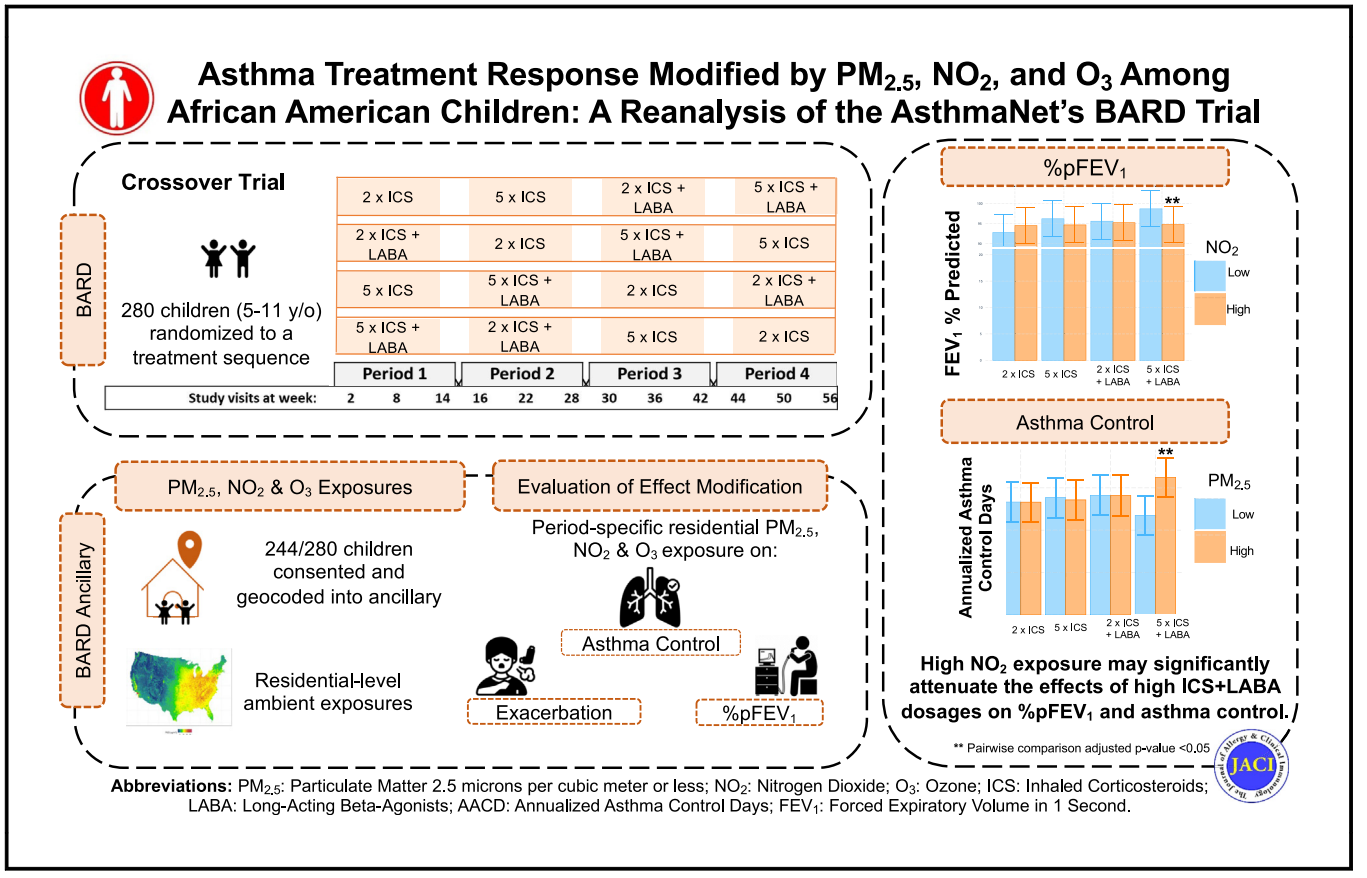
Asthma treatment response modified by fine particulate matter, nitrogen dioxide, and ozone among Black children: A reanalysis of the AsthmaNet Best African American Response to Asthma Drugs trial

Lizbeth F. Gómez, PhD MPH, Ellen J. Kinnee, MS, Michael T. Young, PhD, Joel D. Kaufman, MD, MPH, Anne M. Fitzpatrick, PhD, MSCR, APRN, Sharmilee M. Nyenhuis, MD, FAAAAI, et al

GRAPHICAL ABSTRACT



Capsule summary: This study shows that ambient air pollution may diminish the efficacy of ICS+LABA step-up therapy in children. To improve outcomes, clinicians should consider environmental exposures when managing pediatric asthma.

J Allergy Clin Immunol 2025;156:330-8.

https://doi.org/10.1016/j.jaci.2025.04.009

Asthma treatment response modified by fine particulate matter, nitrogen dioxide, and ozone among Black children: A reanalysis of the AsthmaNet Best African American Response to Asthma Drugs trial

Lizbeth F. Gómez, PhD MPH,[a] Ellen J. Kinnee, MS,[b] Michael T. Young, PhD,[c] Joel D. Kaufman, MD, MPH,[c] Anne M. Fitzpatrick, PhD, MSCR, APRN,[d] Sharmilee M. Nyenhuis, MD, FAAAAI,[e] Julian Solway, MD,[f] Steven R. White, MD,[f] Edward T. Naureckas, MD,[f] Wanda Phipatanakul, MD, MS,[g] Michael E. Wechsler, MD, MMSc,[h] Susan J. Kunselman, MS,[i] David T. Mauger, MS, PhD,[i] Leslie A. McClure, MS, PhD,[j] Usama Bilal, MD, MPH, PhD,[k] Stephen C. Lazarus, MD, FCCP, FERS,[l] Fernando Holguin, MD, MPH,[m] and Jane E. Clougherty, MSc, ScD[a]

Philadelphia, Pittsburgh, and University Park, Pa; Seattle, Wash; Atlanta, Ga; Chicago, Ill; Boston, Mass; Denver and Aurora, Colo; St Louis, Mo; and San Francisco, Calif

Background: Asthma morbidity significantly affects children of all racial backgrounds; however, Black children experience a greater disease burden than children from other racial groups. Despite the known influence of air pollution on asthma outcomes, its role in the efficacy of asthma treatments remains underexplored.

Objective: We sought to examine how exposure to particulate matter <2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) influenced treatment outcomes in the National Institutes of Health AsthmaNet Best African American Response to Asthma Drugs trial.

Methods: The trial randomized 224 Black children to 4 asthma treatments consisting of an inhaled corticosteroid (ICS) and long-acting β-agonist (LABA) administered in a randomized crossover fashion. Treatment efficacy was assessed by the frequency of asthma exacerbations, percent predicted FEV_1, and annualized asthma control days. Residential exposures to $PM_{2.5}$, NO_2, and O_3 were estimated using a validated spatiotemporal model. Mixed-effects models were used to evaluate the interaction between pollution exposure and treatment efficacy, adjusting for age, household triggers, and trial site.

Results: $PM_{2.5}$, NO_2, and O_3 exposures ranged substantially across participants from 2.28 to 15.3 μg/m^3, 2.34 to 63.7 ppm, and 2.57 to 23.7 ppb, respectively. NO_2 and $PM_{2.5}$ exposures were not associated with increased exacerbations post-treatment (*P* for interaction = .15 and .08, respectively). However, NO_2 exposure significantly modified the effect of high-dose ICS+LABA therapy on lung function. Children with below median NO_2 exposures while receiving ICS+LABA therapy had a reduction of 5.86 (95% CI 1.16, 10.56) in percent predicted FEV_1 compared with children with above median NO_2 exposures.

Conclusion: Residential high NO_2 exposure may significantly attenuate the efficacy of ICS+LABA therapy on lung function in Black children. These findings suggest the need to consider environmental factors in clinical trials and asthma management strategies. (J Allergy Clin Immunol 2025;156:330-8.)

Key words: *Asthma, ICS, LABA, environmental health, air pollution, randomized clinical trial*

Abbreviations used

AACD:	Annualized asthma control days
BARD:	Best African American Response to Asthma Drugs
GLI:	Global Lung Function Initiative
ICS:	Inhaled corticosteroid
LABA:	Long-acting β-agonist
NHLBI:	National Heart, Lung, and Blood Institute
NIH:	National Institutes of Health
NO_2:	Nitrogen dioxide
O_3:	Ozone
%PFEV$_1$:	Percent predicted FEV_1
$PM_{2.5}$:	Particulate matter ≤2.5 μm

Asthma is one of the most prevalent chronic illnesses among children worldwide,[1] and it is a major public health burden in the United States.[2-7] Asthma morbidity and mortality disproportionately impact minoritized communities,[8] with the most pronounced

From the [a]Department of Environmental and Occupational Health, Drexel University Dornsife School of Public Health, Philadelphia; [b]University Center for Social and Urban Research, University of Pittsburgh, Pittsburgh; the [c]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle; the [d]Department of Pediatrics, Emory University, Atlanta; the [e]Department of Pediatrics-Allergy and Immunology, and the [f]Department of Medicine, Pulmonary and Critical Care, University of Chicago, Chicago; the [g]Division of Immunology, Boston Children's Hospital, Boston; the [h]Department of Medicine, National Jewish Health, Denver; the [i]Department of Public Health Sciences, Pennsylvania State University, University Park; [j]College of Public Health and Social Justice, Saint Louis University, St Louis; the [k]Department of Epidemiology and Urban Health Collaborative, Drexel University Dornsife School of Public Health, Philadelphia; the [l]Division of Pulmonary & Critical Care Medicine, University of California San Francisco, San Francisco; and [m]Medicine-Pulmonary Sciences & Critical Care, University of Colorado School of Medicine, Aurora.

Received for publication October 8, 2024; revised March 22, 2025; accepted for publication April 4, 2025.

Available online April 15, 2025.

Corresponding author: Lizbeth F. Gómez, PhD, MPH, Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104. E-mail: lizbeth.gomez@pennmedicine.upenn.edu.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749

https://doi.org/10.1016/j.jaci.2025.04.009

disparities observed in underrepresented communities and communities with higher exposure to air pollution. For instance, Black children experience more severe symptoms, poorer asthma control, and higher hospitalization rates than any other racial or ethnic group,[9-11] despite adequate treatment adherence.

For asthma, inhaled corticosteroids (ICSs) are recognized as effective first-line therapy, but persistent poorly controlled asthma often requires adding a long-acting β_2-agonist (LABA). LABAs are pharmacological agents that play a pivotal role in the management of patients with moderate to severe persistent asthma who are not adequately controlled by ICSs alone.[12] Whereas ICSs address underlying inflammation, combination therapy with LABA enhances overall asthma control, reduces exacerbations, and improves the quality of life for patients. However, despite adherence to these combination therapies, Black patients continue to exhibit higher exacerbation rates than their White counterparts.[9]

One potential explanation for this can relate to asthma treatment guidelines derived from randomized clinical trials that have external validity issues or that lack diversity in study populations.[13] However, the Best African American Response to Asthma Drugs (BARD) trial, part of the National Institutes of Health (NIH) National Heart Lung and Blood Institute (NHLBI) AsthmaNet research initiative, was designed to address these issues by enrolling only Black participants.[14] In this randomized, double-blind, crossover trial, the efficacy of various doses of an ICS, with and without an LABA, was compared among children ages 5 to 11 years.

BARD trial analyses, as in many randomized clinical trials, do not account for environmental factors that are known to influence treatment response. This is despite extensive evidence linking ambient air pollution—particularly particulate matter <2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3)—to asthma morbidity.[15-17] Children exposed to higher levels of $PM_{2.5}$ and NO_2 are more likely to develop asthma compared with children with lower exposure.[18] However, very few studies have explored how outdoor air pollution may impact the effectiveness of asthma treatments. Current asthma treatment protocols fail to consider the critical role of environmental triggers, even though their connection to asthma etiology and exacerbation is well documented. This oversight is particularly troubling given the significant disparities in asthma prevalence and severity among children exposed to higher levels of pollution.[9,15,19-21]

In the present study, we examined the potential for ambient air pollution exposure to modify the effect of ICS+LABA combination treatment on asthma outcomes among Black children. To do so, we leveraged data from the AsthmaNet BARD clinical trial and incorporated individual-level estimates for air pollution exposure during the trial follow-up. Our objective was to determine variations in asthma control metrics—specifically, overall control, lung function, and exacerbation frequency—in relation to exposure levels of $PM_{2.5}$, NO_2, and O_3 to test the potential alteration of individual responses to ICS+LABA treatment as a function of concurrent exposure to air pollutants during the trial duration.

METHODS

Study design and subjects

BARD was a randomized, 4-treatment, 4-period crossover clinical trial undertaken as part of the NHLBI AsthmaNet nationwide research network, previously described in detail.[14] Briefly, 280 children ages 5 to 11 years with inadequately controlled asthma using low-dosage corticosteroids were assigned to a random sequence of commonly prescribed treatments. These treatments consisted of baseline low ICS dose (2×ICS or 100 μg fluticasone propionate), double ICS with LABA (2×ICS+LABA or 100 μg fluticasone propionate and 50 μg salmeterol), quintuple ICS (5×ICS or 250 μg fluticasone propionate), and quintuple ICS with LABA (5×ICS+LABA or 250 μg fluticasone propionate and 50 μg salmeterol). All regimens were taken twice daily, and escalating ICS dosages were based on National Asthma Education and Prevention Program guidelines. Participants who met the inclusion criteria were randomly assigned to the above-described treatments, in random order, for a total of 14 weeks per treatment regimen. The first 2 weeks of each period were a washout of the prior treatment and thus were not included in these analyses (see Fig E1 in this article's Online Repository available at www.jacionline.org).

The current ancillary analysis of the BARD trial results includes 224 children (80% retention of total sample size) who were randomized in the trial and for whom we obtained caregiver's consent to use their address for analysis. Enrolled participants self-reported Black ancestry (having at least 1 Black grandparent) and exhibited a baseline FEV_1 after bronchodilator use (after 4 puffs of albuterol [90 μg per puff]) of at least 40% of the predicted value. Additionally, participants had a diagnosis of asthma confirmed by β-agonist reversibility (an increase in the percent predicted FEV_1 [$\%PFEV_1$] of at least 12%), a methacholine provocation concentration causing a 20% decrease in the $\%PFEV_1$ of 16 mg/mL or less, or an absolute difference in the percentage of the predicted $\%PFEV_1$ of at least 12 percentage points over 2 measurements documented within the previous year.[14]

Outcomes

Annualized asthma control days. Asthma control days are defined as a diary entry of a day without (1) the use of an albuterol rescue inhaler; (2) the use of oral steroids; (3) daytime or nighttime asthma symptoms, such as wheeze, cough, phlegm, chest tightness, or shortness of breath; (4) unscheduled visits to an asthma-related health care provider or missed school due to asthma; or (5) morning or night peak flow below 90% of predicted. The number of control days was then divided by the number of days each individual was enrolled in the study to obtain an annualized rate (annualized asthma control days [AACD]). Additionally, asthma control was assessed at baseline via the Childhood Asthma Control Test, in which scores range from 0 (uncontrolled) to 27 (well controlled).[22]

Lung function. Lung function was assessed by clinical research staff via spirometry at the end of each of the 4 treatment periods of 14 weeks following the AsthmaNet Spirometry Manual of Procedures. Assessment of reversibility to 4 puffs of albuterol according to ATS criteria was used to determine each participant's $\%PFEV_1$ (Fig E2 in the Online Repository at www.jacionline.org).We performed a sensitivity test to remove from current analyses all participants who would not have met the inclusion criteria of $\%PFEV_1$ >80 at baseline if we had used Global Lung Function Initiative (GLI) formulas. We then reran all modules with lung function outcome after removing children who would not have qualified (Fig E9 in the Online Repository at www.jacionline.org).

Asthma exacerbations. Asthma exacerbations were defined as events characterized by a significant worsening of

asthma symptoms, leading to the initiation of systemic glucocorticoids. Including the onset of systemic glucocorticoids during encounters with health care providers, asthma-specific visits to emergency departments requiring treatment with systemic glucocorticoids, hospitalizations due to asthma in which systemic glucocorticoids are administered, admissions to intensive care units, or instances of intubation for asthma. When 2 systemic glucocorticoid treatments occurred at least 1 week apart from each other, each was considered a separate exacerbation.

Modifiers: $PM_{2.5}$, NO_2, and O_3. Air pollutants exposures were estimated for each participant using a national spatiotemporal regionalized universal kriging model.[23] The models combine hundreds of fine-scale spatial covariates, including roadway information, with $PM_{2.5}$, NO_2, and O_3 measurements from US Environmental Protection Agency Air Quality System and Interagency Monitoring of Protected Visual Environments monitoring sites and researcher-led monitoring campaigns. We calculated outdoor residential average air pollutant concentrations ($PM_{2.5}$, NO_2, and O_3 concentrations in $\mu g/m^3$, ppm, and ppb, respectively) of participants during each of the 4 treatment periods based on the centroid of their home census block.

Home environment. Information about pediatric asthma and allergy history was collected at baseline and captured secondhand smoke exposure of participants at home and *in utero*. We also included household socioeconomic information and home environment details, which were recorded at least once during follow-up by research coordinators.

Geocoding. Each participant's residential address throughout the 56-week trial, including any residential moves, was collected by clinical coordinators and geocoded to x,y coordinates in ArcGIS (Esri, Redlands, Calif). Based on these geocoded locations, 2-week average concentrations of $PM_{2.5}$ ($\mu g/m^3$), NO_2 (ppm), and O_3 (ppb) were assigned to each participant by mapping exposures to the centroid of their residential census block. A custom-generated composite address locator using offline reference data was used to ensure patient protection and maximize the positional accuracy of address locations. The geocoding process achieved a 100% match rate for participants who consented to provide their addresses (n = 224). To adhere to human subject protection standards, all patient addresses were removed from the analytic dataset after the geocoding process was completed.

Statistical methods

To examine whether $PM_{2.5}$, NO_2, and O_3 modify the number of asthma exacerbations, we fitted generalized linear mixed models with a Poisson link function using the glmer function of the lme4 package in R (R Foundation for Statistical Computing, Vienna, Austria). We fitted mixed models to test effect modification by $PM_{2.5}$, NO_2, and O_3 on the $\%PFEV_1$ and AACD using the lmer function of the lme4 package version 1.1-30 in R.[24] All models included a random intercept for each participant to account for clustered data by person (ie, repeated measures within person, across 4 treatment periods), an intercept for each trial site, and an interaction between treatments and air pollutant (ie, median dichotomized, quartiles). Model coefficients and SEs were estimated under restricted maximum likelihood estimation.

We used the glht function from the multcomp package version 1.4-25 in R to perform multiple hypothesis tests and adjust for multiple comparisons, using single-step adjustment method. All models were adjusted for age and household tobacco and vape use. The outcomes of interest, ie, AACD and $\%PFEV_1$, are presented in terms of the change associated with increased residential exposure to outdoor air pollutants and exacerbation events as incidence rate ratios. Specifically, these changes are quantified as dichotomized (above or below median) $PM_{2.5}$, NO_2, and O_3.

In sensitivity analyses, we categorized exposures by quartiles. This approach allowed for the evaluation of treatment effect modification across increasing levels of pollutant exposure, rather than relying solely on median dichotomized values. Lastly, we fitted models with adjusted pulmonary function test results based on GLI formulas. We used SAS version 9.4 (SAS Institute Inc, Cary, NC) for database management and R version 4.2. for statistical analysis. We show descriptive statistics in frequencies and percentages for binary variables and means ± SDs for continuous variables.

TABLE I. Baseline characteristics of study participants (n = 224)

Characteristic	Value
Demographic features	
Age (y), mean ± SD	8.47 ± 1.82
Male sex, no. (%)	133 (59)
Hispanic or Latino ethnic background, no. (%)*	20 (8.9)
Percent below poverty line, mean ± SD	23.29 ± 13.10
Asthma history in previous 12 mo, no. (%)	
One or more asthma episodes resulting in emergency care or unscheduled office visit	86 (35.2)
Overnight hospitalizations	35 (14.3)
One or more courses of systemic glucocorticoids	141 (57.8)
Medication use in previous 12 mo, no. (%)	
Leukotriene receptor antagonist or 5-lipoxygenase inhibitor	83 (37)
Oral glucocorticoids	140 (63)
Inhaled or nebulized glucocorticoid monotherapy	187 (83)
Inhaled glucocorticoid+LABA combination therapy	51 (23)
Clinical features	
Median blood eosinophil absolute count (cells/mm^3), median (IQR)†	387.82 (180-502.5)
$\%PFEV_1$ (% of predicted value), mean ± SD	96.6 ± 16.83
Childhood Asthma Control Test score, mean ± SD‡	21.39 ± 3.77
Household features, no. (%)	
Pregnancy smoking§	33 (13.9)
Pregnancy vaping‖	2 (1.3)
Household baseline tobacco use	82 (33.6)
Household baseline vaping¶	10 (6.3)

IQR, Interquartile range.
*Race and ethnic group were reported by the patients or their parents or guardians.
†Data were missing for 4 children.
‡The score on the Childhood Asthma Control Test ranges from 0 to 27, with higher values representing better asthma control.
§Data were missing for 8 children.
‖Data were missing for 85 children.
¶Data were missing for 81 children.

RESULTS

Demographic results

From January 2014 through March 2016, 280 participants were randomized in the BARD crossover clinical trial. Of those,

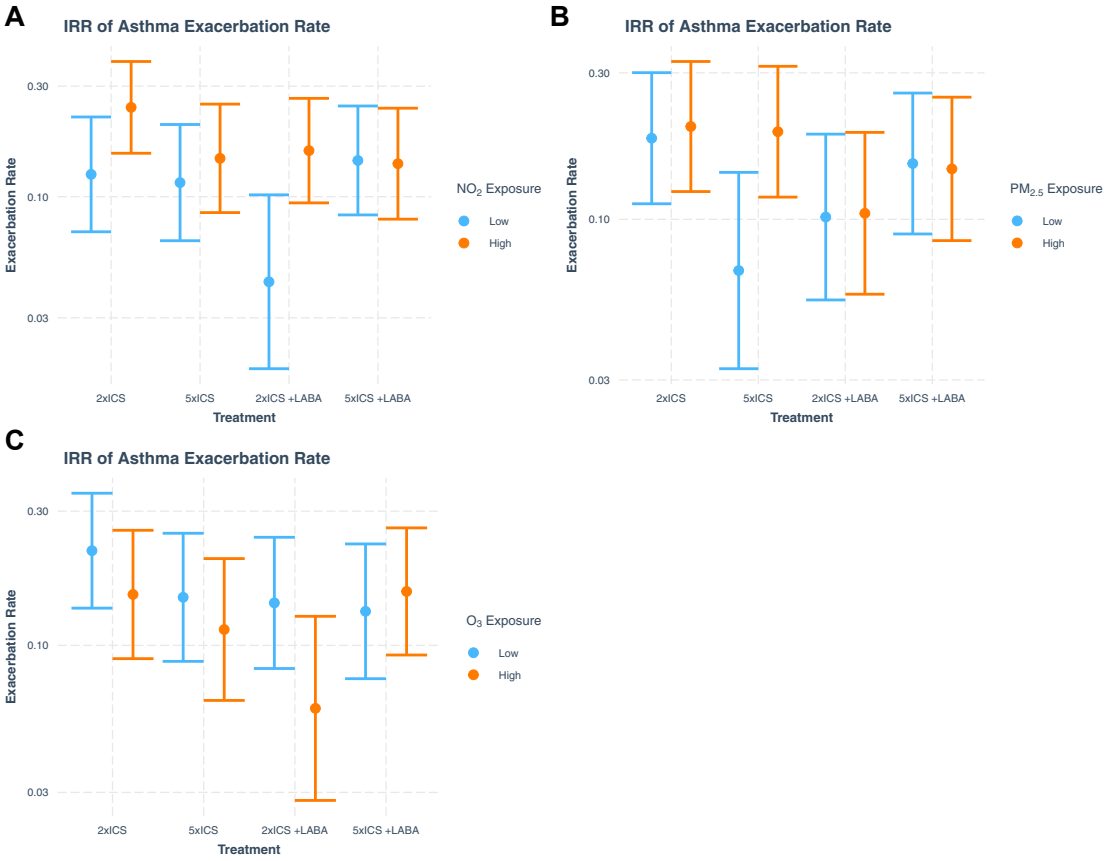


FIG 1. Interaction plots showing predicted model results. Predicted number of asthma exacerbations events among children in the BARD ancillary study. **(A)** Predicted model with an interaction term between treatment and NO_2. **(B)** Predicted model with an interaction term between treatment and $PM_{2.5}$. **(C)** Predicted model with an interaction term between treatment and O_3. Models are adjusted for age, household vaping, and smoking status. Random intercepts for trial site and participant were included. *IRR,* Incidence rate ratio.

224 participants were included in this ancillary study (80% retention rate). The baseline characteristics of BARD trial participants are reported in Table I. Most participants were male (59%), non-Hispanic/Latino (91%), and lived in census blocks with median incomes above the federal poverty rate. At baseline, 13.9% of parents reported smoking while pregnant, 33.6% of households reported at least 1 smoker, and 1 child had a wood-burning stove as a primary source of heat. Participants excluded from the current analysis did not have differences in sociodemographic or asthma-related clinical characteristics compared with included children (Table E1 in the Online Repository at www.jacionline.org). Average treatment period–specific air pollutant exposures are summarized in Table E2 (in the Online Repository at www.jacionline.org) and did not differ substantially across treatments.

Asthma exacerbations

Results of the generalized linear mixed model analyses for the number of asthma exacerbations are reported in Fig 1 and summarized in Table E3 (in the Online Repository at www.jacionline.org). We found that $PM_{2.5}$, NO_2, and O_3 did not significantly modify the effect of any of the treatments on the number of exacerbation events. There were no statistically significant differences in the response to treatment between exposures to levels of air pollution. Though not statistically significant, the predicted number of exacerbations after adding LABA (2×ICS+LABA), was higher for participants exposed to high NO_2 compared with participants in low NO_2 areas (0.65 [95% CI 0.30, 1.43] vs 0.34 [0.09, 1.25]) (Fig 1, *A*). The expected number of exacerbations after treatment with 5×ICS was higher for children living in areas of high $PM_{2.5}$ exposure compared with the effect of treatment with 5×ICS in low $PM_{2.5}$ areas (0.96 [95% CI 0.46, 2.03]) (Fig 1, *B*). The number of exacerbations after adding LABA (2 × ICS+LABA) did not yield any significant differences when compared to treatment with 2 × ICS alone and did not vary by levels of Ozone exposures (Fig 1, *C*).

Annualized asthma control days

$PM_{2.5}$ moderately modifies the effect of treatment on annualized asthma control days (ie, days of well-controlled asthma symptoms). On average, treatment with 5×ICS+LABA significantly decreased the number of control days, but only among participants with below median $PM_{2.5}$ exposures (−14.97 days [95% CI −52.11, 22.16]) (Table E4 in the Online Repository at www.jacionline.org). In contrast, among participants with above median $PM_{2.5}$ exposures, the higher ICS dose with LABA conferred more control days (43.44 days [95% CI 1.26, 85.63]) (Fig 2, *B*). The interactions between the effect of treatment and NO_2

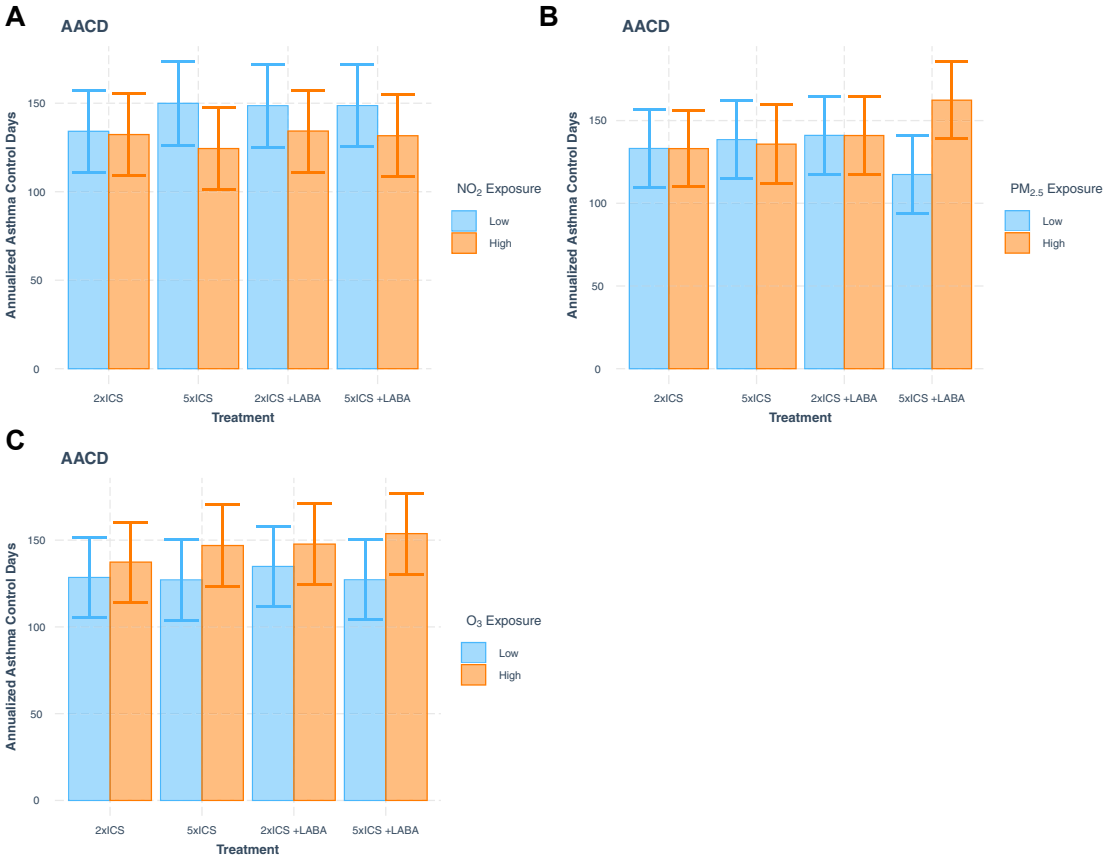


FIG 2. Interaction plots showing predicted model results. Predicted number of asthma control days among children in the BARD ancillary study. **(A)** Predicted model with an interaction term between treatment and NO_2. **(B)** Predicted model with an interaction term between treatment and $PM_{2.5}$. **(C)** Predicted model with an interaction term between treatment and O_3. Models are adjusted for age, household vaping, and smoking status. Random intercepts for trial site and participant were included.

(Fig 2, *A*) did not yield differences in effects (*P* for interaction = .59) However, among participants with above median $PM_{2.5}$ exposures, the higher ICS dose with LABA conferred more control days (43.44 days [95% CI 1.26, 85.63]) (Fig 2, *B*). The interaction with O_3 not reach statistical significance (*P* for interaction = .76) (Fig 2, *C*).

Percent predicted FEV_1

Results from models that evaluated lung function via % $PFEV_1$ are reported in Table E5 (in the Online Repository at www.jacionline.org) and Fig 3. We found a statistically significant interaction effect between treatment and NO_2 (*P* for interaction = .05), and we found that, on average, treatment with 5×ICS+LABA significantly increased %$PFEV_1$ among participants in the low NO_2 exposure areas (5.86 [95% CI 1.16, 10.56]) compared with participants in the high NO_2 exposure areas (0.57 [95% CI −4.66, 5.8]) (Fig 3, *A*). Models that evaluated the interaction between treatment and $PM_{2.5}$ and O_3 did not reach statistical significance (*P* for interaction = .12 and .13, respectively) (Fig 3, *B* and *C*).

In sensitivity analyses, we found that categorizing the exposures of interest using quartiles did not result in any differences from the above-reported results (Figs E3-E5 in the Online Repository at www.jacionline.org). We saw no difference in the therapeutic response when excluding participants who would not have met the inclusion criteria based on adjusted GLI formula baseline FEV_1.

DISCUSSION

In this secondary analysis, we investigated whether ambient air pollution exposure alters treatment efficacy—an area that has been insufficiently explored—within a pediatric clinical trial. We sought to investigate the roles of exposure to $PM_{2.5}$, NO_2, and O_3 in the association between crossover treatments with combination therapy and markers of treatment efficacy for asthma pharmaceutical interventions. We found there were no significant differences in the effect of treatment on exacerbation events among children across levels of $PM_{2.5}$, NO_2, and O_3 residential exposures. Nonetheless, there was an apparent effect modification by $PM_{2.5}$ and NO_2 on measures of asthma control and lung function, though these should be interepreted with caution because within-group results are imprecise. We found no significant difference in the AACD between high versus low $PM_{2.5}$ exposure areas when participants were treated with 2×ICS+LABA and 5×ICS+LABA.

Likewise, participants with low NO_2 exposures had modestly better asthma control than participants with high NO_2 exposure for all treatments. This finding supports our hypothesis that

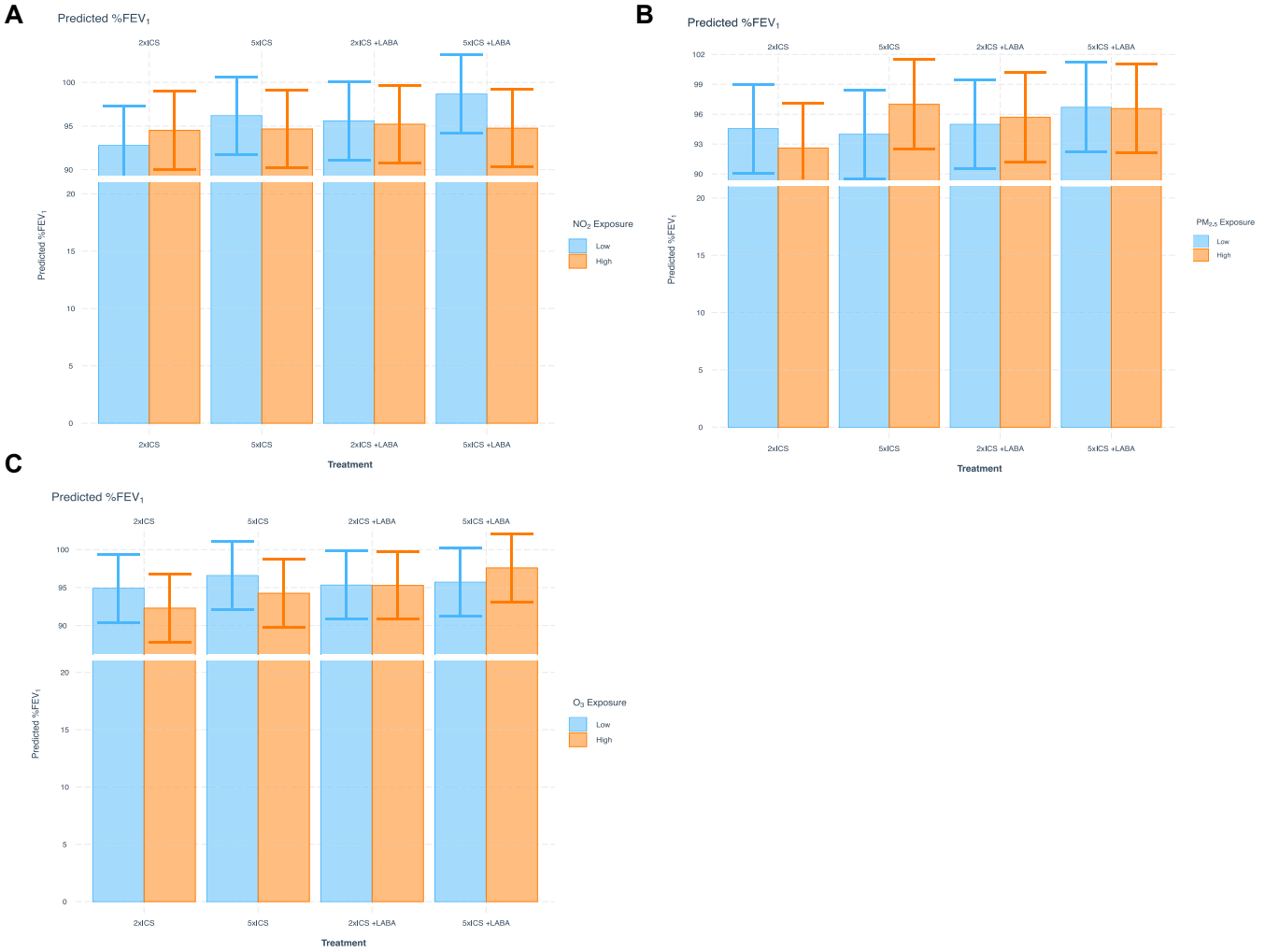


FIG 3. Interaction plots showing predicted model results. Predicted %PFEV$_1$ among children in the BARD randomized clinical trial. **(A)** Predicted model with an interaction term between treatment and NO_2. **(B)** Predicted model with an interaction term between treatment and $PM_{2.5}$. **(C)** Predicted model with an interaction term between treatment and O_3. Plots were created with ggbreak in R. Models are adjusted for age, household vaping, and smoking status. Random intercepts for trial site and participant were included.

increased exposure to NO_2 has the potential to reduce asthma control and contributes to the burgeoning understanding of how the environment may impact responses to asthma treatment. Further, our results lend support to our hypothesis that ambient air pollution interacts with asthma treatment. To that end, we also report findings on a significant increase in %PFEV$_1$ among participants in low NO_2 areas when treated with 5×ICS+LABA compared with high NO_2 areas. Consistent with existing studies, our results suggest that pharmaceutical treatments alone may not suffice to manage and improve asthma outcomes effectively in children. Observational studies reveal that compared with children not exposed to short-term $PM_{2.5}$, particulate matter <10 μm, and O_3, children exposed to higher levels of volatile organic compounds are more likely to experience severe asthma symptoms.[25] This underscores the importance of addressing the influence of ambient air pollution on treatment effectiveness in both clinical trials and clinical practice.[21,26] Additionally, these findings may have implications for the health disparities observed among Black children with asthma. Systemic racism has led to greater exposure to these pollutants in marginalized communities, potentially impacting treatment responsiveness even when medication adherence is maintained.[27,28]

The precise mechanisms by which increased exposure to air pollution interacts with ICSs or LABAs and acts on asthma symptoms remain to be fully understood. However, evidence of the impact of nitric oxide (NO) and NO_2 reveals that cigarette smoking significantly reduces endogenous NO production in the airways, affects endothelial function through negative feedback regulation, and alters NO levels in both asthmatic patients and smokers, which may influence respiratory health.[29-31] Likewise, studies show that biological responses targeted by both ICSs and LABAs are impacted by air pollution. That is, exposure to air pollution can either upregulate or downregulate the expression of glucocorticoid receptors in various tissues, thereby impacting their binding affinity to glucocorticoids. This could modify the stress response and other physiological processes mediated by glucocorticoids.[32] Similarly, pollutant-induced oxidative stress can also impair the downstream signaling of β_2-adrenergic receptors. For example, reactive oxygen species can lead to the phosphorylation of proteins involved in the

receptor signaling pathway, such as G protein–coupled receptor kinases, which in turn can lead to receptor desensitization and internalization.[33]

Strengths and limitations

One limitation of this study is that 20% of the trial population was not included in our analyses. We did not have information on 56 participant addresses, and therefore these individuals were excluded from the current analysis. We acknowledge there is a limitation in the power of our analyses. Given that this is a secondary analysis of a completed trial, tests reported in this article were not included in the original power calculations. However, our findings are still hypothesis generating and underscore the importance of considering the potential for air pollution to modify pharmaceutical efficacy for asthma, particularly after adjustments for multiple testing. Another limitation relates to the school environment, as children spend a considerable amount of time in school, and we did not have data on environmental triggers within school settings. Whereas we cannot draw conclusions on the effect of the school environment, we accounted for key home-based asthma triggers that are highly relevant for children ages 5 to 11. Lastly, predicted lung function calculations presented do not include race corrections that reflect current guidelines, as the nature of the crossover design removes confounding by individual-level characteristics, including race. Thus, the racial component of the prediction equation would simply cancel out. Nonetheless, a key consideration in the interpretation of our findings is the potential impact of baseline % $PFEV_1$ classification on treatment response estimates. Recent literature, including an official statement from the American Thoracic Society,[34] highlights concern about historical underestimation of disease severity due to racial classification in pulmonary function test values. However, when we recalculated baseline %$PFEV_1$ using GLI formulas, there was no difference in observed treatment effects on lung function (Fig E9).

The strengths of this secondary analysis relate to robust screening protocols, inclusion of multiple cities across the United States, and incorporation of geographic information system–based methods to represent each geographic setting. We used a robust method to assess air pollutant exposure by assigning mean $PM_{2.5}$, NO_2, and O_3 exposures over follow-up using a validated national spatiotemporal model. Further, these estimates were assigned to each participant from the date of enrollment until the date of trial conclusion at the residential location, thus adjusting for seasonality and accounting for spatiotemporal variability in pollution. Given that we did not have information on residential addresses for participants who did not consent, we were unable to evaluate how selection into the ancillary study, if any, was influenced by spatial and logistical access to each trial site.

The findings from this secondary analysis contribute valuable insights into the ongoing discourse and advocate for enhanced patient–provider communications regarding the potential impacts of environmental exposures on the efficacy of asthma medications. Furthermore, our study calls for the inclusion of data on participants' lived experiences and home environments in clinical trial analyses—information that, though often collected, is seldom used.

Conclusions

Our study shows a relationship between NO_2 exposure and response to treatment in children with asthma. While increasing ICSs demonstrated efficacy in reducing exacerbation events, this protective effect was observed primarily among children residing in areas with below-average NO_2 levels. These outcomes not only reinforce the existing evidence concerning the detrimental effects of ambient air pollution on pediatric asthma, but also highlight its potential to diminish the therapeutic benefits of pharmaceutical interventions. In pursuit of equitable clinical care, it would enhance clinical trials to more broadly consider the various factors affecting treatment efficacy. Our findings underscore the importance of accounting for environmental coexposures, such as ambient air pollution, which can significantly alter treatment outcomes. Moving forward, adopting an integrated approach that combines pharmacological and environmental strategies will be crucial in optimizing asthma management for pediatric patients.

DISCLOSURE STATEMENT

This work was funded by the NIH NHLBI (1R01HL114536-01 to J.E.C. and F.H.). The AsthmaNet trials were funded by NIH grants HL098302, HL098096, HL098075, HL098090, HL098177, HL098098, HL098107, HL098112, HL098103, and HL098115.

Disclosure of potential conflict of interest: In the last 3 years, J. Solway has received research and research training funding from the NIH, National Science Foundation, and Burroughs Wellcome Fund. He has a potential financial interest in PulmOne Advanced Medical Devices, Ltd (Israel) and financial interest in SynthBits, neither of which relates directly to this study. S. C. Lazarus reports receiving grants from the Department of Defense and serving as a principal investigator for BLOCK-MI, a Department of Defense–sponsored network. He has also received grants from the American Lung Association Airway Clinical Research Centers Network and the Pulmonary Trials Cooperative and serves as a principal investigator for the NHLBI-supported Pulmonary Trials Cooperative Network. M. E. Wechsler has received grants and personal fees from Novartis, Sanofi, and GSK; personal fees from Regeneron, Mylan, Genentech, Sentien Restorbio, Equillium, Genzyme, GALA Therapeutics, Pulmatrix, and Cohero Health; and both personal fees and nonfinancial support from Teva, Boehringer Ingelheim, and AstraZeneca. He has also received nonfinancial support from Merck outside the scope of the submitted work. F. Holguin serves on the adjudication committee for the ASPEN trial with INSMED. W. Phipatanakul serves as a consultant for Genentech, Novartis, Sanofi, Regeneron, GSK, and AstraZeneca. D. T. Mauger reports grant support from the NHLBI for the BARD trial and study drug provision by GSK for the BARD trial. He has also received grants from the Patient-Centered Outcomes Research Institute, National Institute of Allergy and Infectious Diseases, and NHLBI for separate clinical trials related to asthma care and prevention. S. R. White is in the speaker's bureau for AstraZeneca, Sanofi, and Regeneron. He is site director and center director for a clinical trial funded by the NHLBI (PrecISE). S. M. Nyenhuis has received funding from the NIH and the Allergy and Asthma Foundation of America. She has served as a consultant for GSK and PRIME education and receives royalties from Springer and Wolters Kluwer. The rest of the authors declare that they have no relevant conflicts of interest.

We gratefully acknowledge AsthmaNet for providing the deidentified trial data used in this project. We also thank the AsthmaNet research assistants for

their dedicated efforts in recruiting participants for our incillary study and BARD participants We especially acknowledge Joel D. Kaufman and Michael T. Young for generously providing the air pollution prediction data, which were integral to this research.

Clinical implications: Ambient air pollution may reduce asthma treatment efficacy in children; clinicians should consider environmental exposures when managing asthma to improve asthma control and lung function.

REFERENCES

1. Bousquet J, Mantzouranis E, Cruz AA, Aït-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: Document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol 2010;126:926-38.
2. Akinbami L, Centers for Disease Control and Prevention National Center for Health Statistics. The state of childhood asthma, United States, 1980-2005. Adv Data 2006;(381):1-24.
3. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012;(94):1-8.
4. de Benedictis FM, Attanasi M. Asthma in childhood. Eur Respir Rev 2016;25:41-7.
5. Busse WW, Lemanske RF. Asthma. N Engl J Med 2001;344:350-62.
6. Carr TF, Bleecker E. Asthma heterogeneity and severity. World Allergy Organ J 2016;9:41.
7. Binney S. Trends in US pediatric asthma hospitalizations, by race and ethnicity, 2012-2020. Prev Chronic Dis 2024;21:E71.
8. Nishimura KK, Galanter JM, Roth LA, Oh SS, Thakur N, Nguyen EA, et al. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. Am J Respir Crit Care Med 2013;188:309-18.
9. Ostro B, Lipsett M, Mann J, Braxton-Owens H, White M. Air pollution and exacerbation of asthma in African-American Children in Los Angeles. Epidemiology 2001;12:200-8.
10. Weitzman M, Gortmaker S, Sobol A. Racial, social, and environmental risks for childhood asthma. Am J Dis Child 1990;144:1189-94.
11. Zheng XY, Ding H, Jiang LN, Chen SW, Zheng JP, Qiu M, et al. Association between air pollutants and asthma emergency room visits and hospital admissions in time series studies: a systematic review and meta-analysis. PLoS One 2015;10:e0138146.
12. Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting β2-agonists and corticosteroids. Eur Respir J 2002;19:182-91.
13. Shea L, Pesa J, Geonnotti G, Powell V, Kahn C, Peters W. Improving diversity in study participation: patient perspectives on barriers, racial differences and the role of communities. Health Expect 2022;25:1979-87.
14. Wechsler ME, Szefler SJ, Ortega VE, Pongracic JA, Chinchilli V, Lima JJ, et al. Step-up therapy in Black children and adults with poorly controlled asthma. N Engl J Med 2019;381:1227-9.
15. Clark NA, Demers PA, Karr CJ, Koehoorn M, Lencar C, Tamburic L, et al. Effect of early life exposure to air pollution on development of childhood asthma. Environ Health Perspect 2010;118:284-90.
16. Ferrante G, La Grutta S. The burden of pediatric asthma. Front Pediatr 2018;6:186.
17. Holst GJ, Pedersen CB, Thygesen M, Brandt J, Geels C, Bønløkke JH, et al. Air pollution and family related determinants of asthma onset and persistent wheezing in children: nationwide case-control study. BMJ 2020;370:m2791.
18. Zanobetti A, Ryan PH, Coull BA, Luttmann-Gibson H, Datta S, Blossom J, et al. Early-life exposure to air pollution and childhood asthma cumulative incidence in the ECHO CREW Consortium. JAMA Netw Open 2024;7:e240535.
19. Brauer M, Hoek G, Smit HA, de Jongste JC, Gerritsen J, Postma DS, et al. Air pollution and development of asthma, allergy and infections in a birth cohort. Eur Respir J 2007;29:879-88.
20. Koenig JQ. Air pollution and asthma. J Allergy Clin Immunol 1999;104:717-22.
21. Zora JE, Sarnat SE, Raysoni AU, Johnson BA, Li WW, Greenwald R, et al. Associations between urban air pollution and pediatric asthma control in El Paso, Texas. Sci Total Environ 2013;448:56-65.
22. Bime C, Gerald JK, Wei CY, Holbrook JT, Teague WG, Wise RA, et al. Measurement characteristics of the childhood Asthma-Control Test and a shortened, child-only version. NPJ Prim Care Respir Med 2016;26:16075.
23. Wang M, Young M, Marshall JD, Piepmeier L, Bi J, Kaufman JD, et al. National $PM_{2.5}$ spatiotemporal model integrating intensive monitoring data and land use regression in a likelihood-based universal kriging framework in the United States: 2000-2019. Environ Pollut 2025;366:125405.
24. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Software 2015;67:1-48.
25. Garcia E, Rice MB, Gold DR. Air pollution and lung function in children. J Allergy Clin Immunol 2021;148:1-14.
26. Lewis TC, Robins TG, Mentz GB, Zhang X, Mukherjee B, Lin X, et al. Air pollution and respiratory symptoms among children with asthma: vulnerability by corticosteroid use and residence area. Sci Total Environ 2013;448:48-55.
27. Burbank AJ, Hernandez ML, Jefferson A, Perry TT, Phipatanakul W, Poole J, et al. Environmental Justice and Allergic Disease: A Work Group Report of the AAAAI Environmental Exposure and Respiratory Health Committee and the Diversity, Equity and Inclusion Committee. J Allergy Clin Immunol 2023;151:656-70.
28. Lovinsky-Desir S, Riley IL, Bryant-Stephens T, De Keyser H, Forno E, Kozik AJ, et al. Research priorities in pediatric asthma morbidity: addressing the impacts of systemic racism on children with asthma in the United States. An Official American Thoracic Society Workshop Report. Ann Am Thorac Soc 2024;21:1349-64.
29. McSharry CP, McKay IC, Chaudhuri R, Livingston E, Fraser I, Thomson NC. Short and long-term effects of cigarette smoking independently influence exhaled nitric oxide concentration in asthma. J Allergy Clin Immunol 2005;116:88-93.
30. Kharitonov SA, Robbins RA, Yates D, Keatings V, Barnes PJ. Acute and chronic effects of cigarette smoking on exhaled nitric oxide. Am J Respir Crit Care Med 1995;152:609-12.
31. Buga GM, Griscavage JM, Rogers NE, Ignarro LJ. Negative feedback regulation of endothelial cell function by nitric oxide. Circ Res 1993;73:808-12.
32. Rider CF, Carlsten C. Air pollution and resistance to inhaled glucocorticoids: evidence, mechanisms and gaps to fill. Pharmacol Ther 2019;194:1-21.
33. Rambacher KM, Moniri NH. The β2-adrenergic receptor-ROS signaling axis: an overlooked component of β2AR function? Biochem Pharmacol 2020;171:113690.
34. Bhakta NR, Bime C, Kaminsky DA, McCormack MC, Thakur N, Stanojevic S, et al. Race and ethnicity in pulmonary function test interpretation: an Official American Thoracic Society Statement. Am J Respir Crit Care Med 2023;207:978-95.