

DATE
04/29/2024

Modification in Responses to Asthma Treatment by Environmental and Social Exposures

A Secondary Analysis of AsthmaNet Clinical Trials



PRESENTED BY
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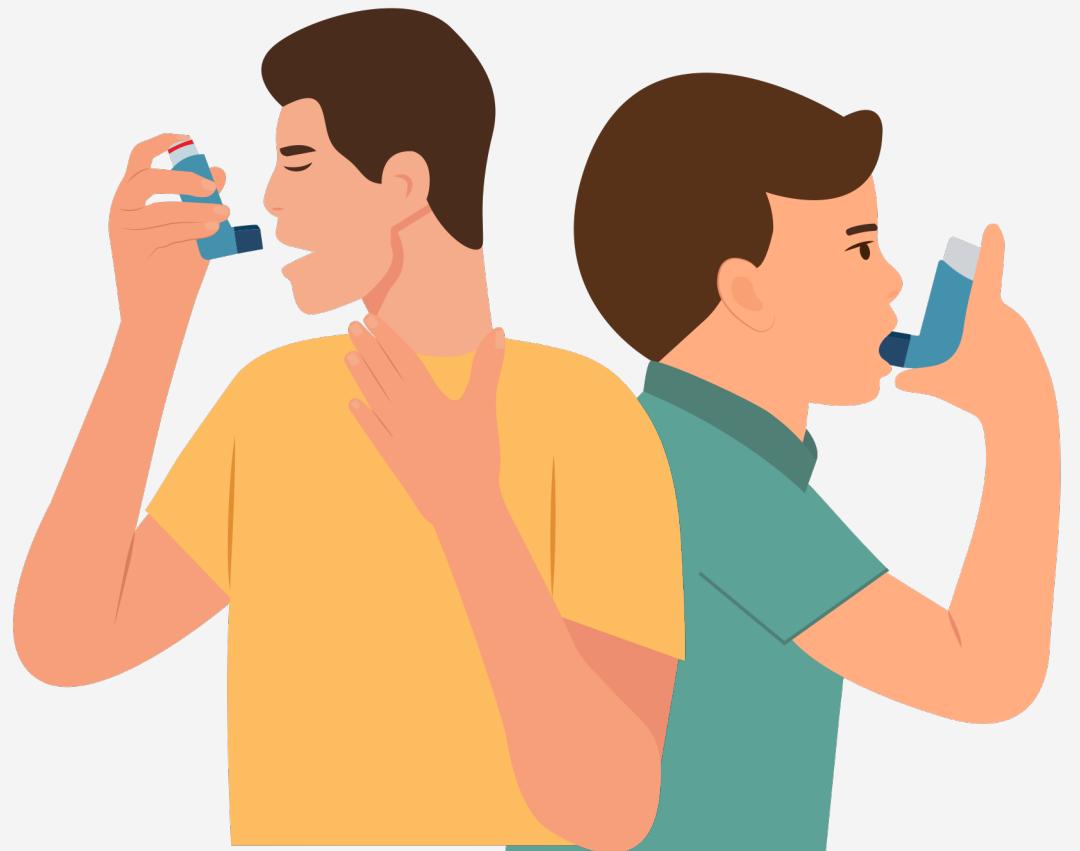
ACKNOWLEDGEMENTS

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Q&A

Background

- Health impacts of air pollution
- Vast research on air pollution (and socio-environmental) exposures and asthma
- Mechanisms by which air pollution and social context act on asthma

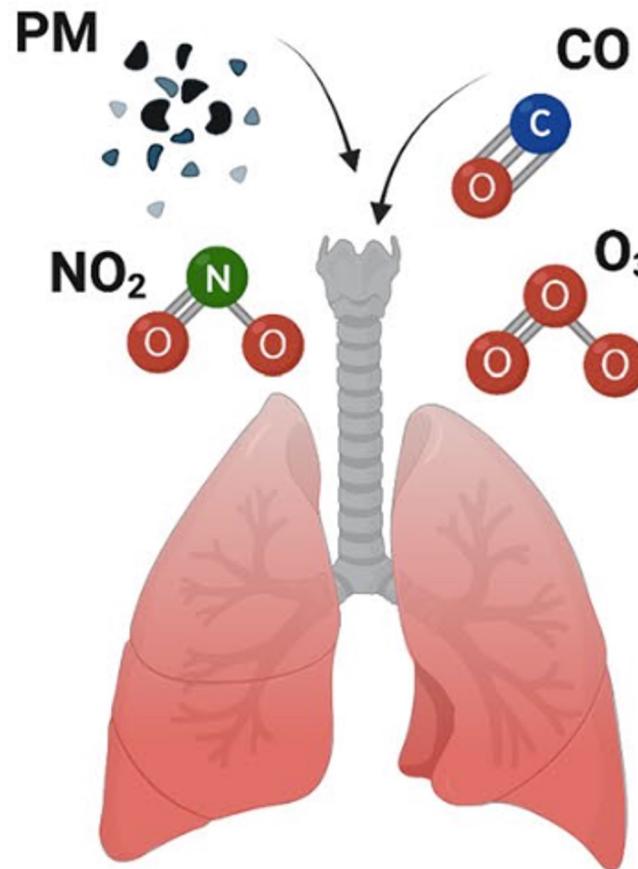


Background

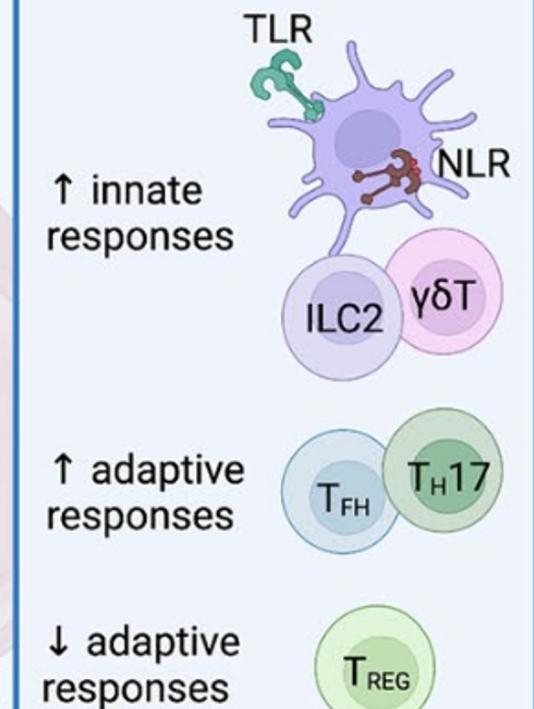
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- Vast research on air pollution and social context
- Mechanisms by which AP and social context c

Air Pollution and Asthma Pathogenesis

Air pollutants in asthma pathogenesis



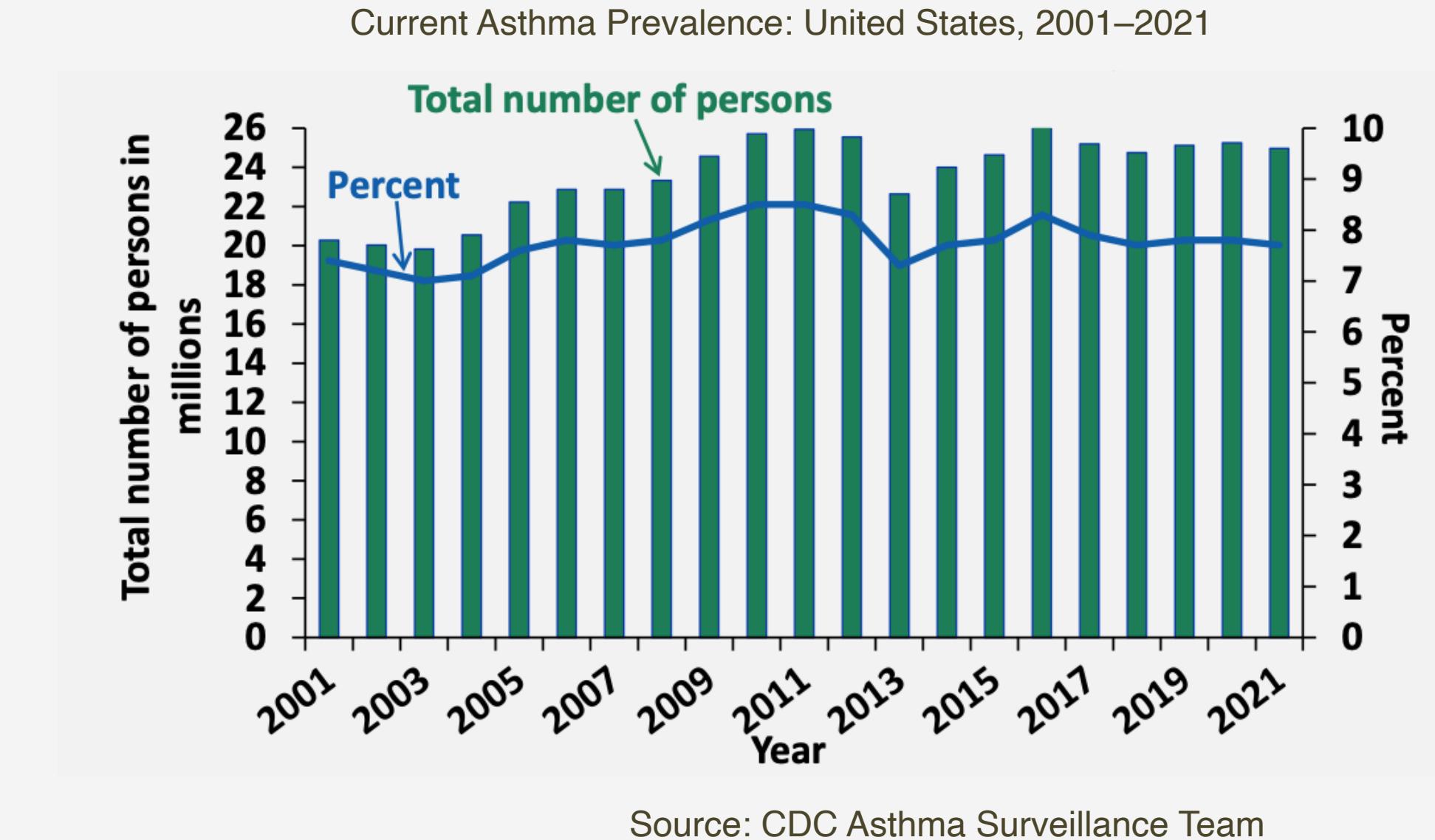
Pollution-induced immune responses in asthma



DOI: 10.1007/s11882-022-01034-1

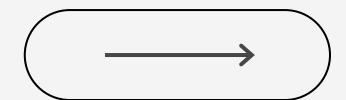
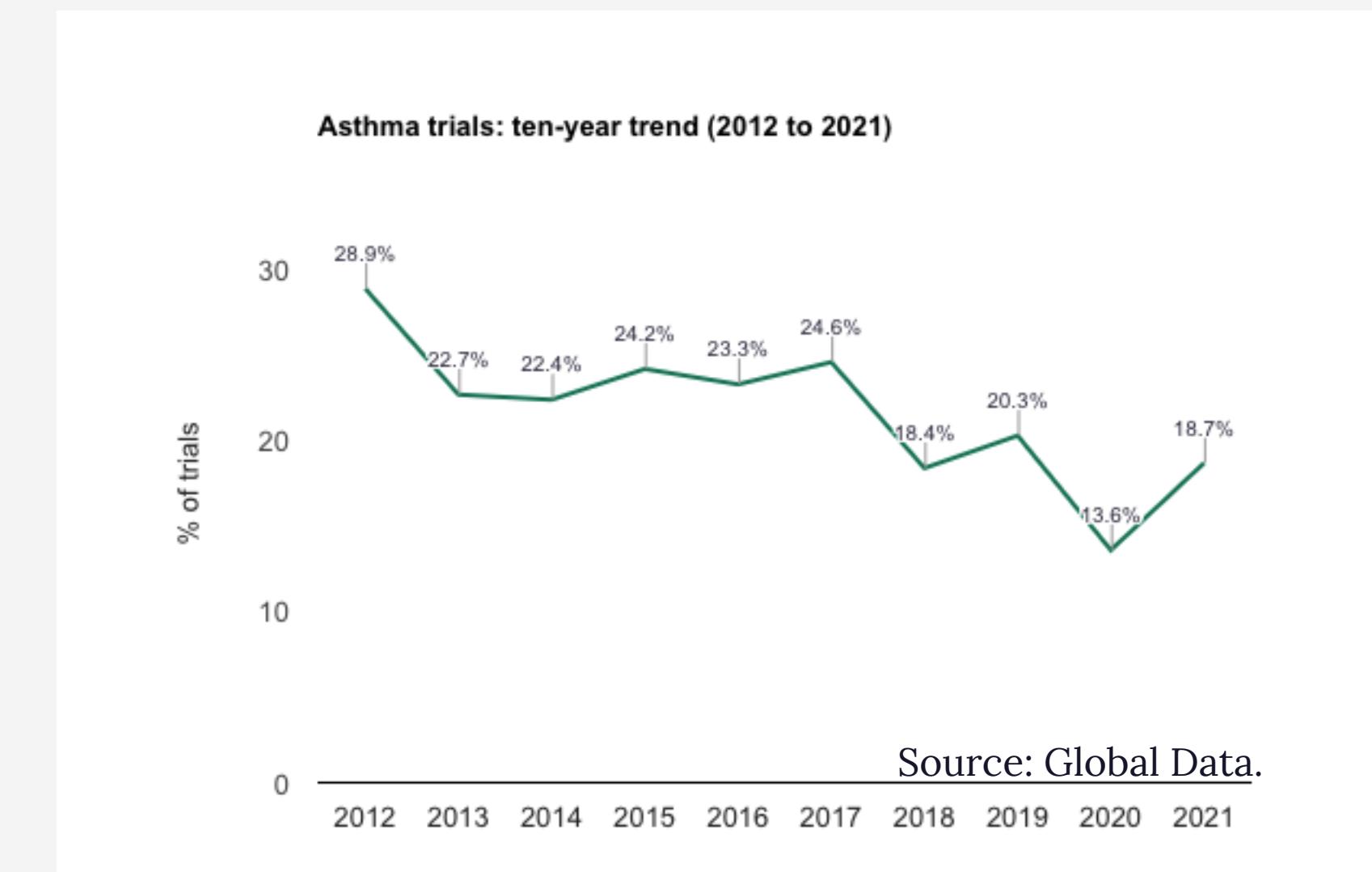
Asthma

- Heterogeneous disease (s)
- Characteristics
 - Reversible airway obstruction
 - Hyperresponsiveness
 - Inflammation
- Prevalent in the US and Worldwide



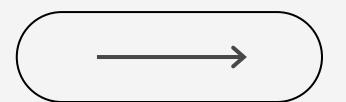
Randomized Clinical Trials for Asthma

- Randomized clinical trials for asthma
 - The gold standard for clinical recommendations
 - High-quality data
 - Longitudinal
- ~19% of the global share of RCT



Clinical Trials

- Clinical trials for asthma
 - The gold standard for clinical recommendations
 - High-quality data
 - Longitudinal
- ~19% of the global share of RCT
 - Generalizability
 - Transportability



The Problem

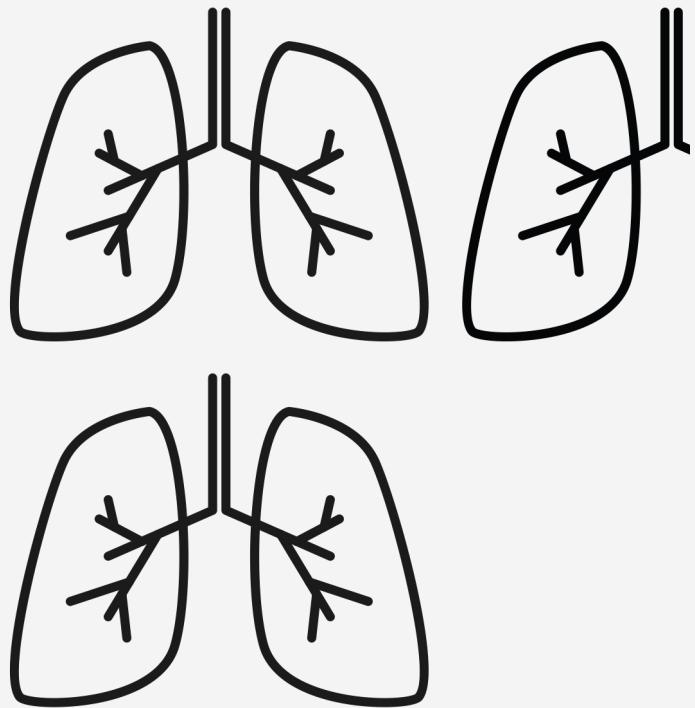
Despite the widespread availability of asthma treatments, their efficacy varies across individuals. These differences in treatment efficacies are often attributed to individual-level risk factors.

The Problem

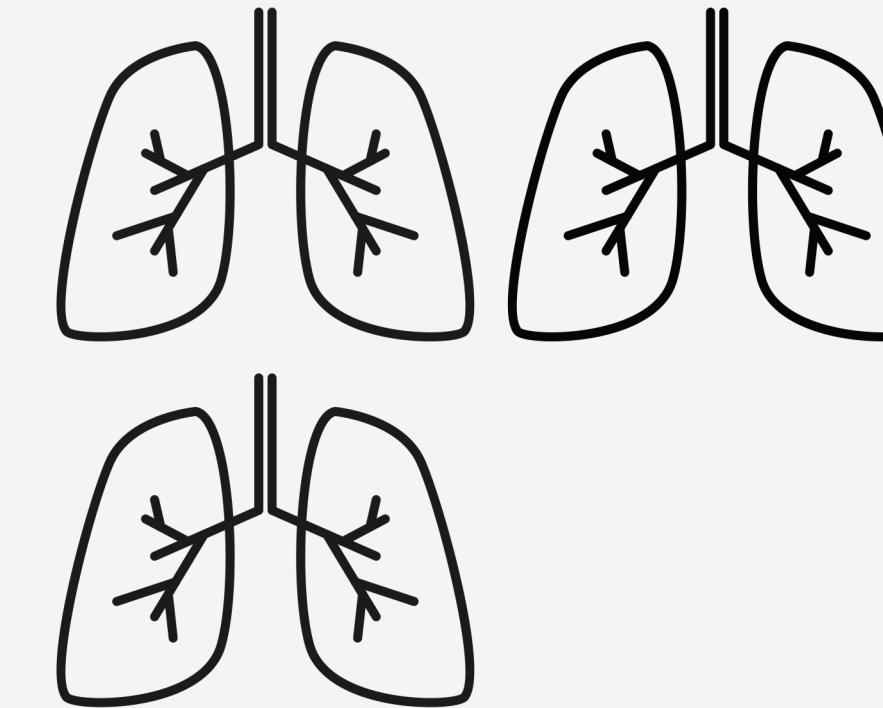
Despite the widespread availability of asthma treatments, their efficacy varies across individuals. These differences in treatment efficacies are often attributed to individual-level risk factors.

However, distinct societal-level patterns exist.

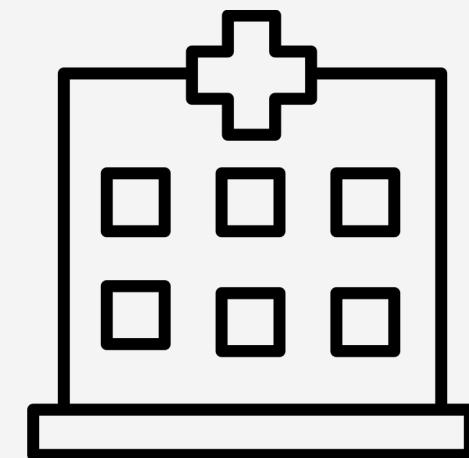
Black and Hispanic individuals in the U.S. face the HIGHEST BURDEN OF ASTHMA



Black Americans
are nearly 1.5
times more likely
to have asthma

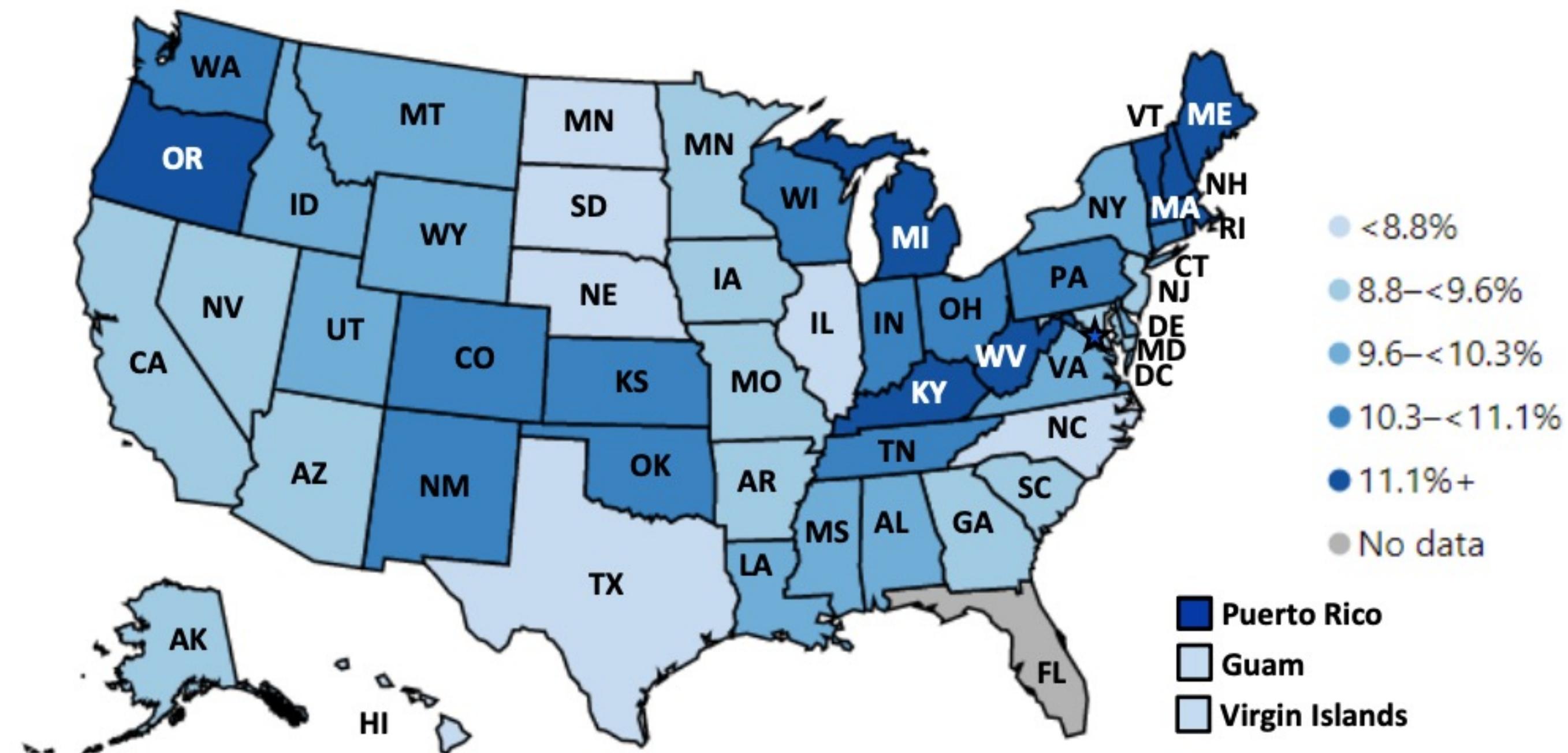


Puerto Ricans
are nearly 2
times more likely
to have asthma



Black Americans are nearly 5 times
more likely to have visit the ER and 3
times more likely to die from asthma

Adult Current Asthma Prevalence (%) by State or Territory (2021)



The Problem

Despite the widespread availability of asthma treatments, their efficacy varies across individuals. These differences in treatment efficacies are attributed to individual-level risk factors

However, distinct societal-level patterns exist.

Few studies have evaluated the potential for air pollution and social context to modify the association between treatment and asthma outcomes.

The Problem

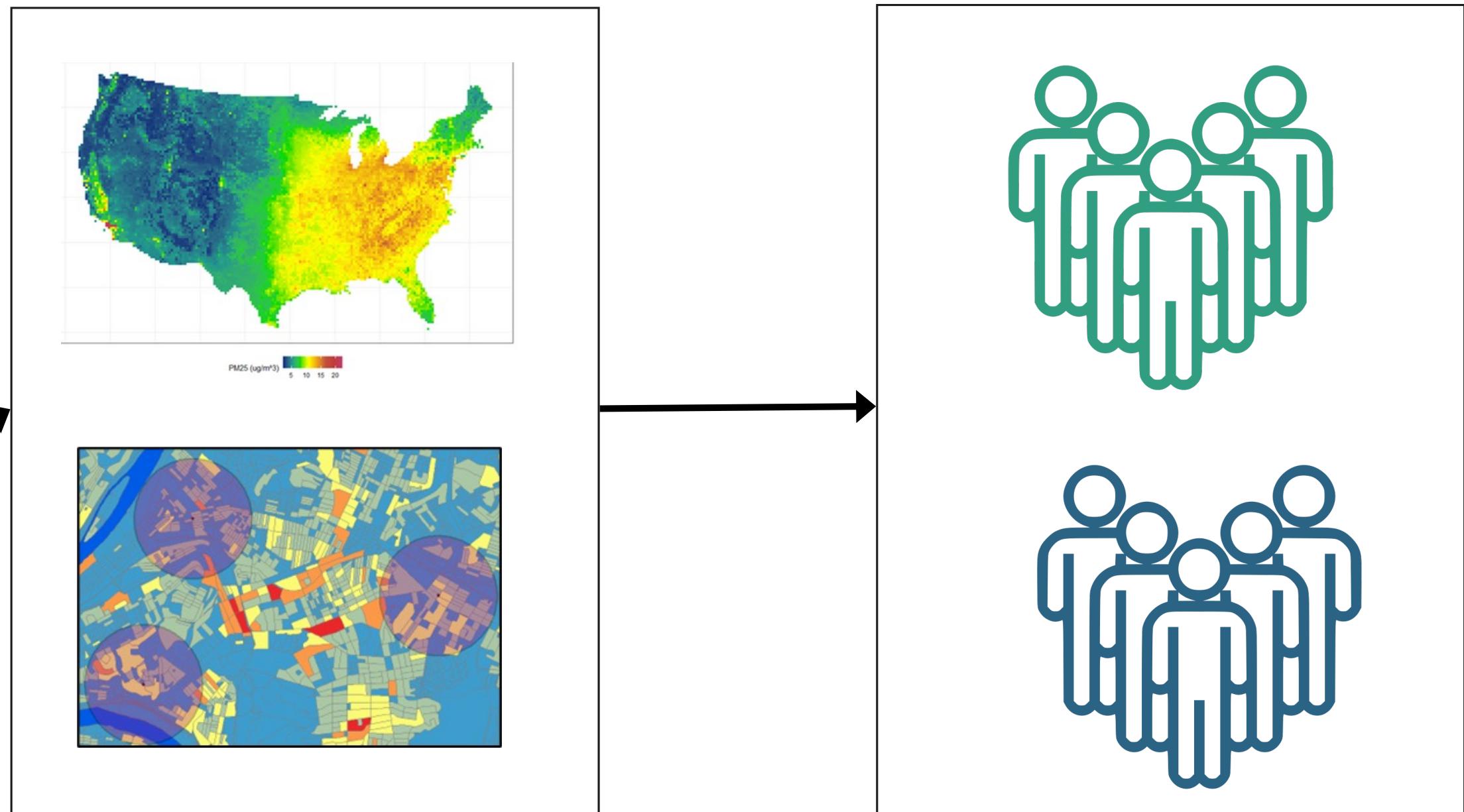
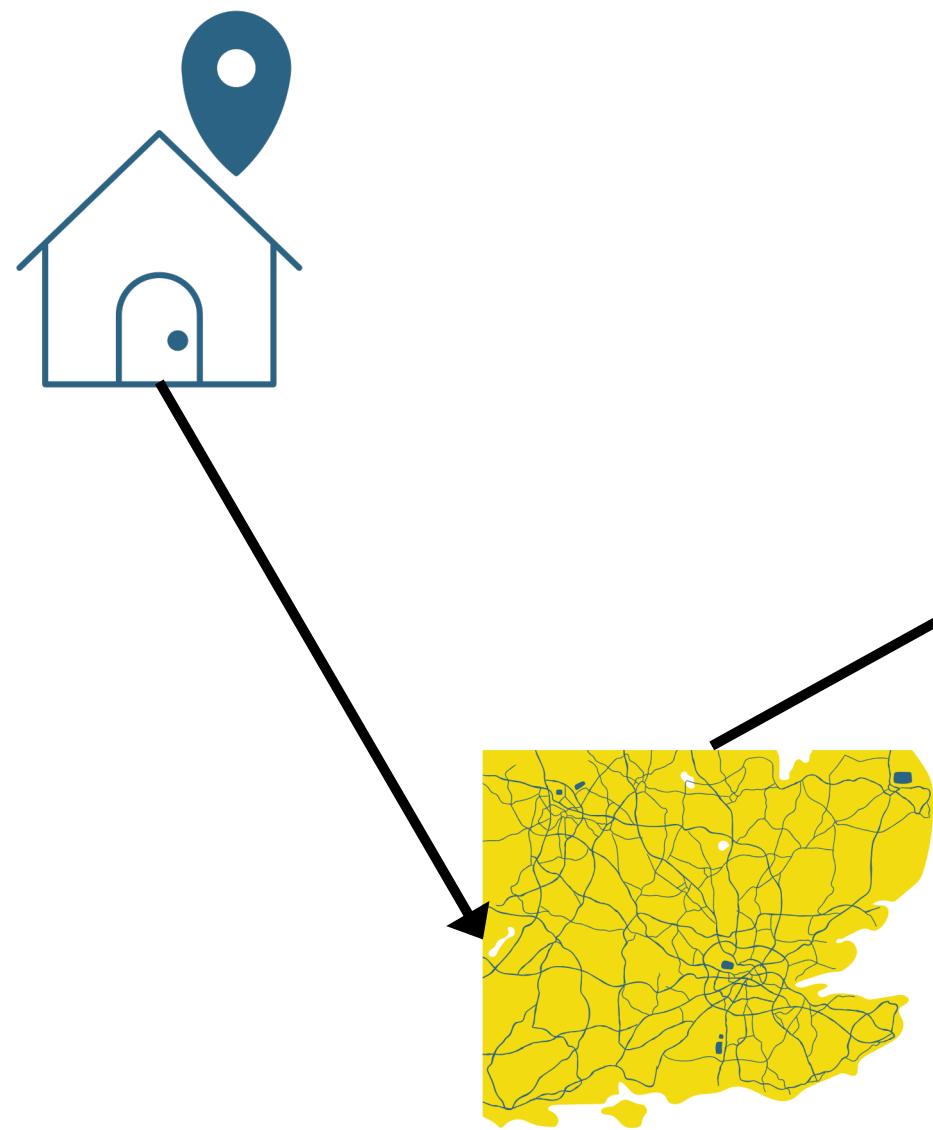
Few studies have evaluated the potential for air pollution and social context to modify the association between treatment and asthma outcomes.

Environmental & Social Co-Exposures

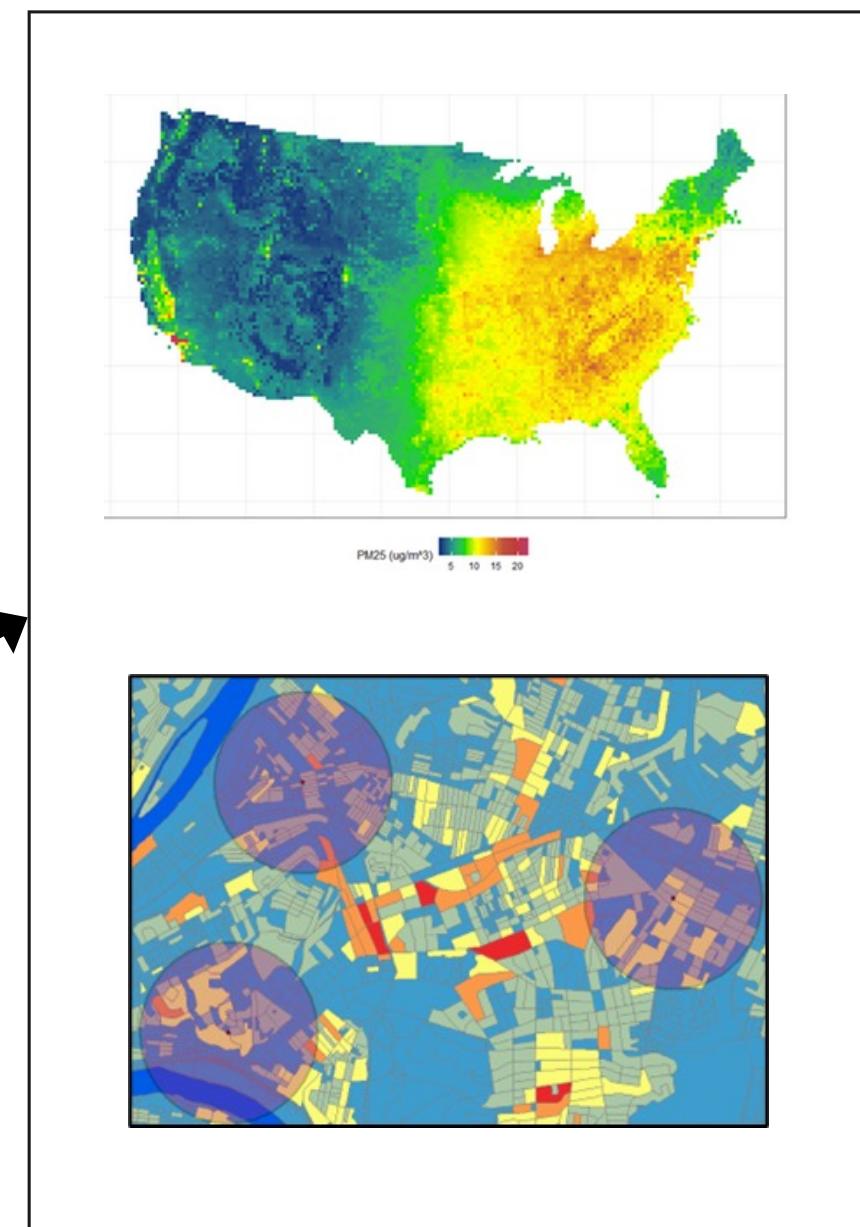
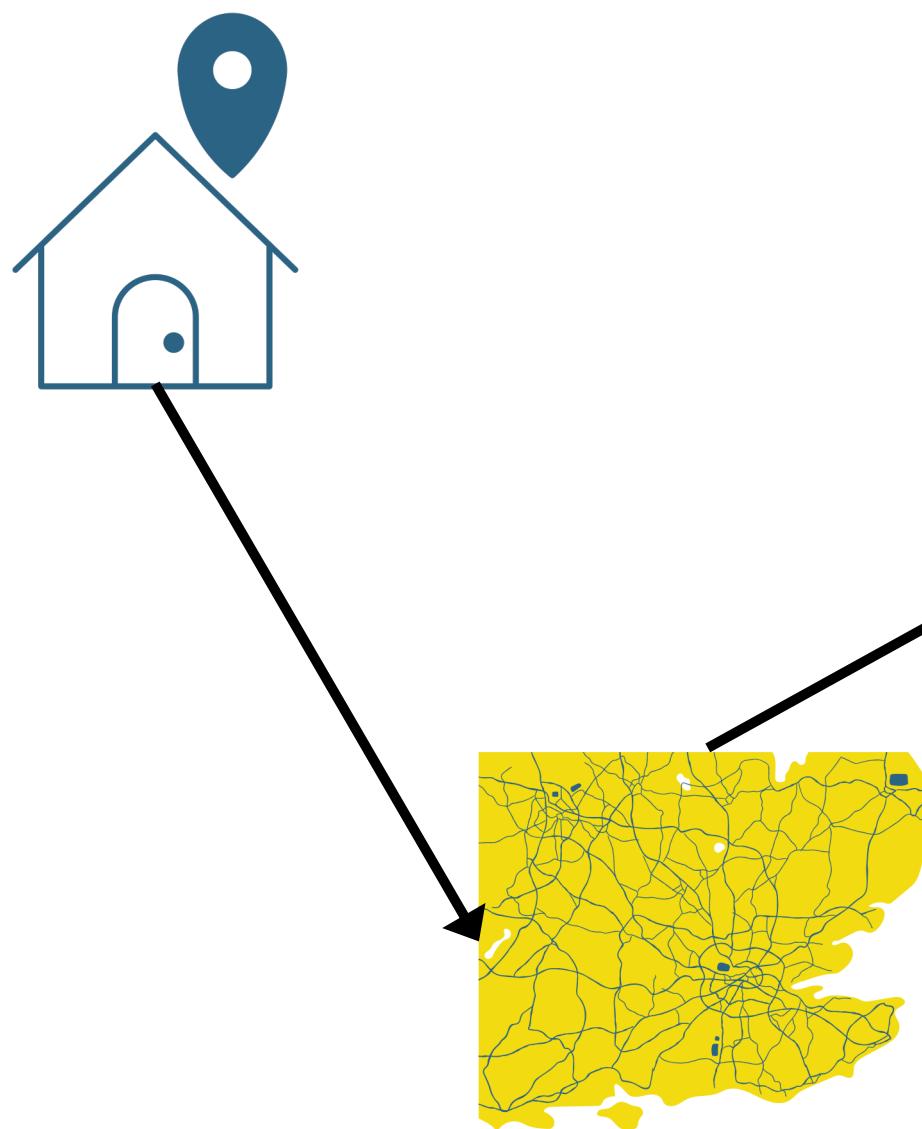
Susceptible Populations

Phenotypes as susceptibilities

GIS-Based Methods

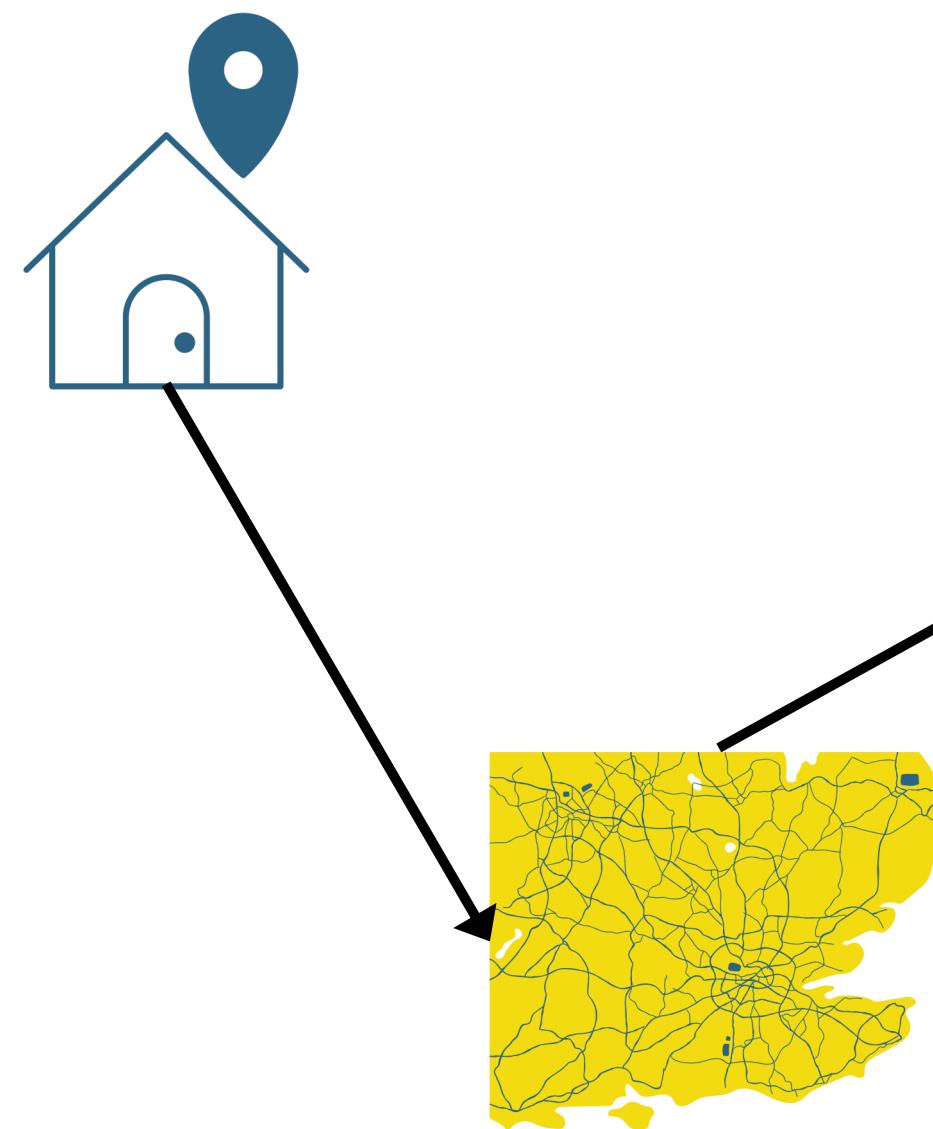


GIS-Based Methods



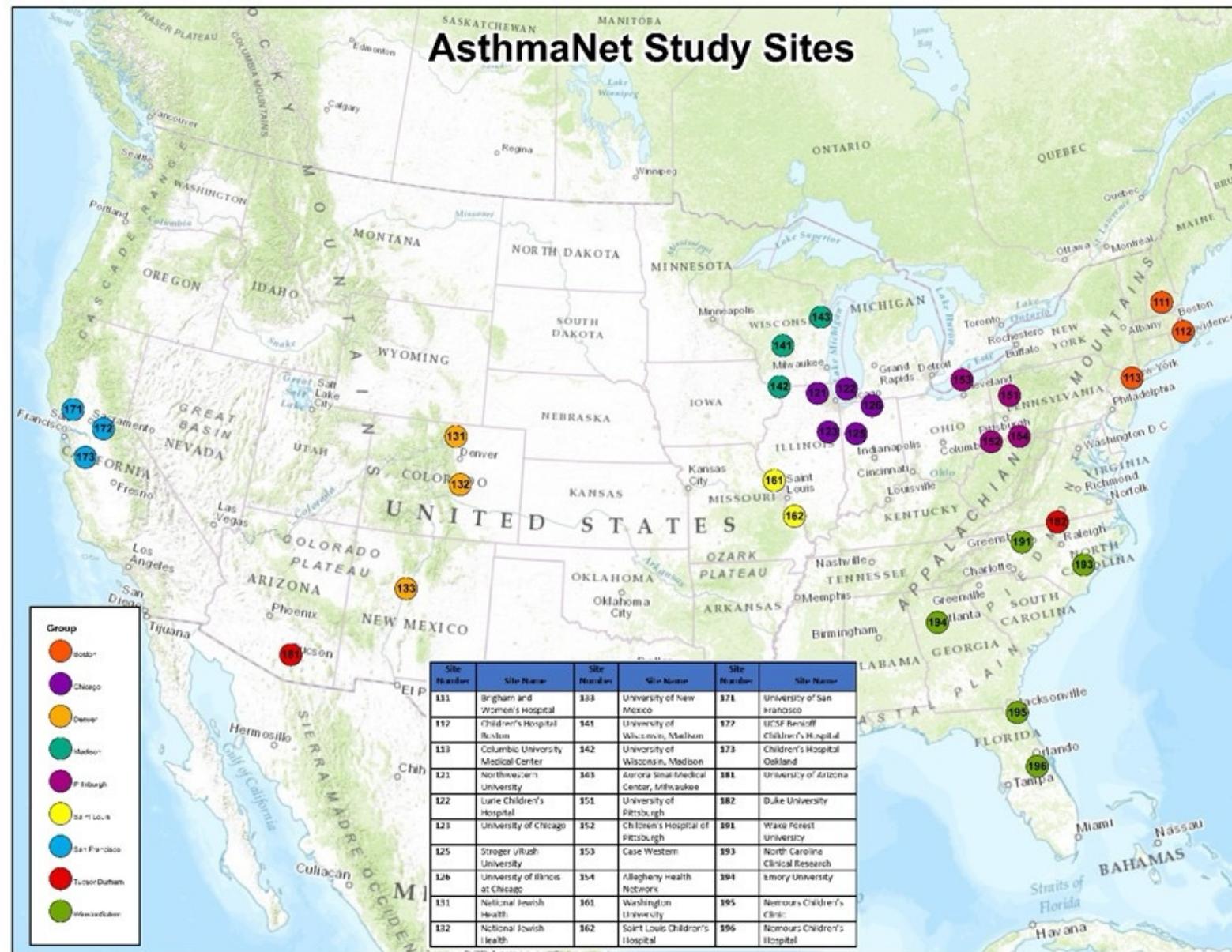
- Modeled air pollution in 2-week concentration resolution
 - Averaged pollutant estimates from a national universal kriging model
- Estimated for individual's geocoded residence

GIS-Based Methods



- Modeled air pollution in 2-week concentration resolution
 - Averaged pollutant estimates using a national universal kriging model
- ACS 5-year summary (2012-16), block group level.
- U.S. Health Resources and Services Administration

AsthmaNet



Same protocols across 17 US cities

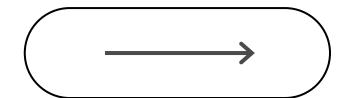
Air Pollution Exposure in AsthmaNet Trials

Trial City	N	NO ₂ (ppb)	PM _{2.5} ($\mu\text{g}/\text{m}^3$)	O ₃ (ppb)
Boston, MA	41	6.66 (2.56)	5.97 (1.10)	27.95 (2.53)
Chicago, IL	18	7.09 (2.80)	10.01 (1.14)	28.18 (1.34)
New York, NY	8	5.19 (0.44)	10.04 (0.25)	29.28 (1.24)
Denver, CO	72	9.46 (4.59)	6.49 (0.79)	22.55 (2.72)
Albuquerque, NM	23	6.12 (1.22)	5.04 (0.93)	24.43 (1.49)
Madison, WI	80	8.84 (3.49)	7.29(1.01)	24.90 (3.92)
Pittsburgh, PA	39	8.96(3.05)	8.72 (1.26)	26.90 (4.63)
Cleveland, OH	26	8.49(1.12)	7.87 (0.96)	25.10 (1.85)
Wake Forest, NC	4	10.68 (2.8)	8.66 (0.82)	25.20 (4.01)
Saint Louis, MO	96	6.43(2.96)	8.50 (0.91)	25.91 (3.84)
San Francisco /Oakland, CA	23	12.85 (7.32)	7.63(1.85)	31.89 (3.89)
Raleigh/Durham, NC	28	10.47 (2.55)	7.94 (1.41)	22.03 (2.32)
Tucson, AZ	59	19.65 (6.56)	6.86 (1.58)	26.96 (4.66)
Atlanta, GA	52	17.64 (4.73)	8.53 (0.91)	27.83 (4.45)
Jacksonville, FL	41	13.22 (5.79)	6.87 (0.33)	28.81 (6.39)
Orlando, FL	34	11.65(5.85)	5.99 (0.47)	24.30 (3.35)

Median (SD) of air pollution exposures by trial city

AIM 1

ICS Step-Up and Asthma as Modified
by Indicators of Healthcare Access



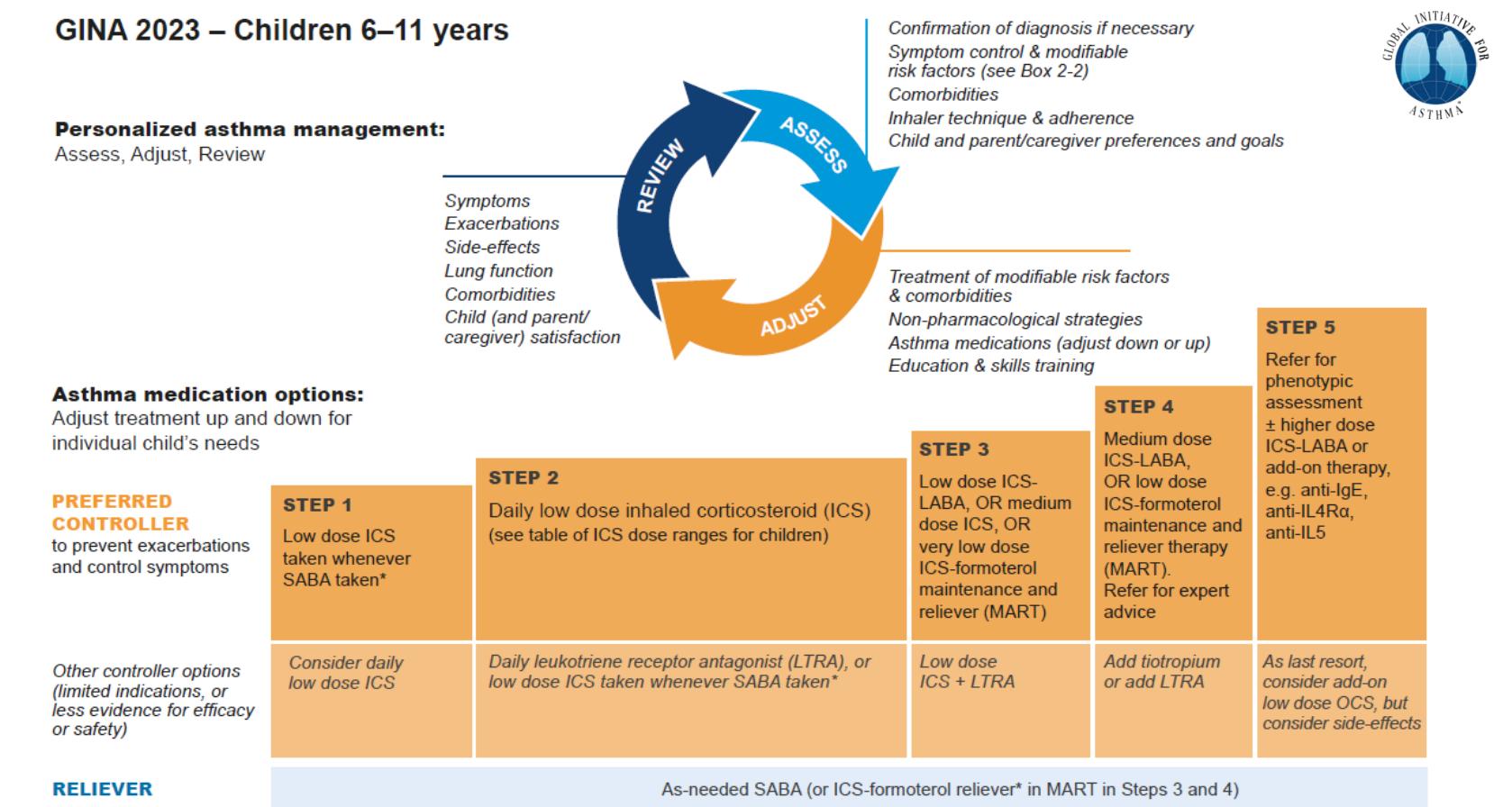
AIM 1

ICS Step-Up and Asthma Modification by Indicators of Healthcare Access

AGES 5-11 YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

Intermittent Asthma		Management of Persistent Asthma in Individuals Ages 5-11 Years					
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6	
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA	
Alternative		Daily LTRA,* or Cromolyn,* or Nedocromil,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA,* or daily low-dose ICS + Theophylline,* and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA or Daily medium-dose ICS + LTRA* or daily medium-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* or daily high-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* + oral systemic corticosteroid or daily high-dose ICS + Theophylline* + oral systemic corticosteroid, and PRN SABA	
Steps 2-4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲						Consider Omalizumab**▲	
Assess Control							

GINA 2023 – Children 6–11 years



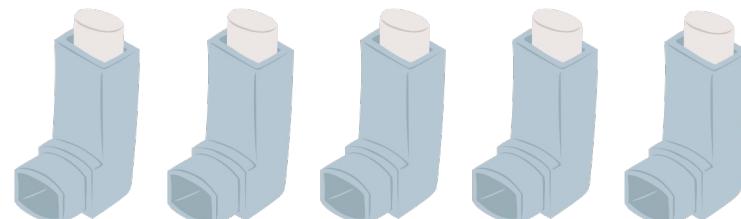
STICS Trial



1xICS



5xICS

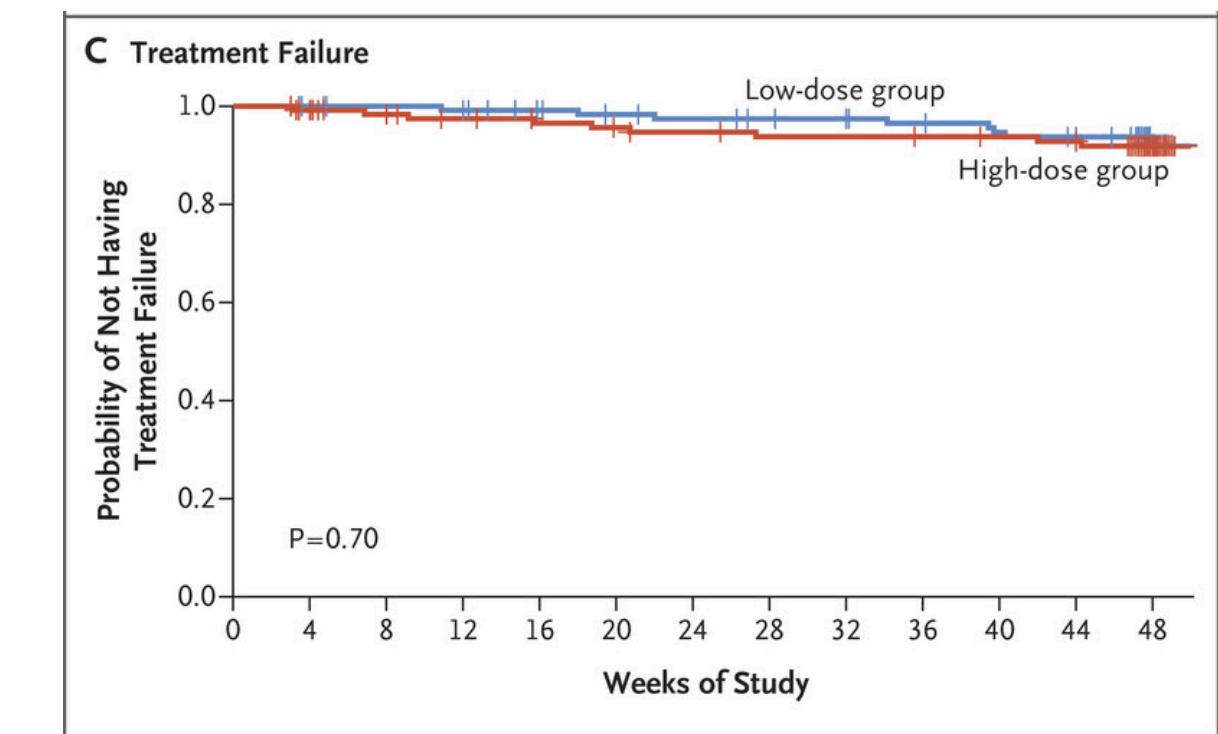
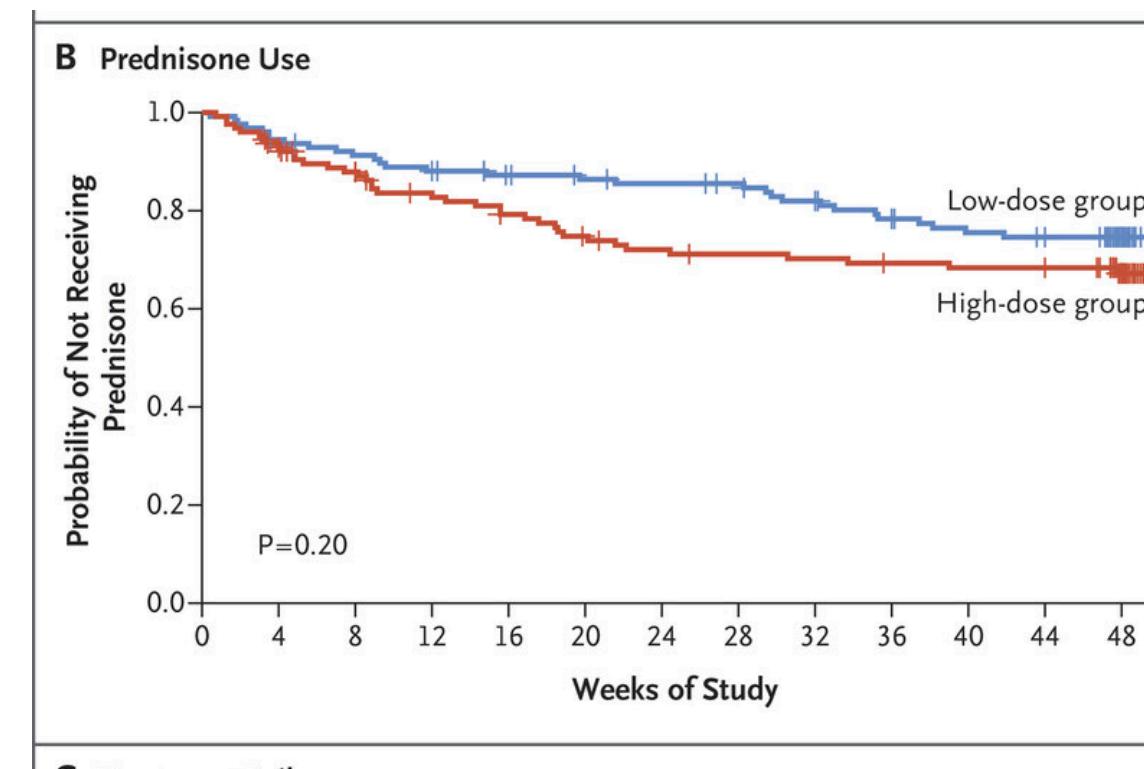
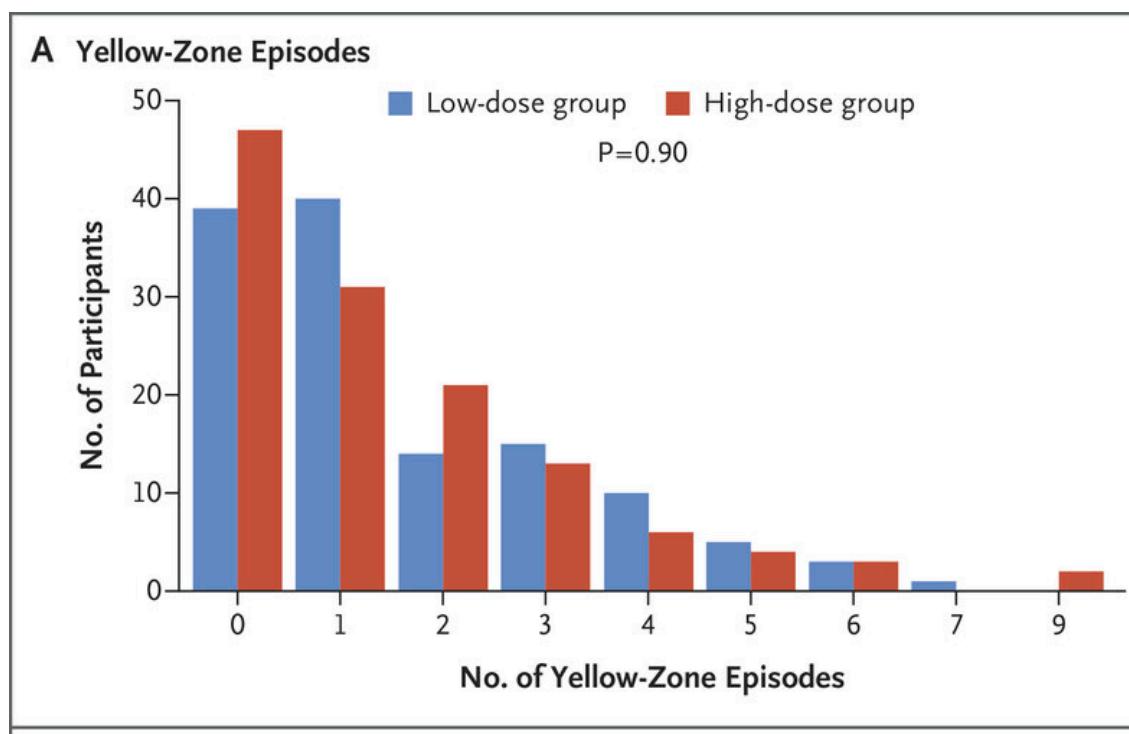


- Two inhalations:
 - 44 ug of Fluticasone 2x/day

- Two inhalations:
 - 44 ug Fluticasone 2x/day
 - During exacerbation (yellow zone), 220 ug of Fluticasone 2x/day

* N = 219

STICS Trial Findings



Outcomes	Low-Dose Group (N=127)	High-Dose Group (N=127)	Treatment Effect (95% CI) \dagger	P Value
Primary outcome				
No. of exacerbations per year (95% CI)	0.37 (0.25 to 0.55)	0.48 (0.33 to 0.70)	1.3 (0.8 to 2.1)	0.30

STICS Ancillary Methods

OUTCOMES

- Rate of severe asthma exacerbations treated with systemic glucocorticoids during the blinded treatment period
- Time to first exacerbation treated with systemic glucocorticoids
- Time to treatment failure

MEDIAN DICHOTOMIZED

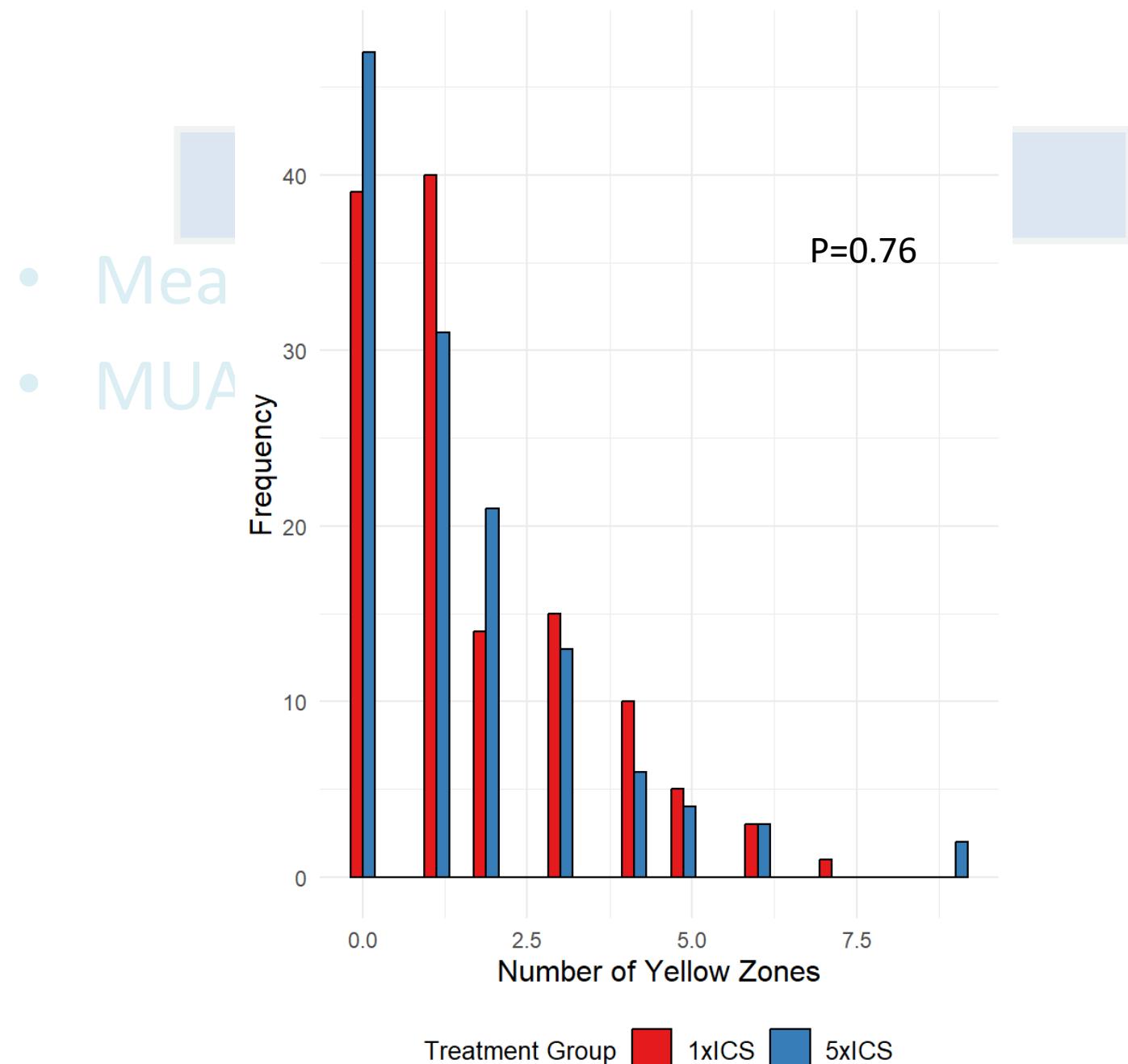
- Mean air pollutant exposure over the blinded treated period
- Poverty, race, weight, BMI, MUA & HPSA

MODELS

- Generalized linear model
 - log link function and response following a negative binomial distribution.
- Stratified Cox Proportional Hazards regression extension for time-to-event outcomes.

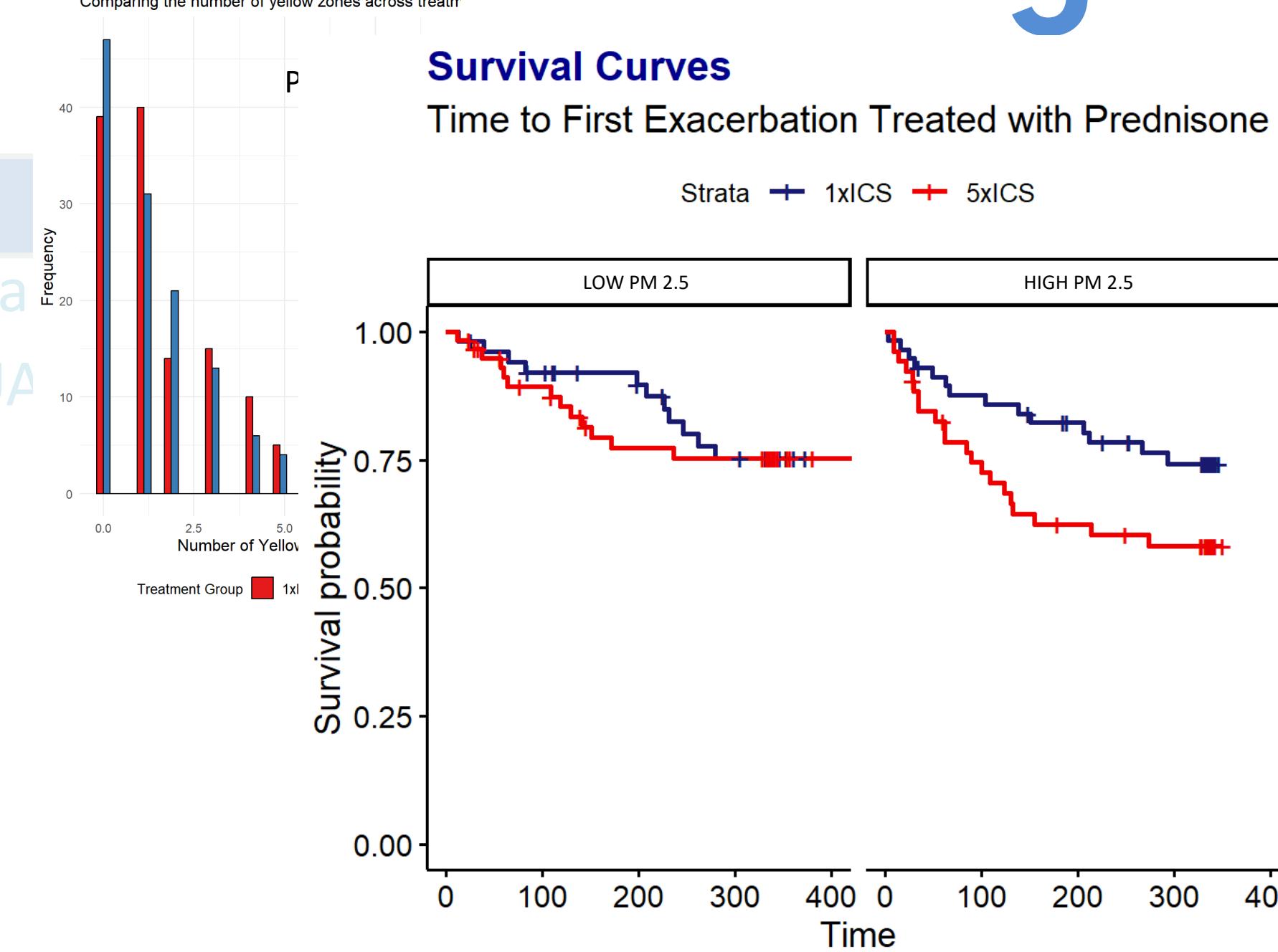
STICS Ancillary Findings

Distribution of Yellow Zones by Treatment
Comparing the number of yellow zones across treatment groups

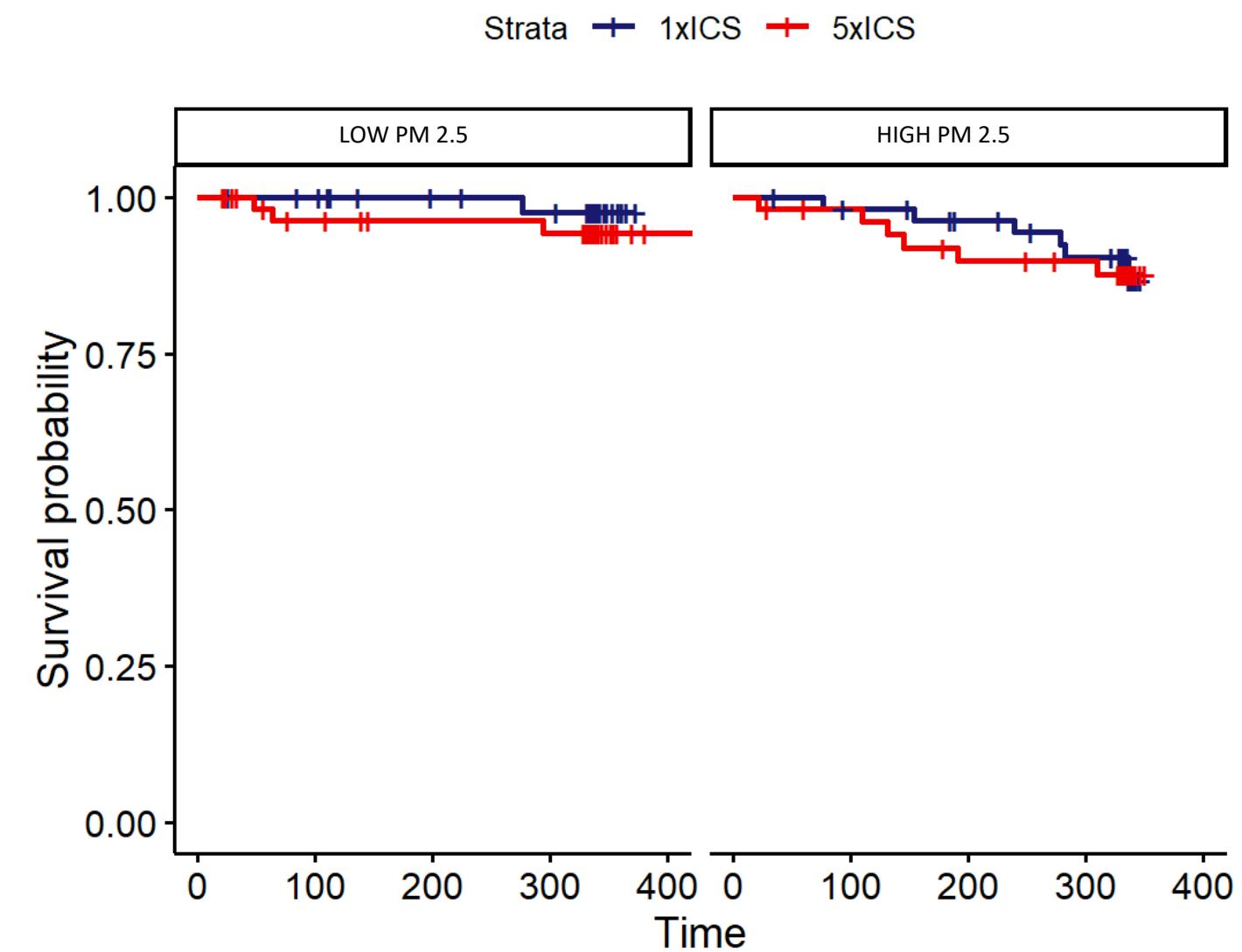


STICS Ancillary Findings: PM_{2.5}

Distribution of Yellow Zones by Treatment
Comparing the number of yellow zones across treatment groups



Survival Curves
Time to Treatment Failure

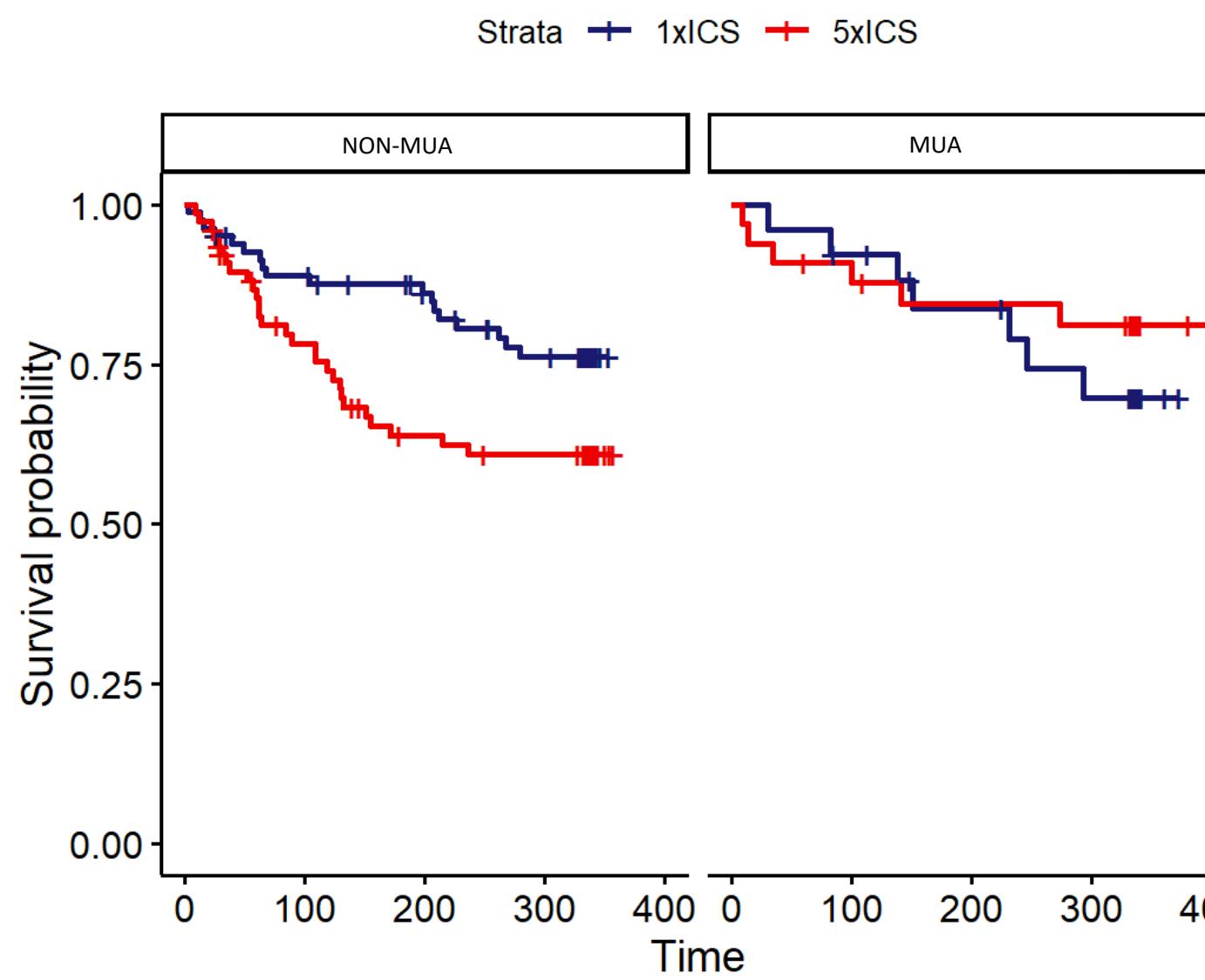


- Measured
- MUA

STICS Ancillary Findings: MUA

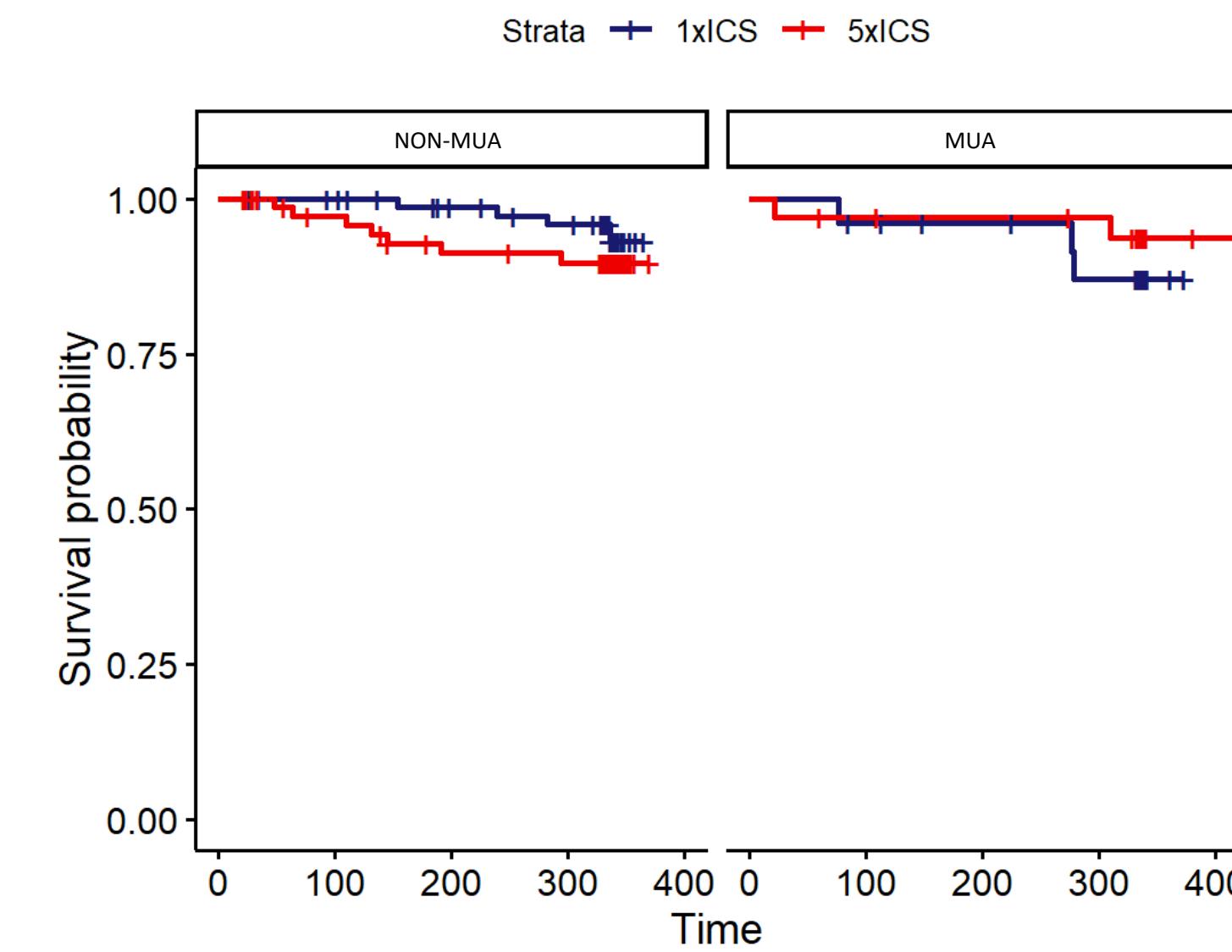
Survival Curves

Time to First Exacerbation Treated with Prednisone



Survival Curves

Time to Treatment Failure

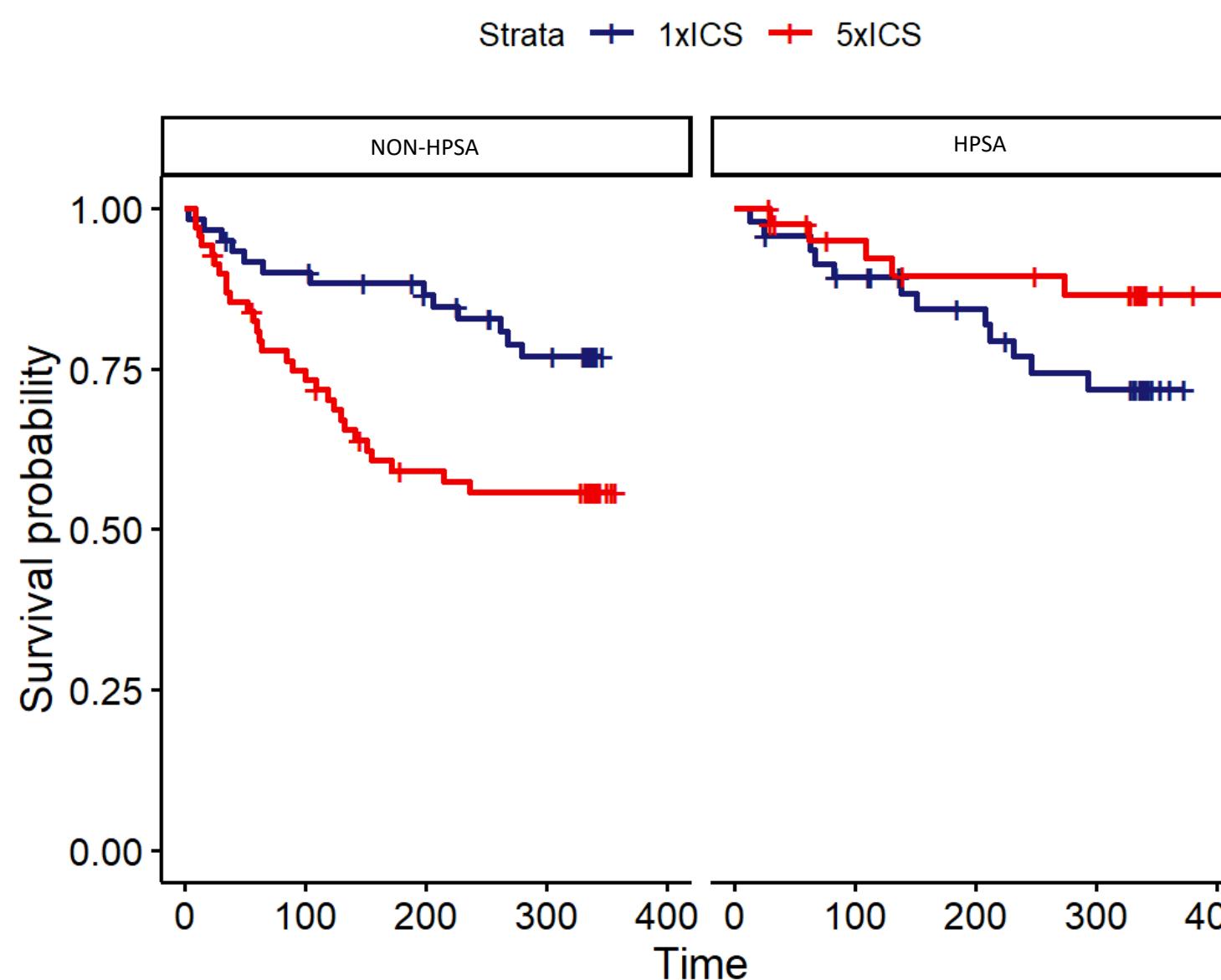


Models adjusted for sex, race, age, pets, percent below poverty level

STICS Ancillary Findings: HPSA

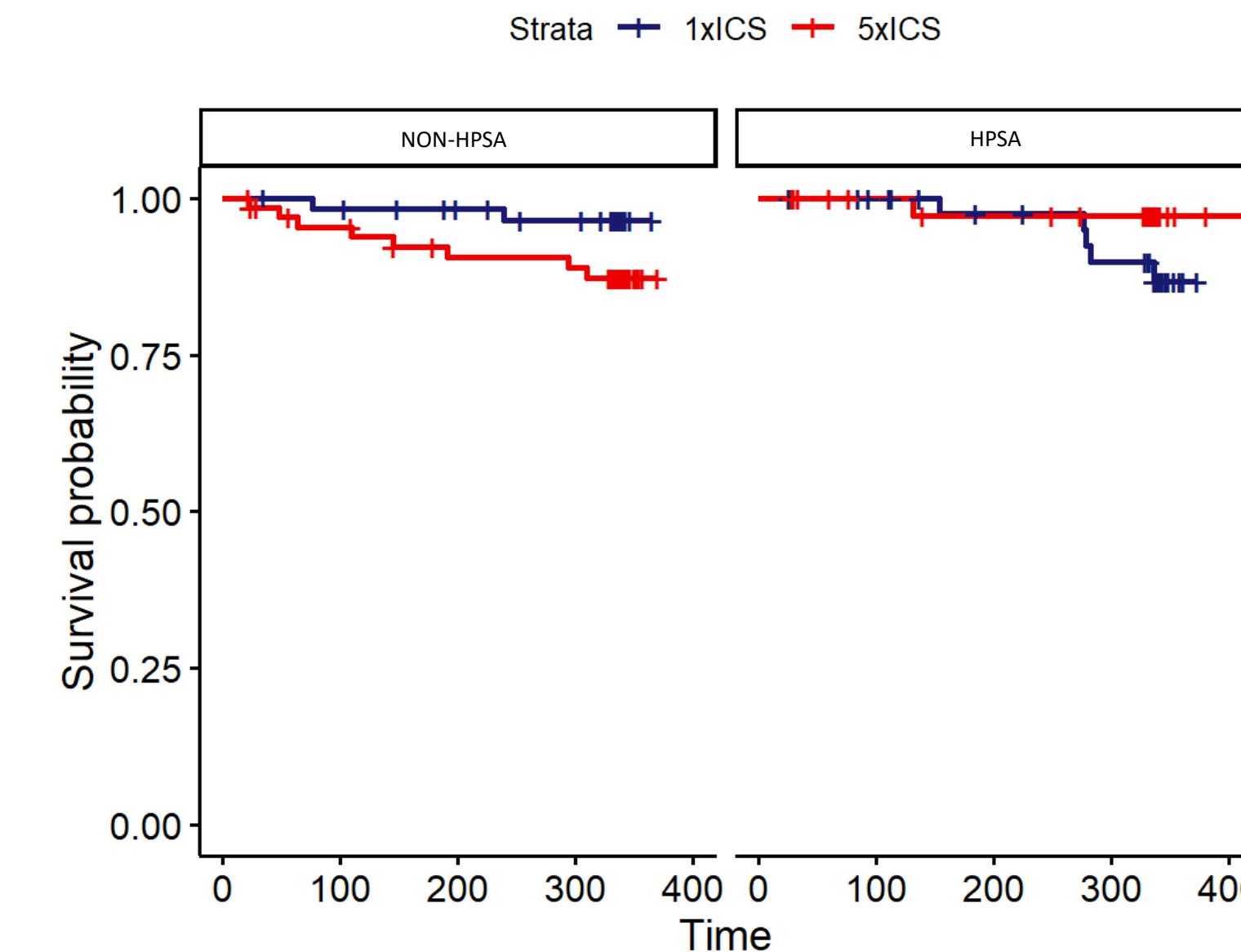
Survival Curves

Time to First Exacerbation Treated with Prednisone



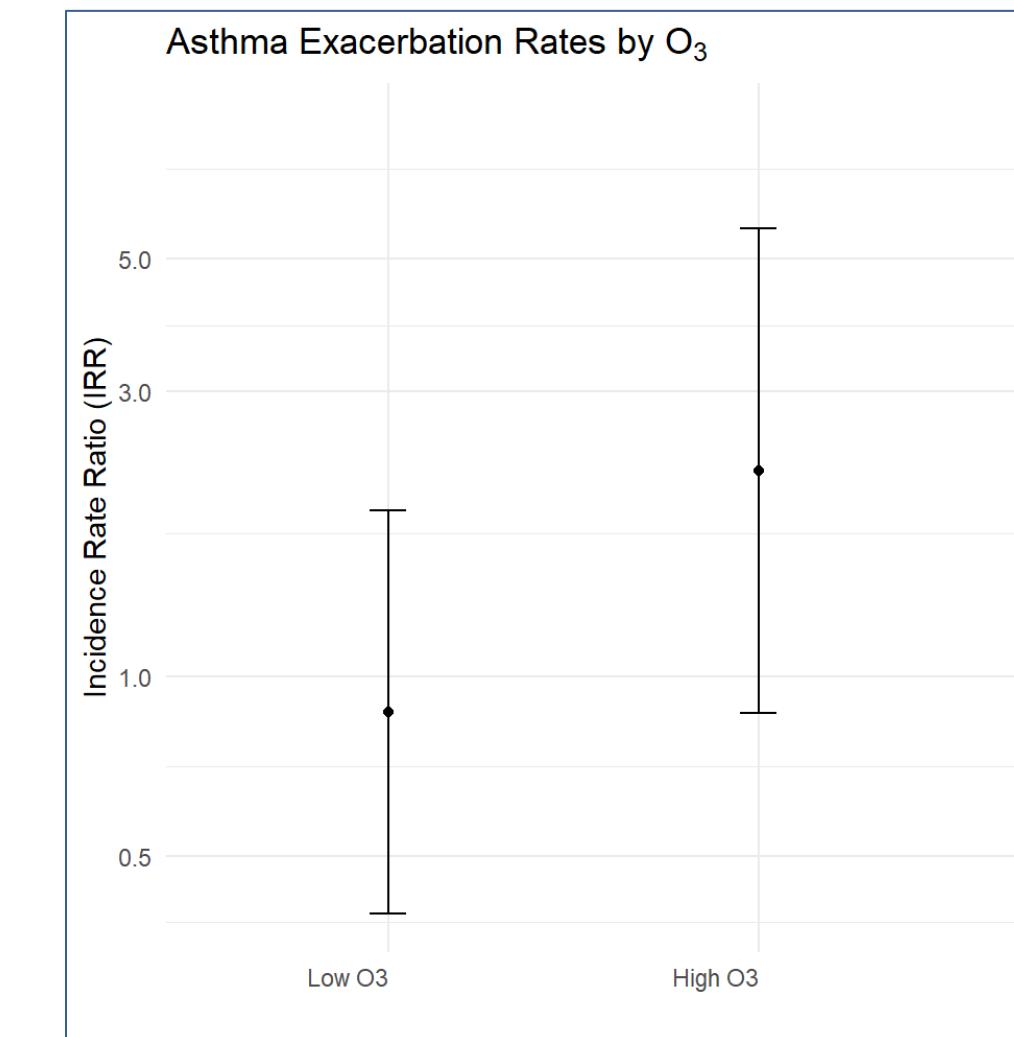
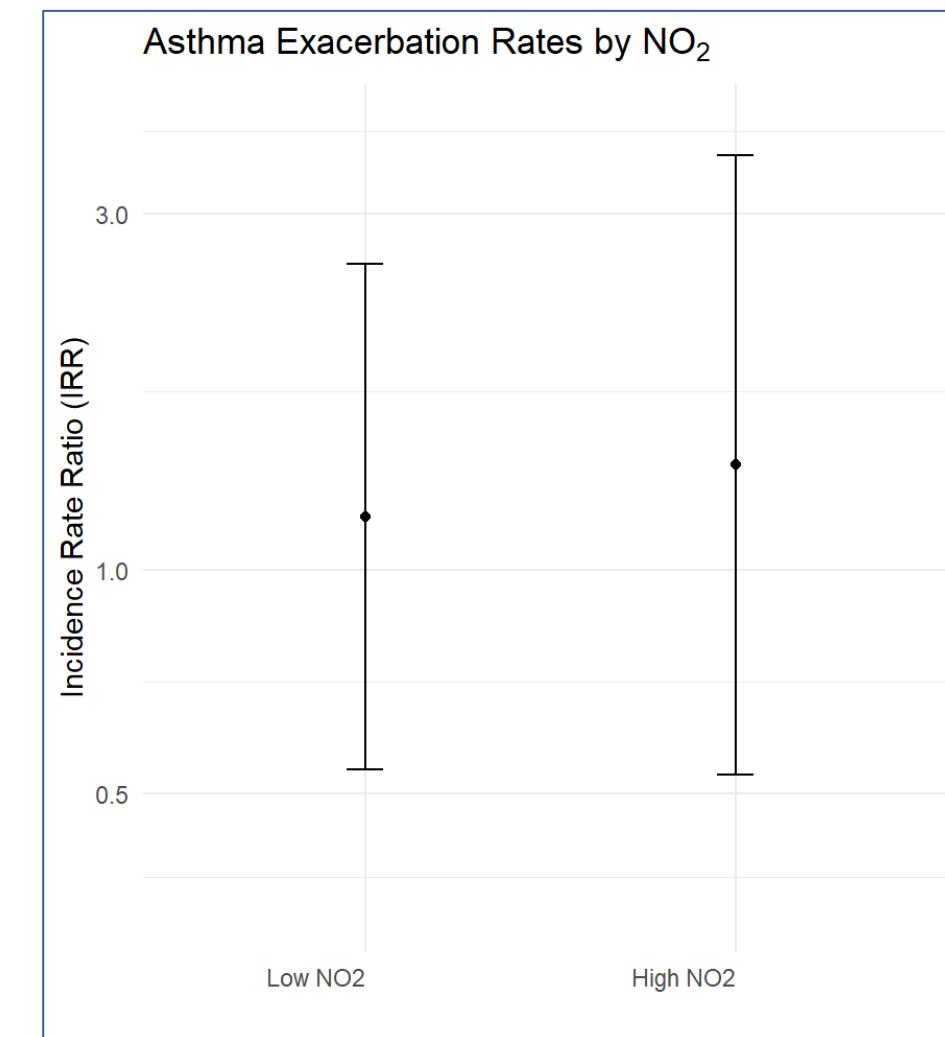
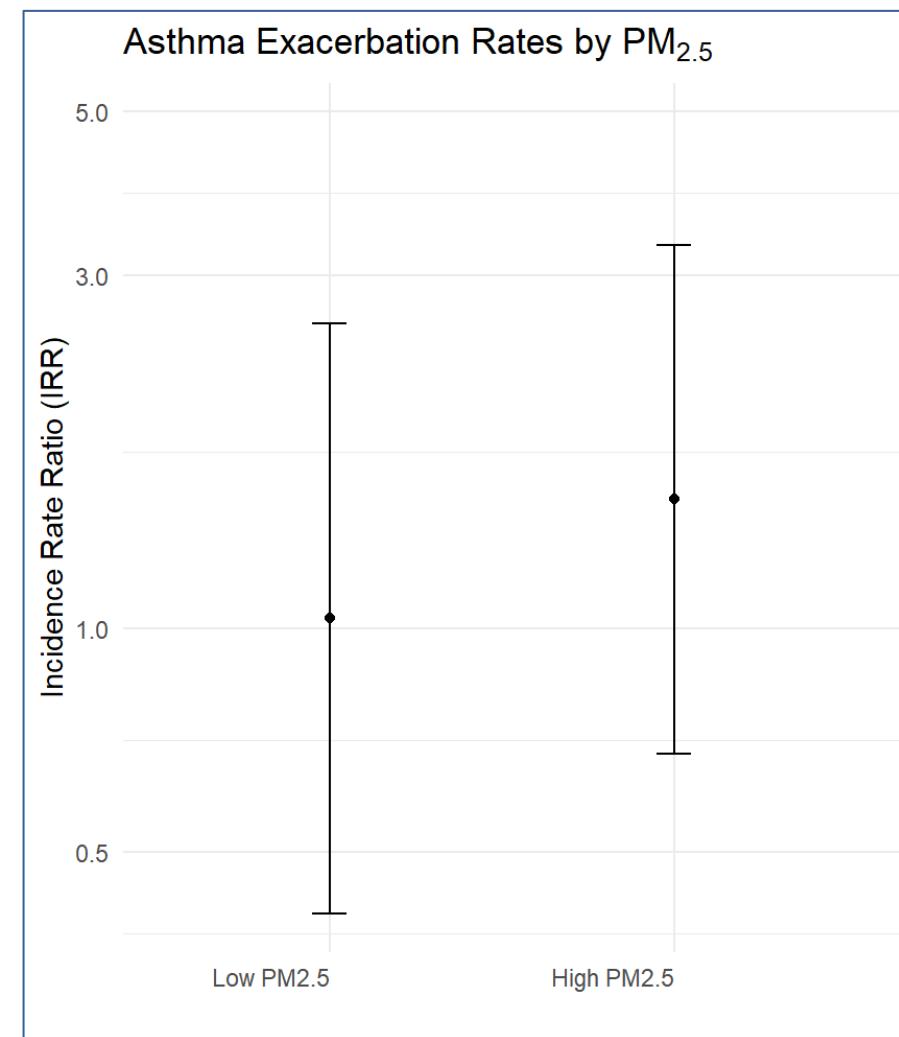
Survival Curves

Time to Treatment Failure



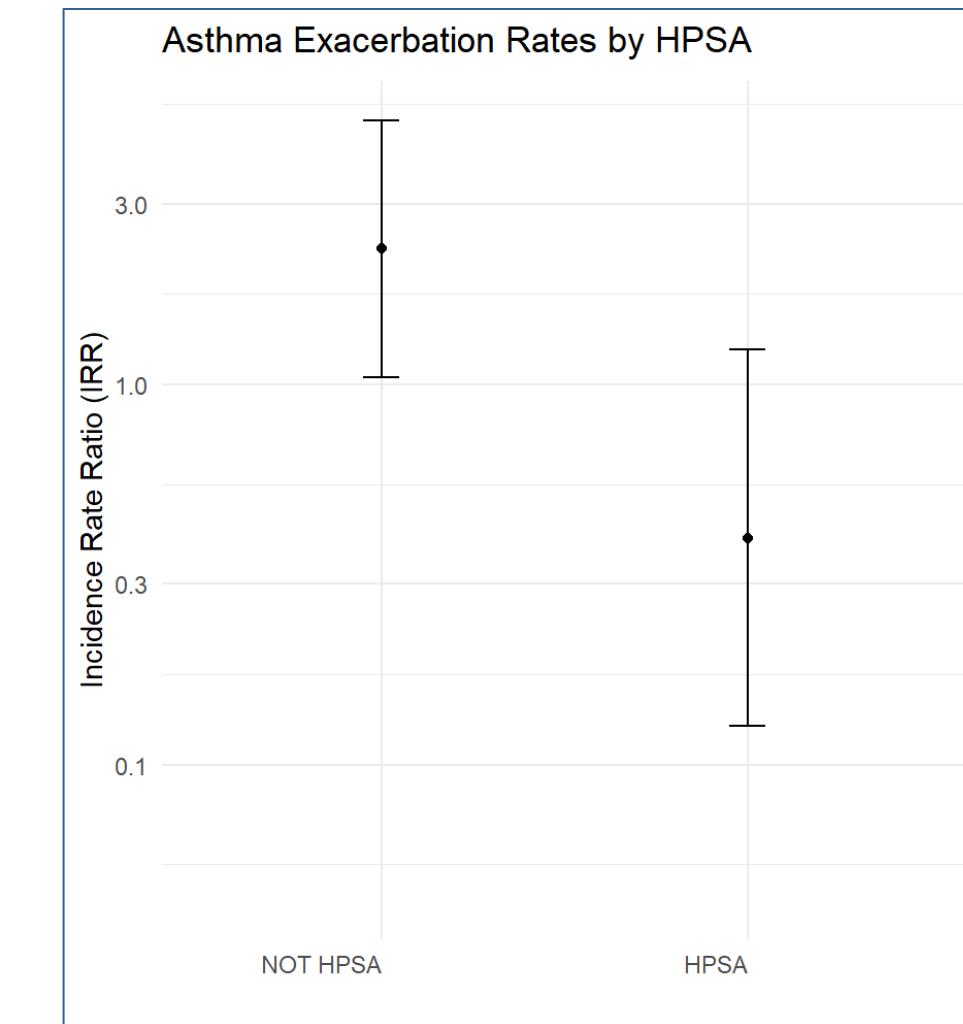
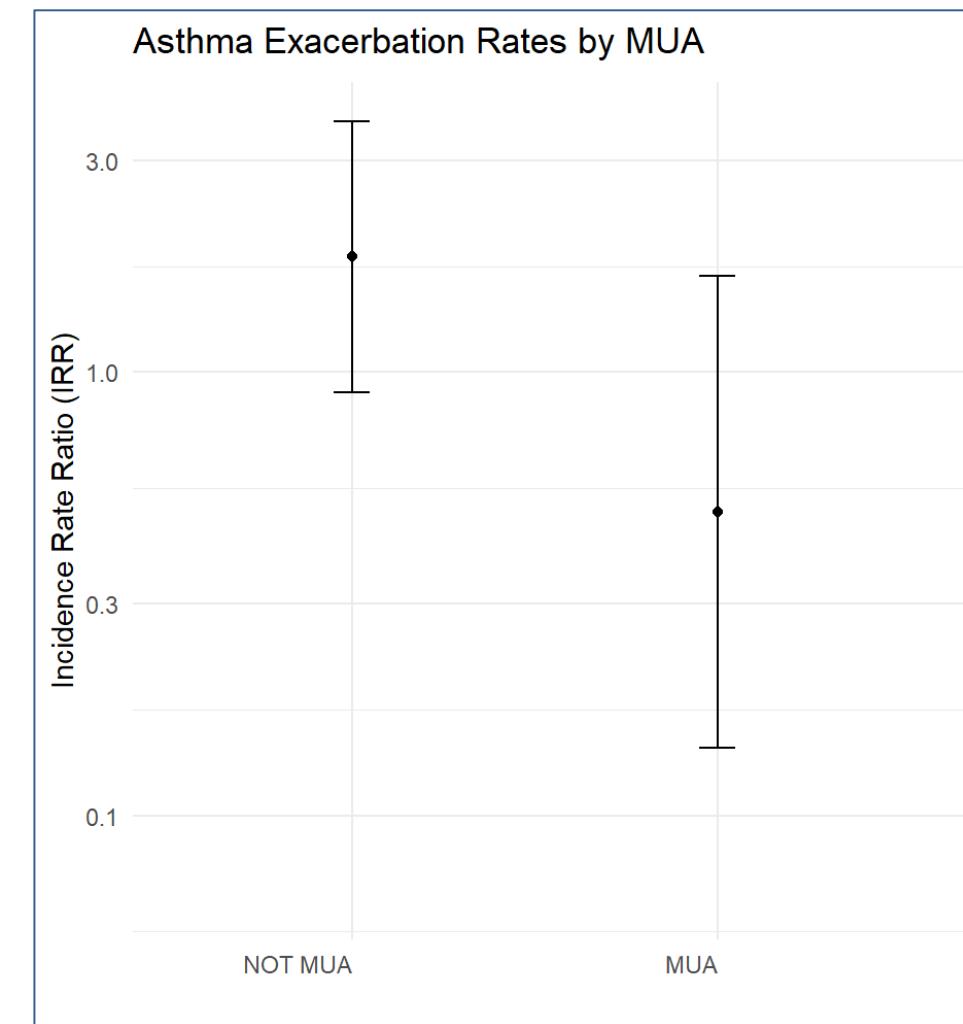
Models adjusted for sex, race, age, pets, percent below poverty level

STICS Ancillary Findings



Models adjusted for sex, race, age, pets, percent below poverty level

STICS Ancillary Findings



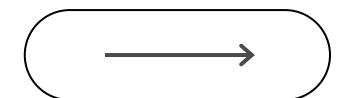
Models adjusted for sex, race, age, pets, percent below poverty level

STICS Ancillary Findings

- We saw no effect modification by any air pollutants on interest on either asthma exacerbation rate or time to first exacerbation, or time to treatment failure.
- Receiving the increased dose of ICS dose, compared to the low dose, conferred an increased asthma exacerbation rate among children living in non-medically underserved areas and non-health provider shortage areas

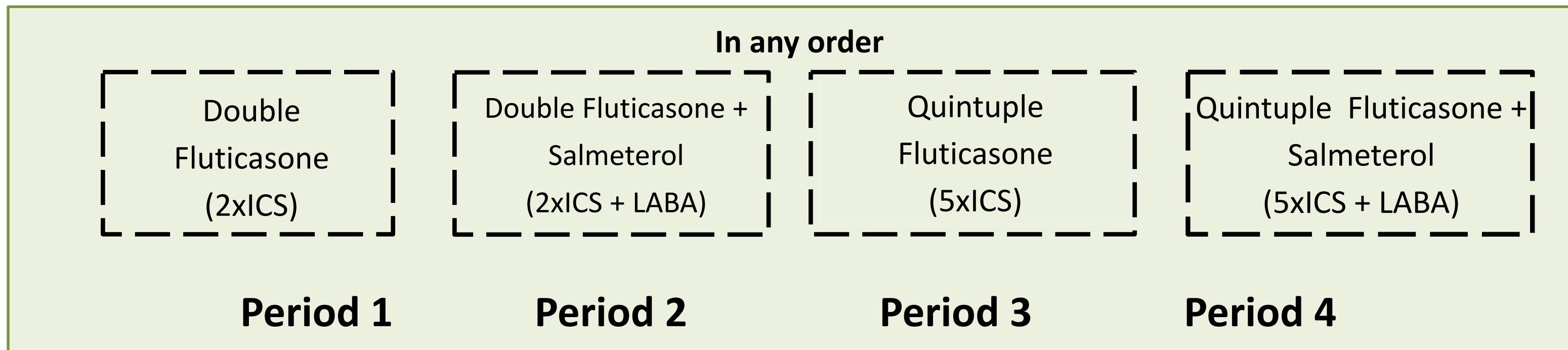
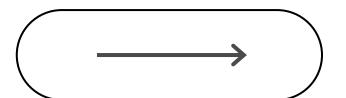
AIM 2

Modification of the association between ICS + LABA Step-up
and Asthma by Air Pollution in Trial Participants with Poorly
Controlled Asthma



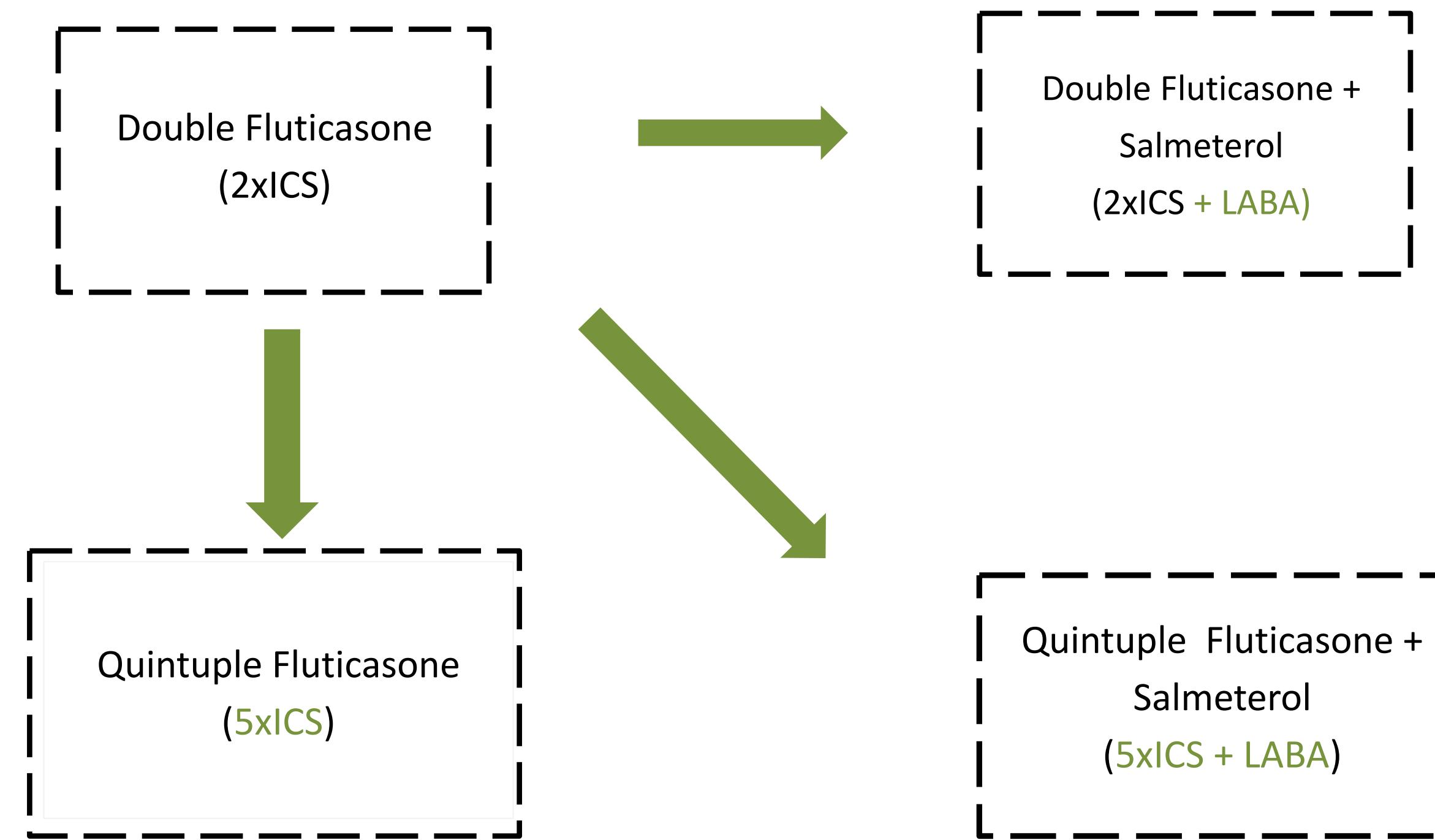
BARD Trial

Adults and Children were sequentially randomized treatment with:



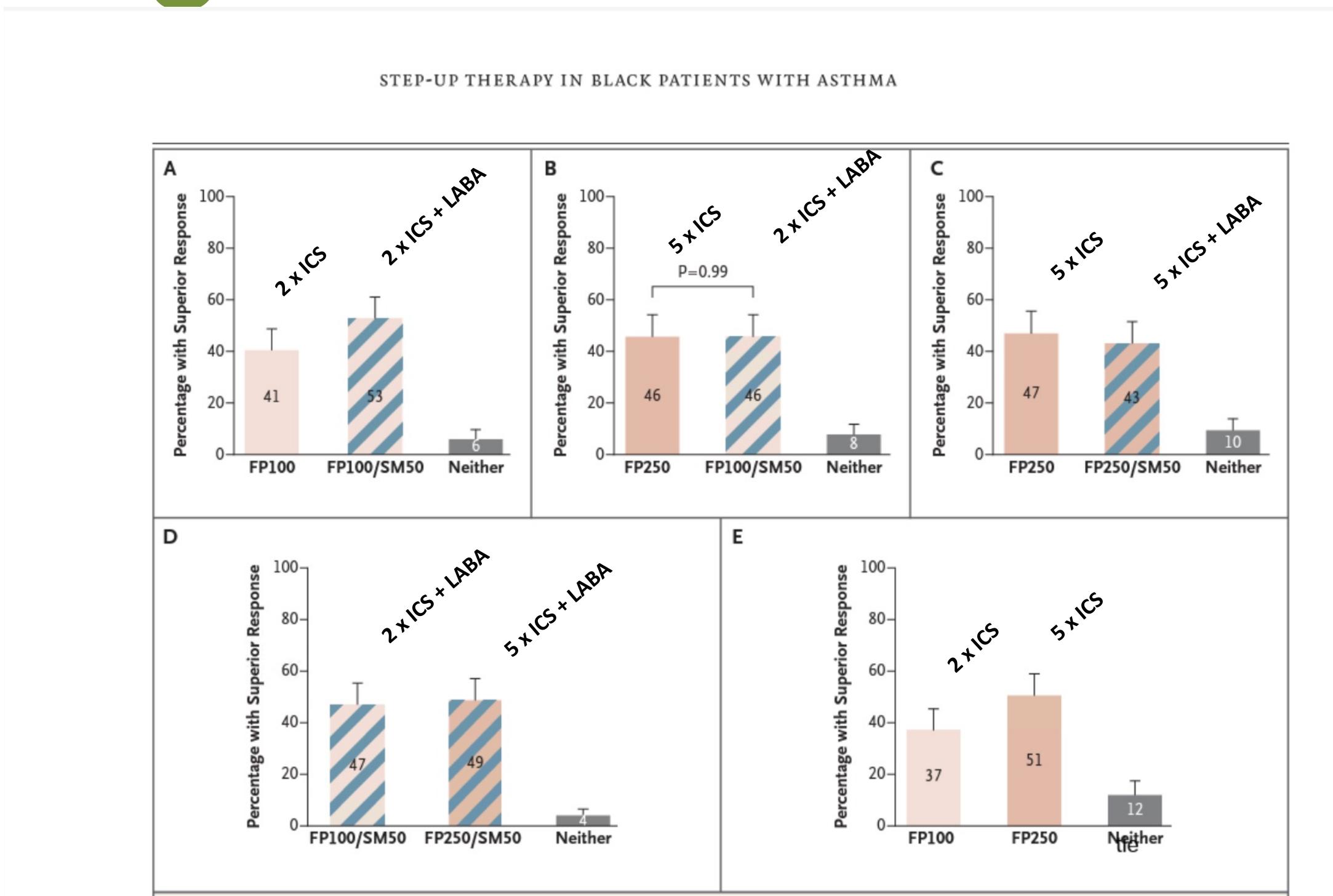
BARD RCT design. Each treatment period lasted 14 weeks (the initial two weeks of each period were considered washout periods).

BARD Trial



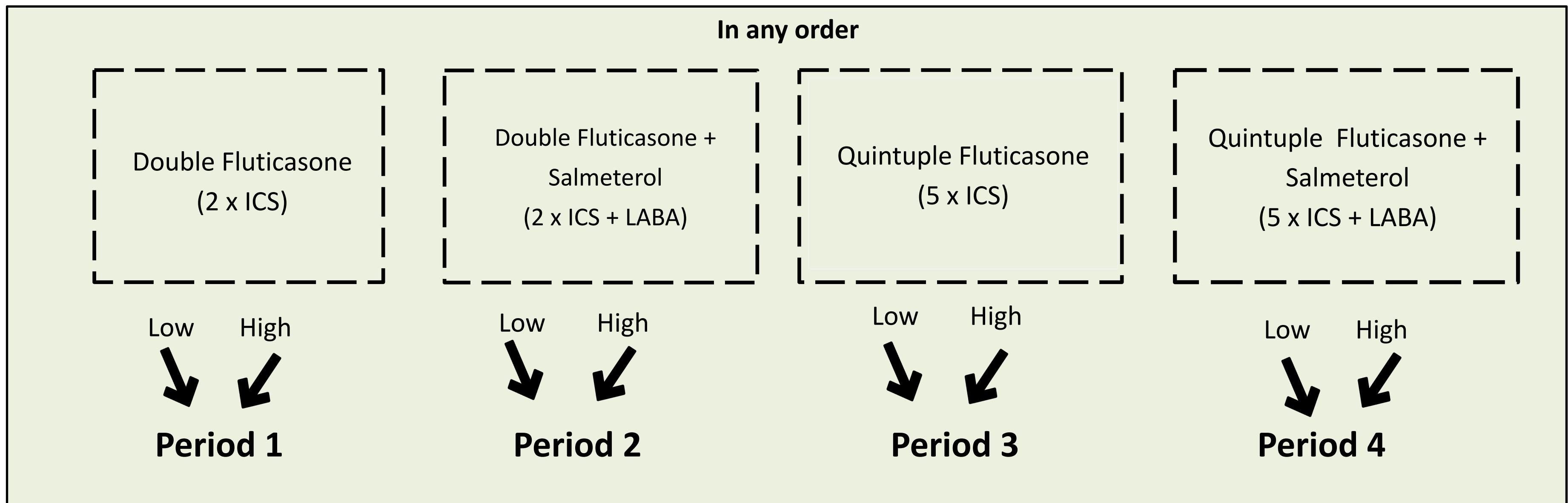
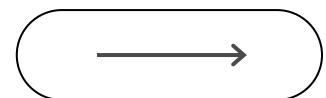
BARD RCT design. Each treatment period lasted 14 weeks (the initial two weeks of each period were considered washout periods).

Original BARD Trial Findings



BARD RCT design. Each treatment period lasted 14 weeks (the initial two weeks of each period were considered washout periods).

Our Approach



BARD Trial Reanalysis

Children }
 Adults

Composite score:
 %PFEV1
 Asthma Control Days
 Asthma Exacerbations

Generalized Mixed Models with Random Intercept

$$\begin{aligned}
 E[Y_{ij}] = & \beta_0 + \beta_1 treatment_{ij} \\
 + \beta_2 air pollutant_{ij} + & \beta_3 treatment_{ij} * Air pollutant_{ij} \\
 + \beta_4 PreRandCovs_i + & b_{0i}
 \end{aligned}$$

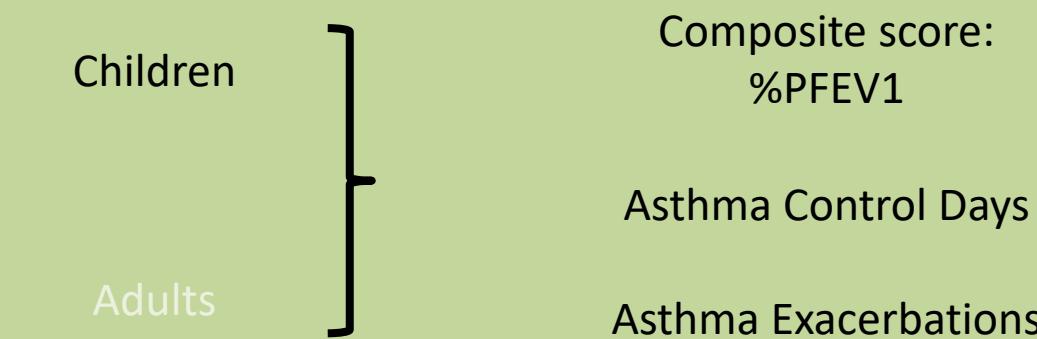
Median Dichotomized Air Pollution Exposure

Treatment Period Specific

- PM_{2.5}
- NO₂
- O₃

BARD Trial Reanalysis

JUST CHILDREN

Mixed Effect Models with Random Intercept

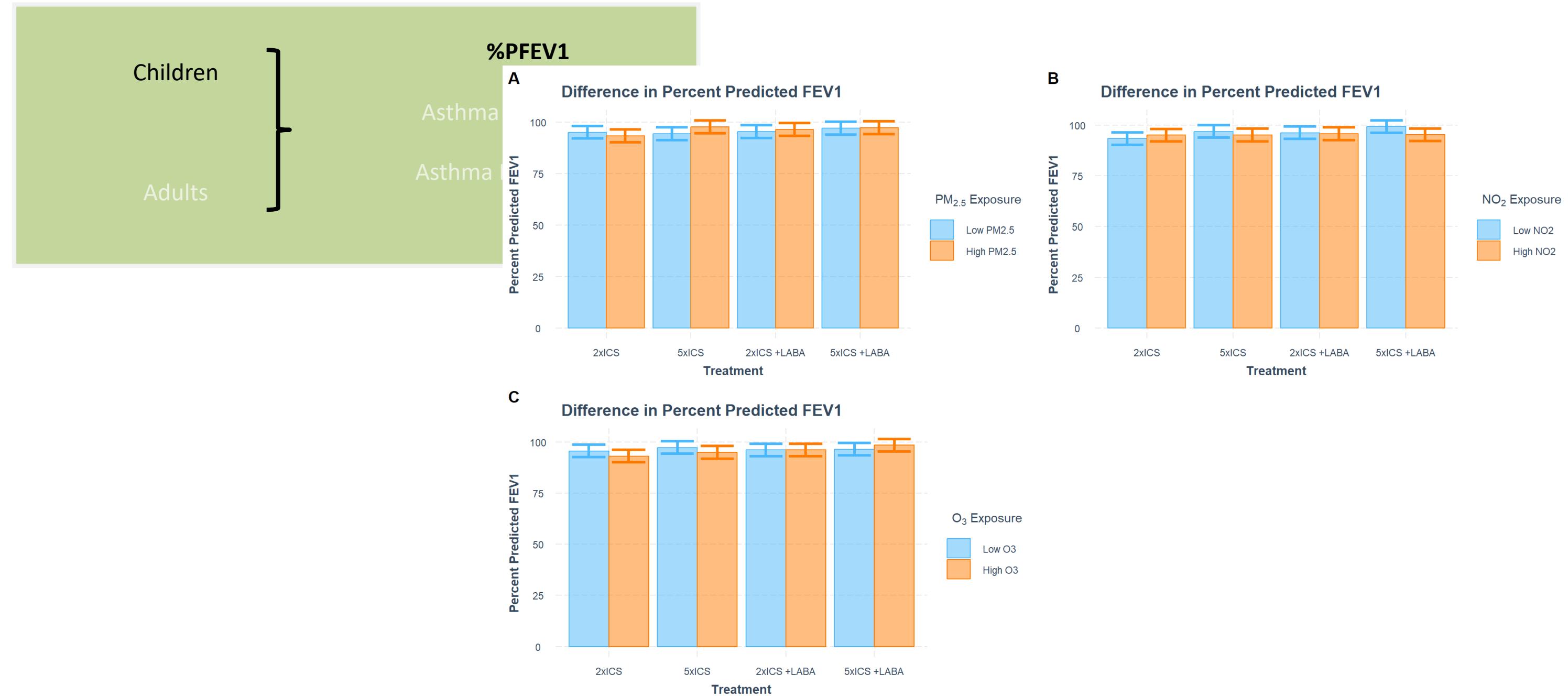
$$E[Y_{ij}] = \beta_0 + \beta_1 treatment_{ij} + \beta_2 Air\ Pollutant_{ij} + \\ \beta_4 treatment_{ij} * Air\ pollutant_{ij} + \beta_5 PreRandCovS_i + \\ b_{0i}$$

Table 1: Analytic Sample Characteristics at Baseline

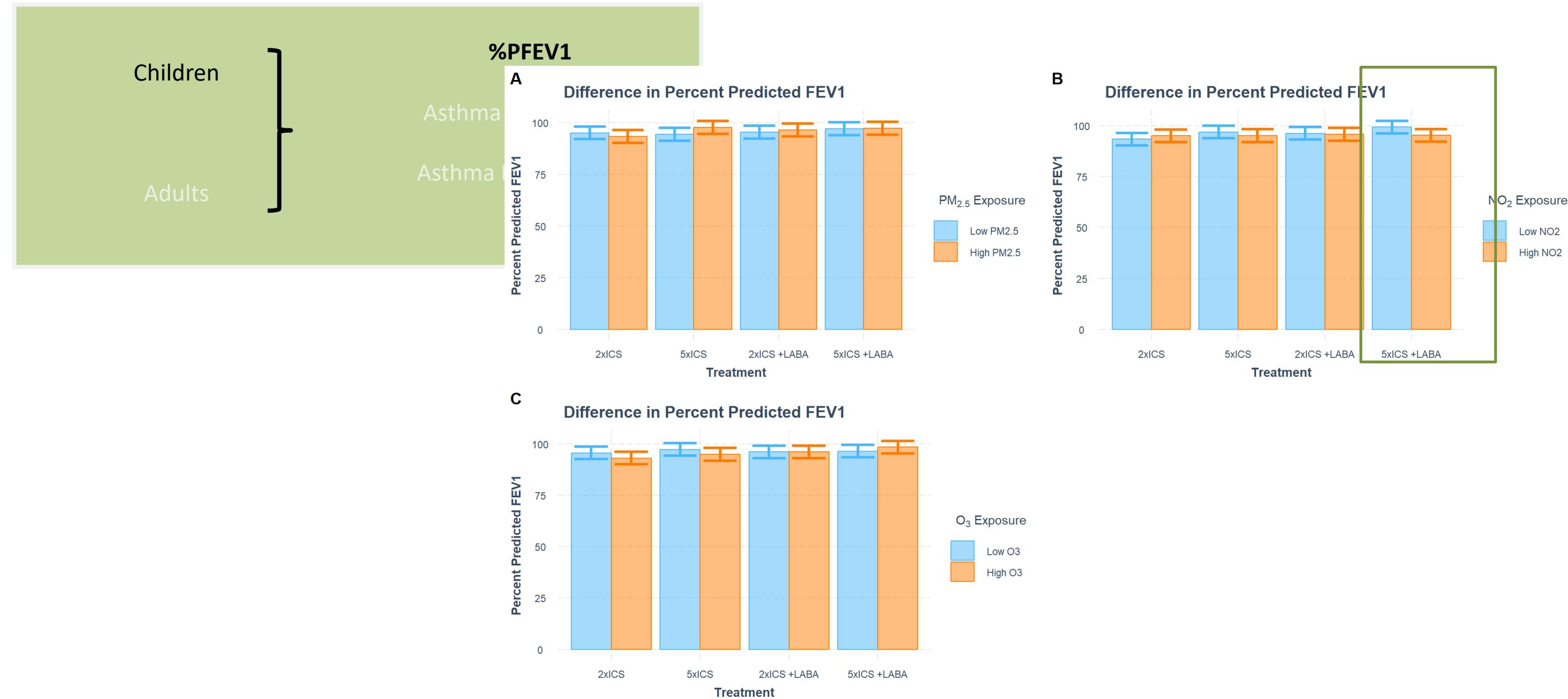
Characteristic	F, N = 91 N N = 91 ¹	M, N = 133 N N = 133 ¹
Age Enrollment	91 8.77 (6.97, 10.28)	133 8.30 (7.06, 9.75)
Ethnic Background	91	133
Hispanic or Latino	6 (6.6%)	14 (11%)
Not Hispanic or Latino	85 (93%)	119 (89%)
FEV:FVC	91 0.82 (0.77, 0.87)	133 0.82 (0.75, 0.86)
% Below Fed Poverty Line	91 24 (15, 33)	133 21 (12, 29)
cCAT Score	91 22 (20, 24)	132 22 (19, 24)
Race	91	133
Black or African American	86 (95%)	124 (93%)
Other	5 (5.5%)	8 (6.0%)
American Indian or Alask*		1 (0.8%)

¹ n (%), F= female, M= male.

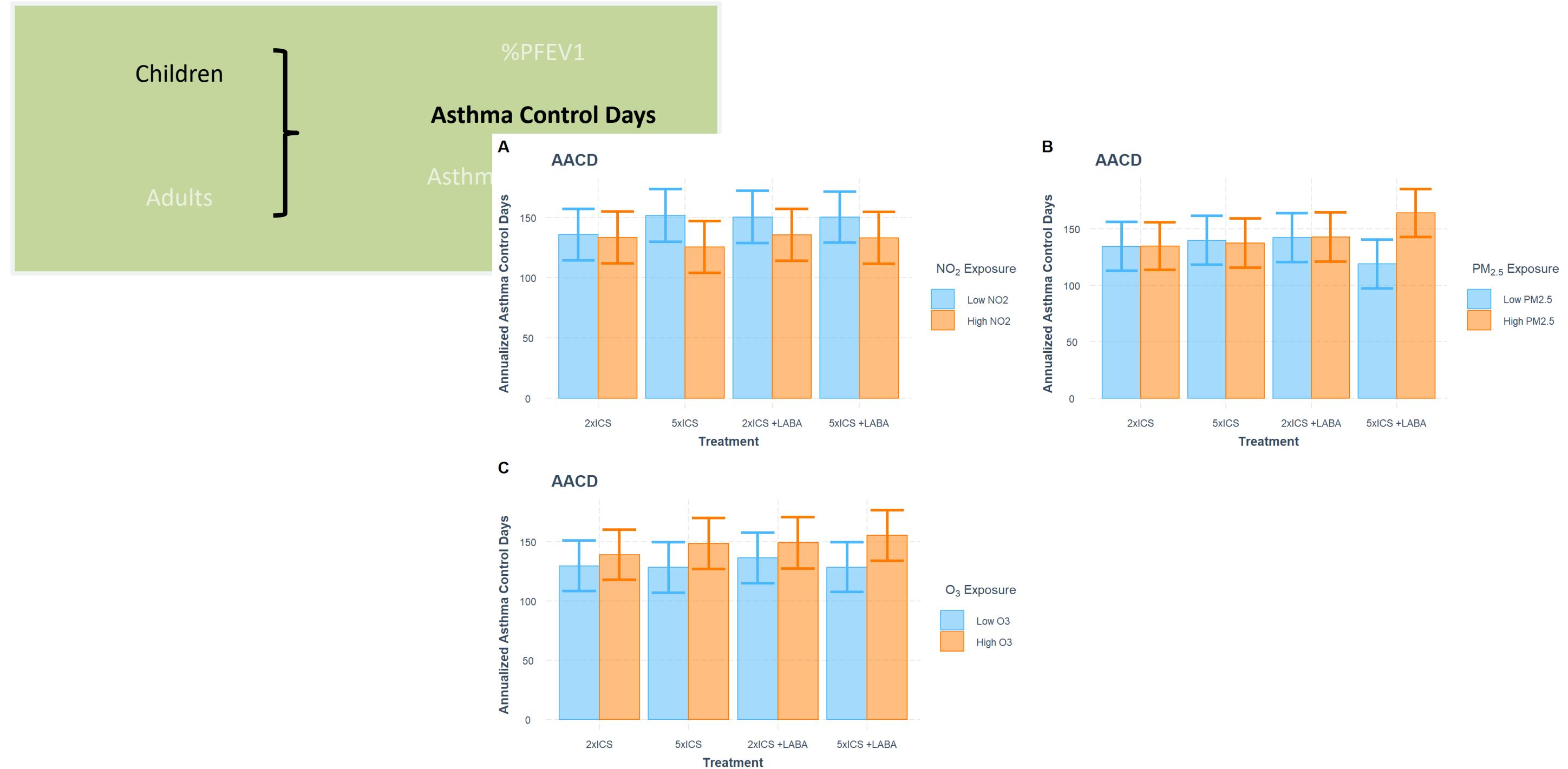
BARD Trial Results



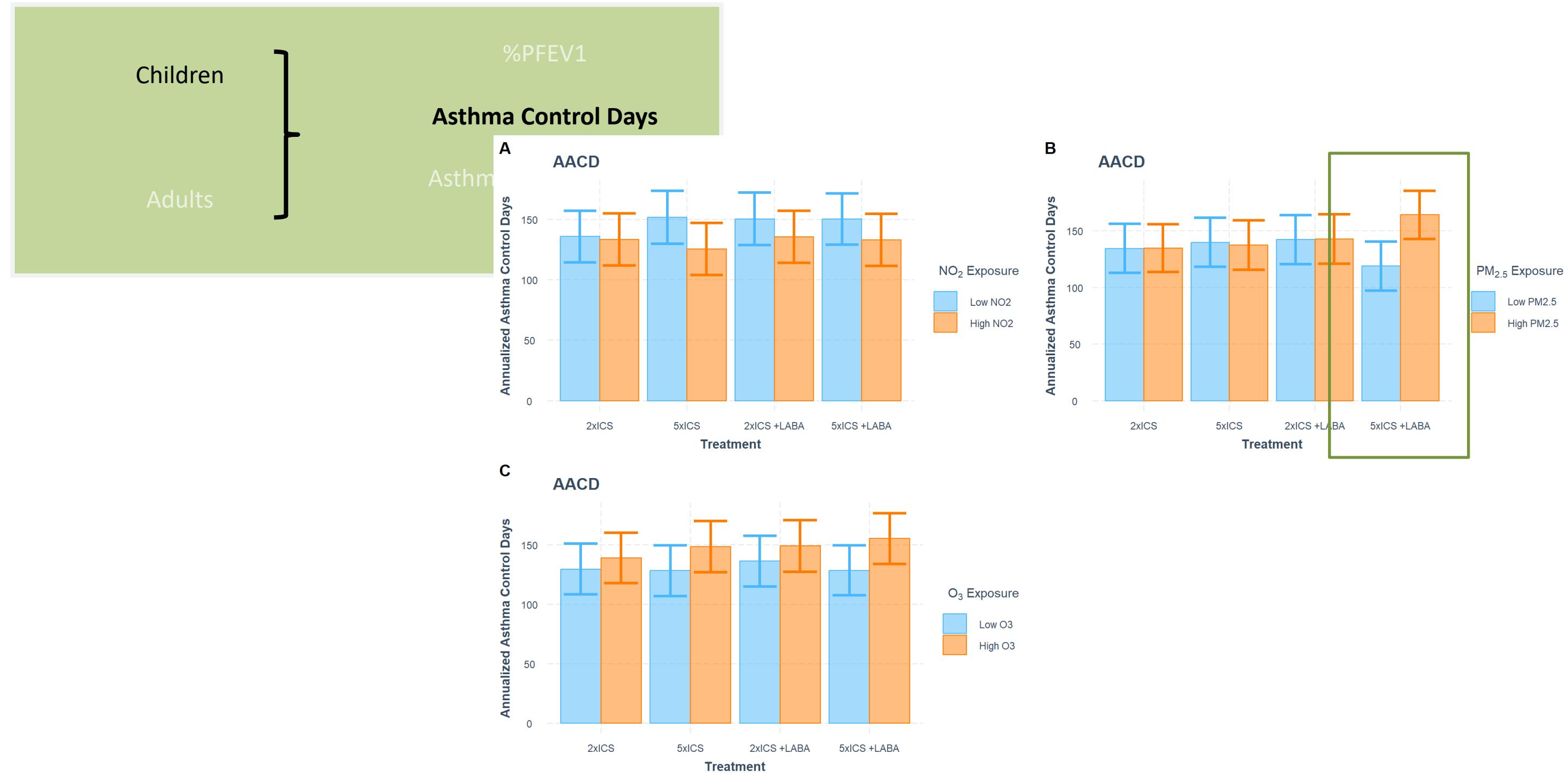
BARD Trial Results



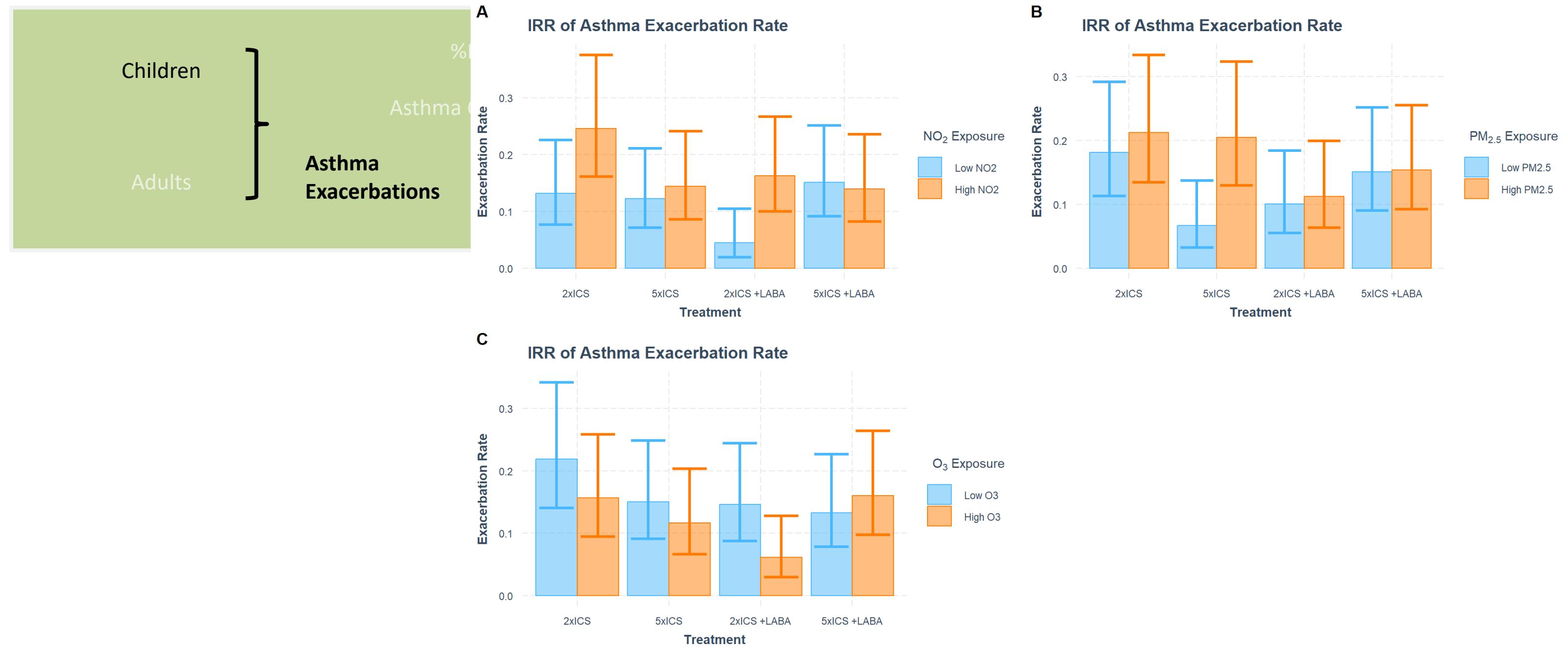
BARD Trial Results



BARD Trial Results



BARD Trial Reanalysis

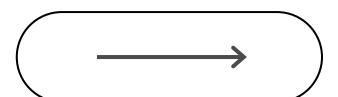


BARD Ancillary Findings

- **Effect Modification:** Treatment efficacy varied based on air pollution levels.
- **Treatment Observations:** 5xICS+LABA improved asthma control and lung function mainly in areas with lower PM_{2.5} levels.
- **Impact of Air Pollution:** High PM_{2.5} may contribute to reduced treatment responsiveness.

AIM 3

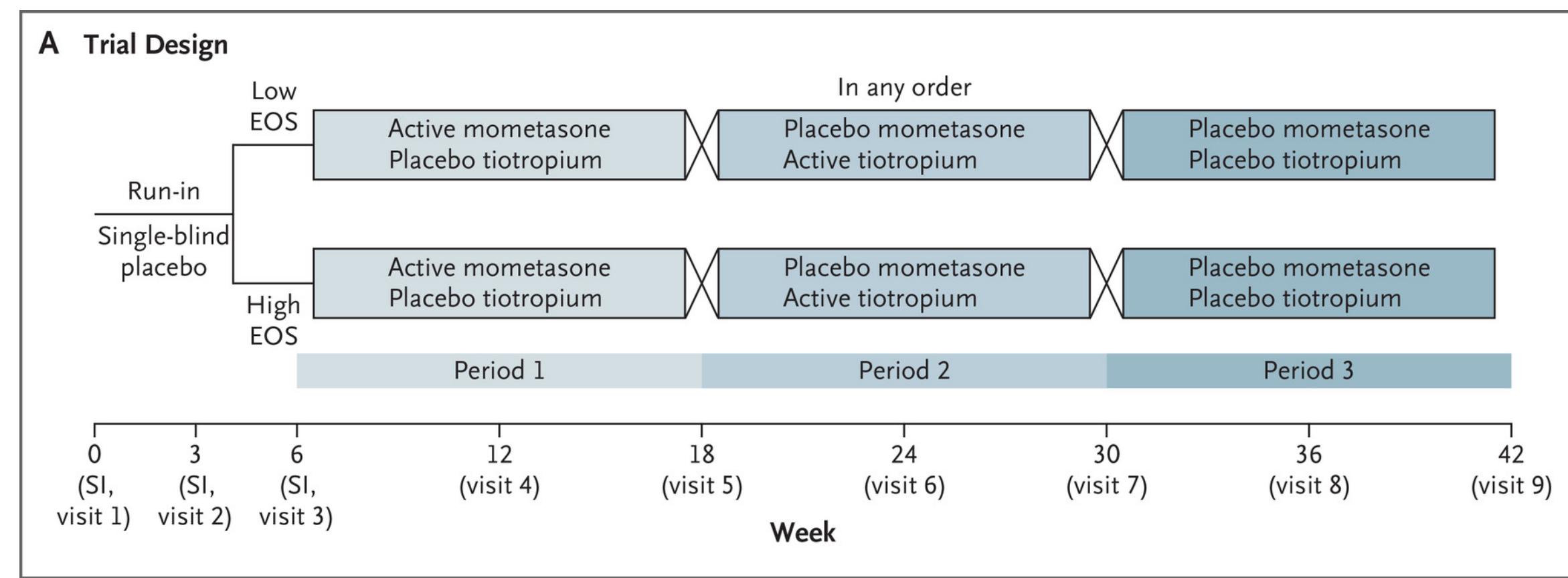
Effects of Air Pollution on Asthma by Asthma
Phenotype and Treatment



SIENA Trial

Evaluated the response to monotherapy:

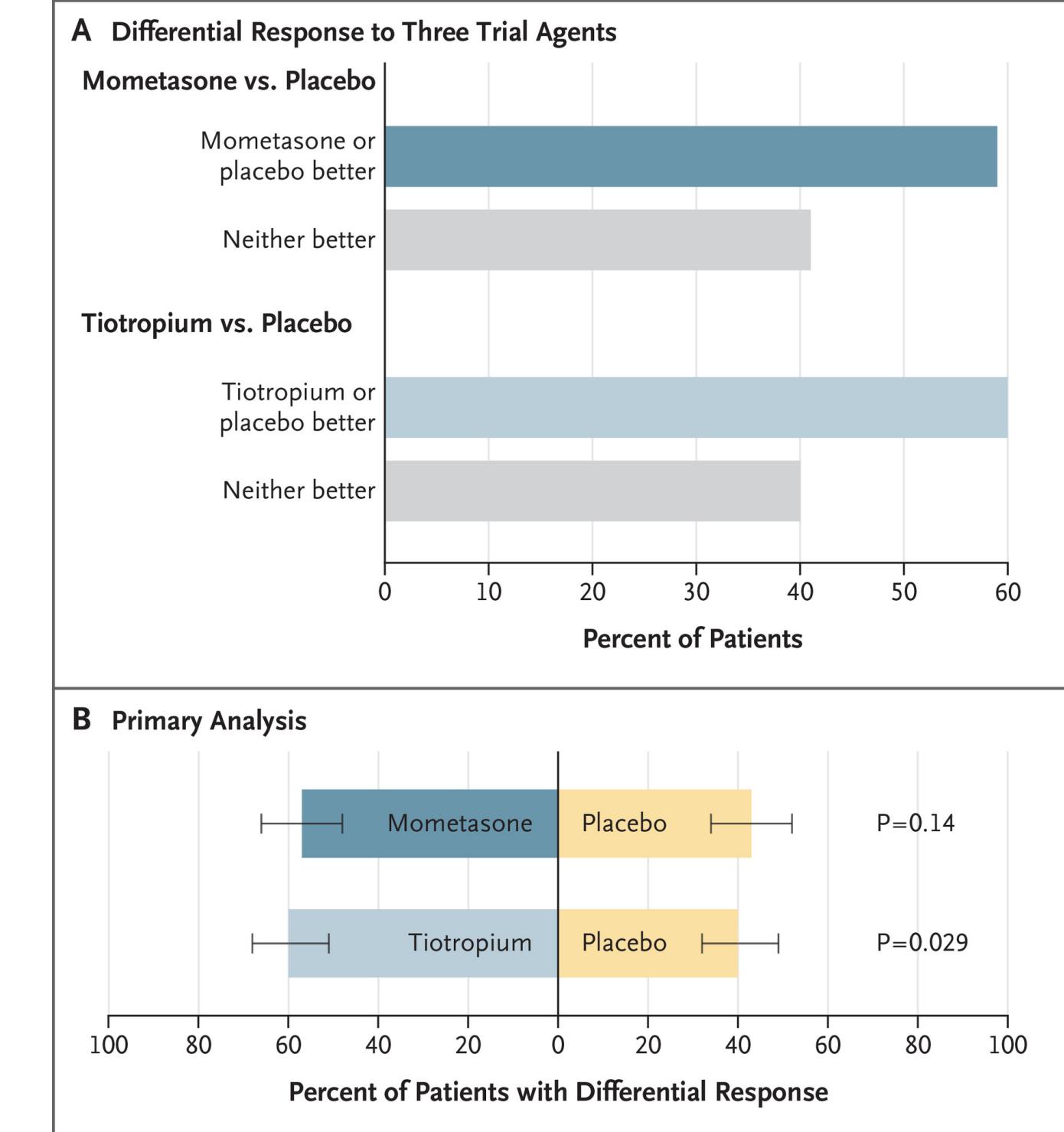
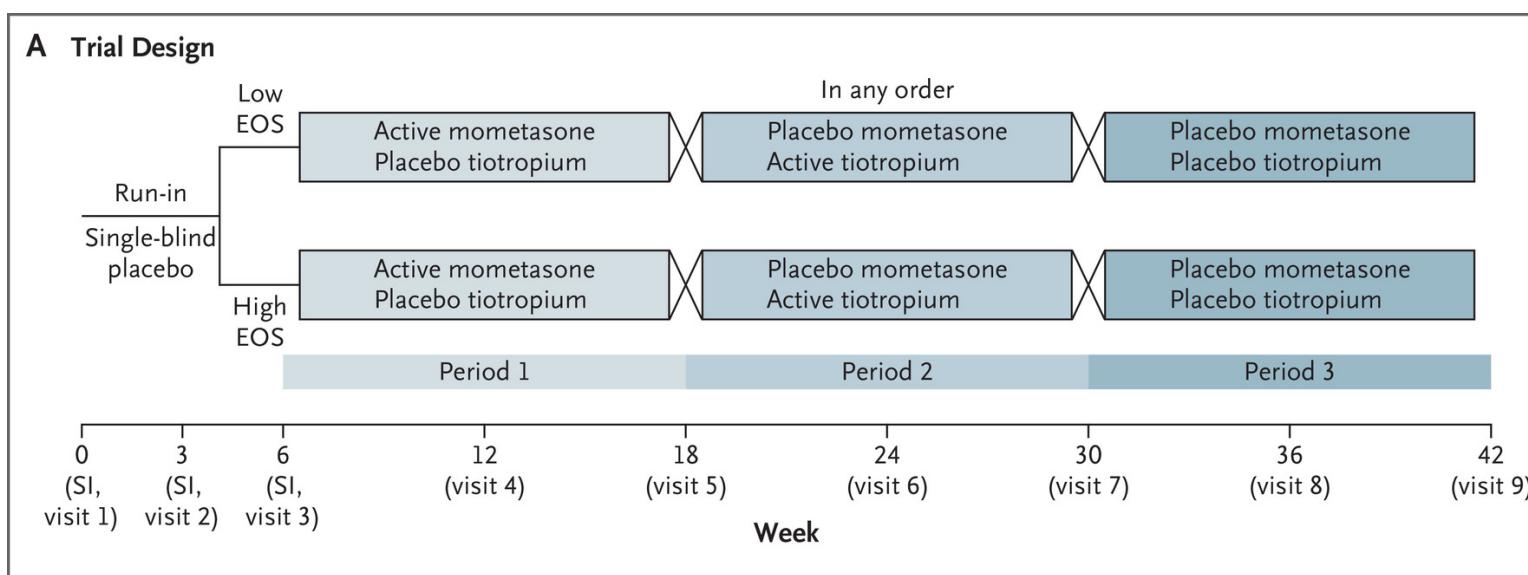
- LAMA vs Placebo
- ICS vs Placebo



SIENA Trial

Evaluated the response to monotherapy:

- LAMA vs Placebo
- ICS vs Placebo
- N = 224

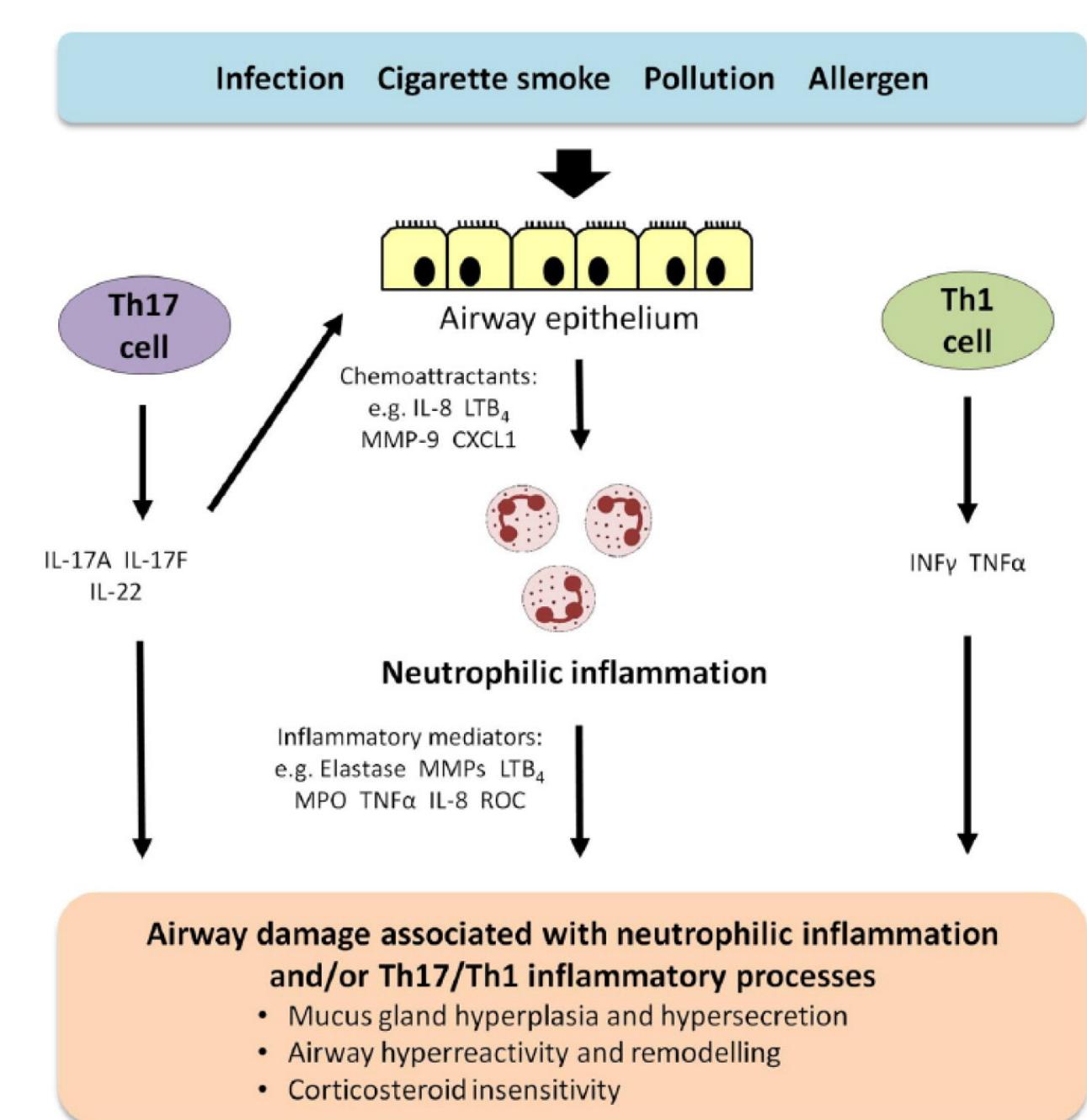


A note on asthma phenotypes and endotypes

Phenotypes: Observable characteristics of the disease based on clinical features, triggers, and response to treatment

Endotypes: Specific pathophysiological mechanisms that drive the observable characteristics of different phenotypes.

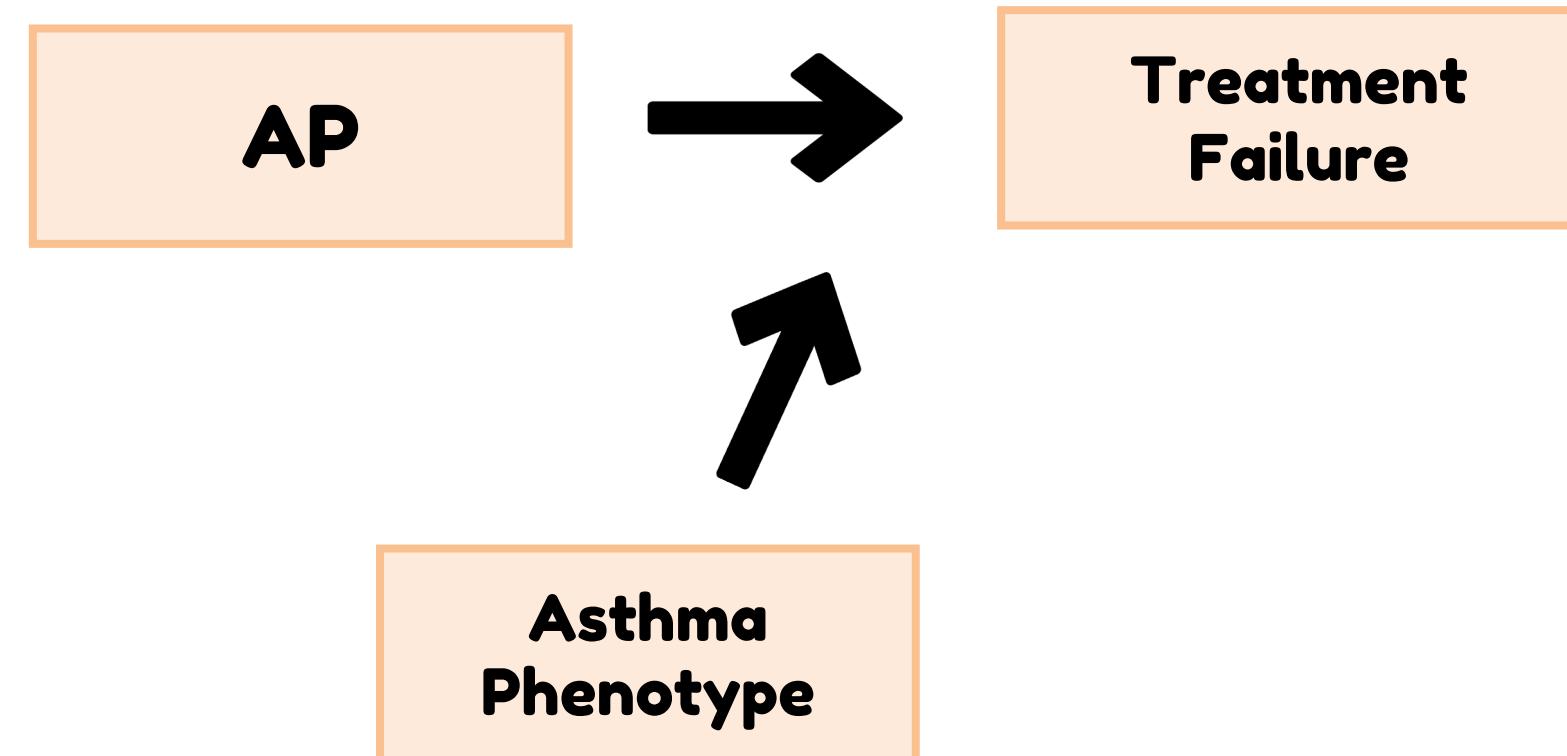
AIM 3



doi:10.1177/1753465816632638

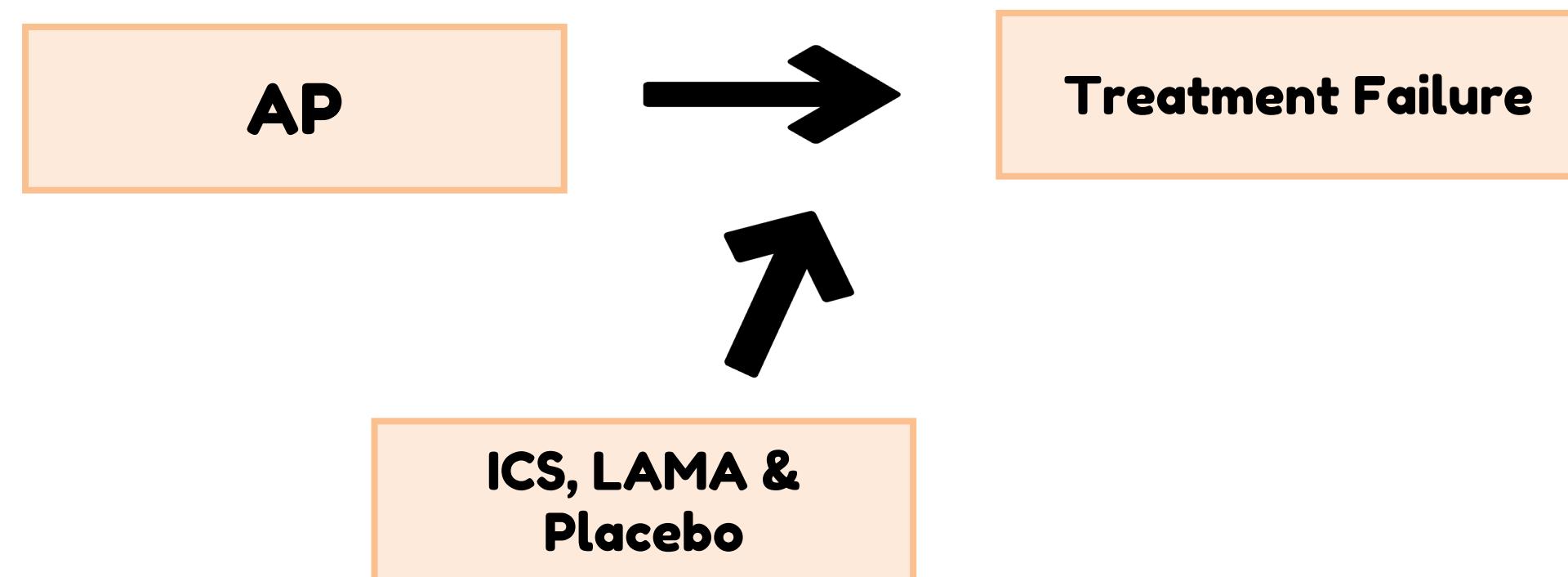
Questions

What is the effect of exposure to air pollution exposure on Asthma Treatment Failure BETWEEN eosinophilic and non-eosinophilic participants?



Questions

What is the effect of exposure to air pollution exposure on Asthma Treatment Failure as modified by treatment with ICS and LAMA compared to placebo?



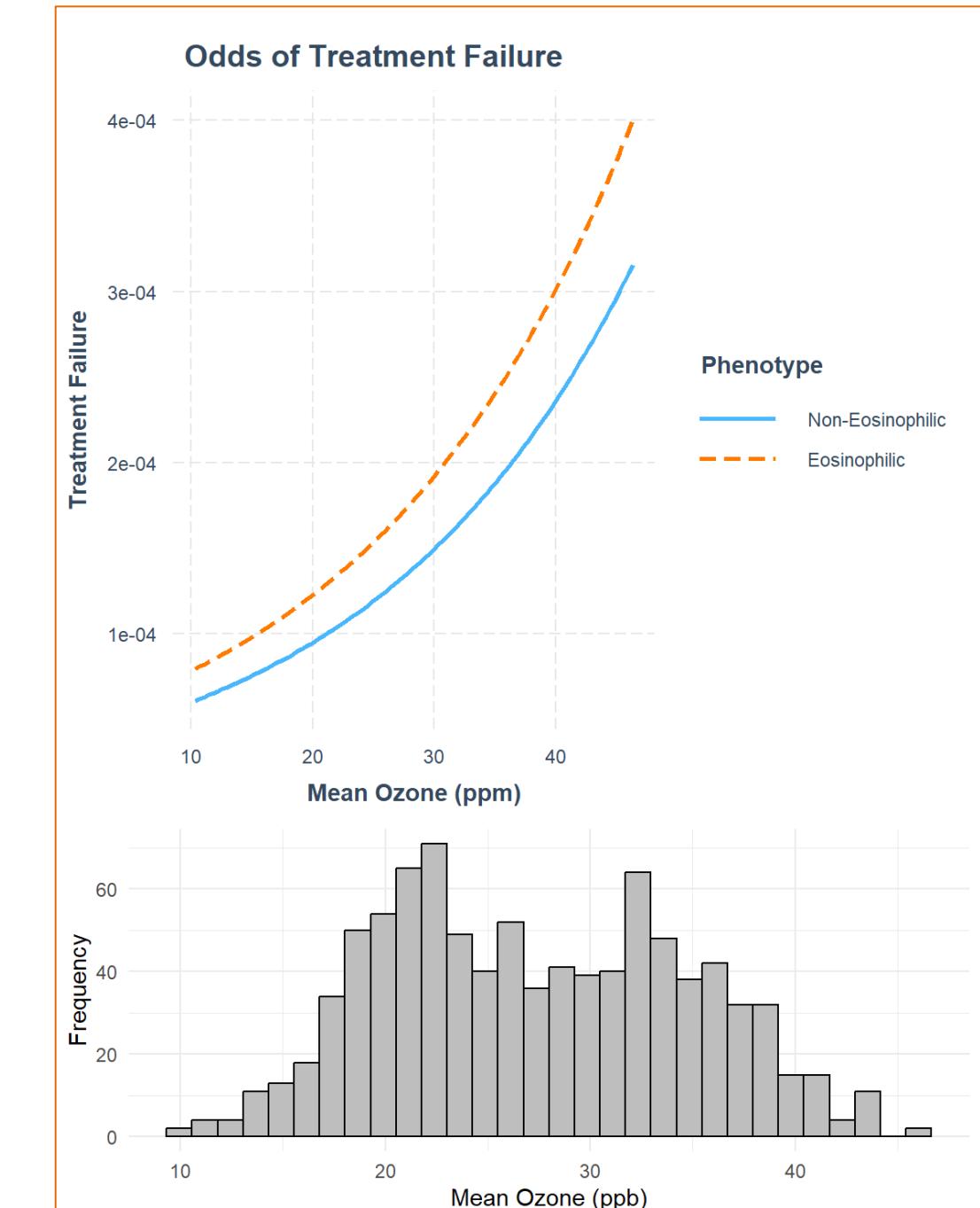
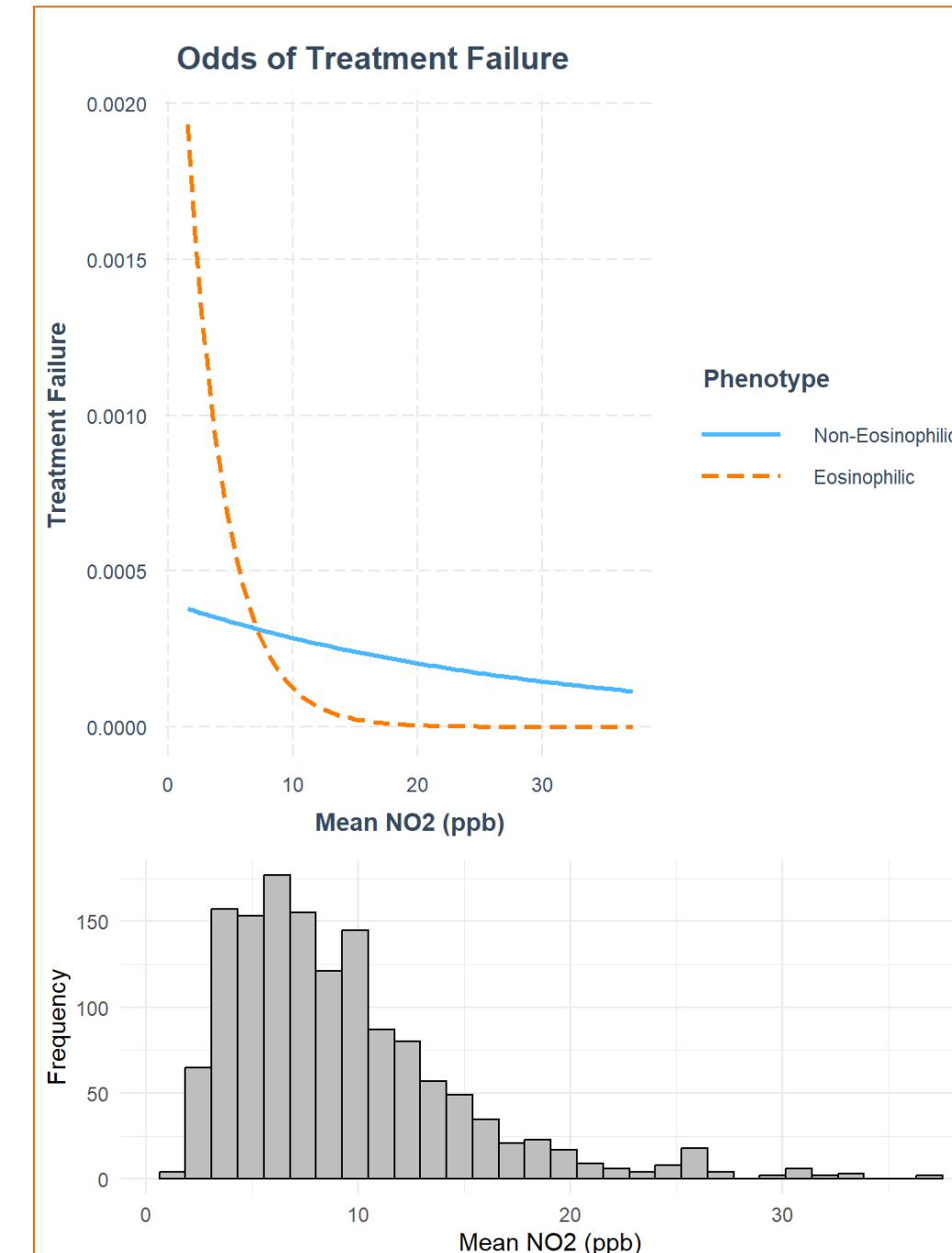
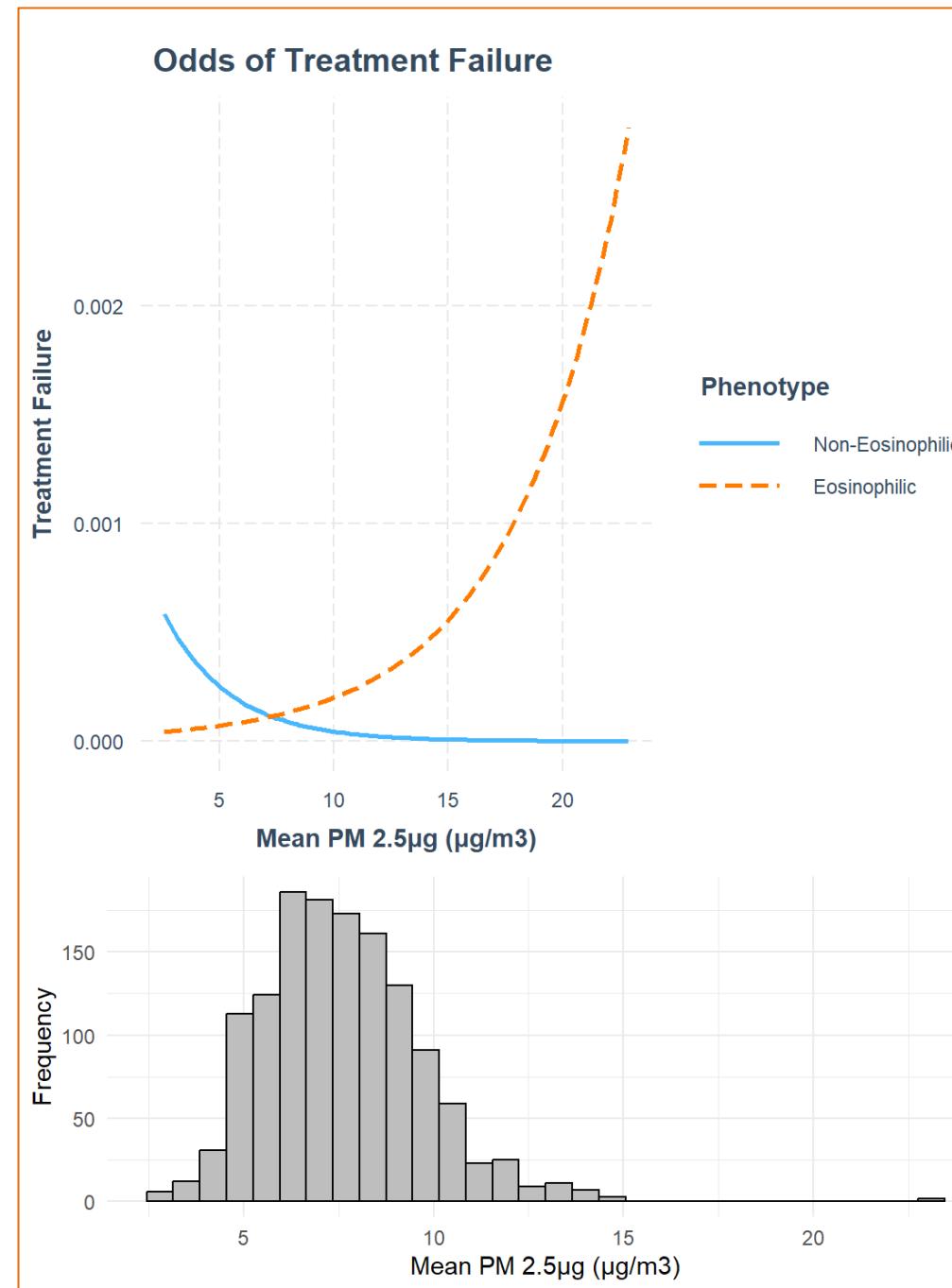
Our Approach

What is the effect of exposure to air pollution exposure on Asthma Treatment Failure BETWEEN eosinophilic and non-eosinophilic participants?

Generalized Linear Mixed Models random intercept for each individual

$$E[Y_{ij}] = \beta_0 + \beta_1 \text{Air Pollutant}_{ij} + \\ \beta_2 \text{Phenotype}_i + \beta_3 \text{Air Pollutant}_{ij} * \text{Phenotype}_i + \\ \beta_4 \text{Covs} + b_{0i}$$

Results



Models adjusted for baseline provocative concentration of inhaled methacholine (PC20),
Median fraction of exhaled nitric oxide, eczema or atopic dermatitis

Our Approach

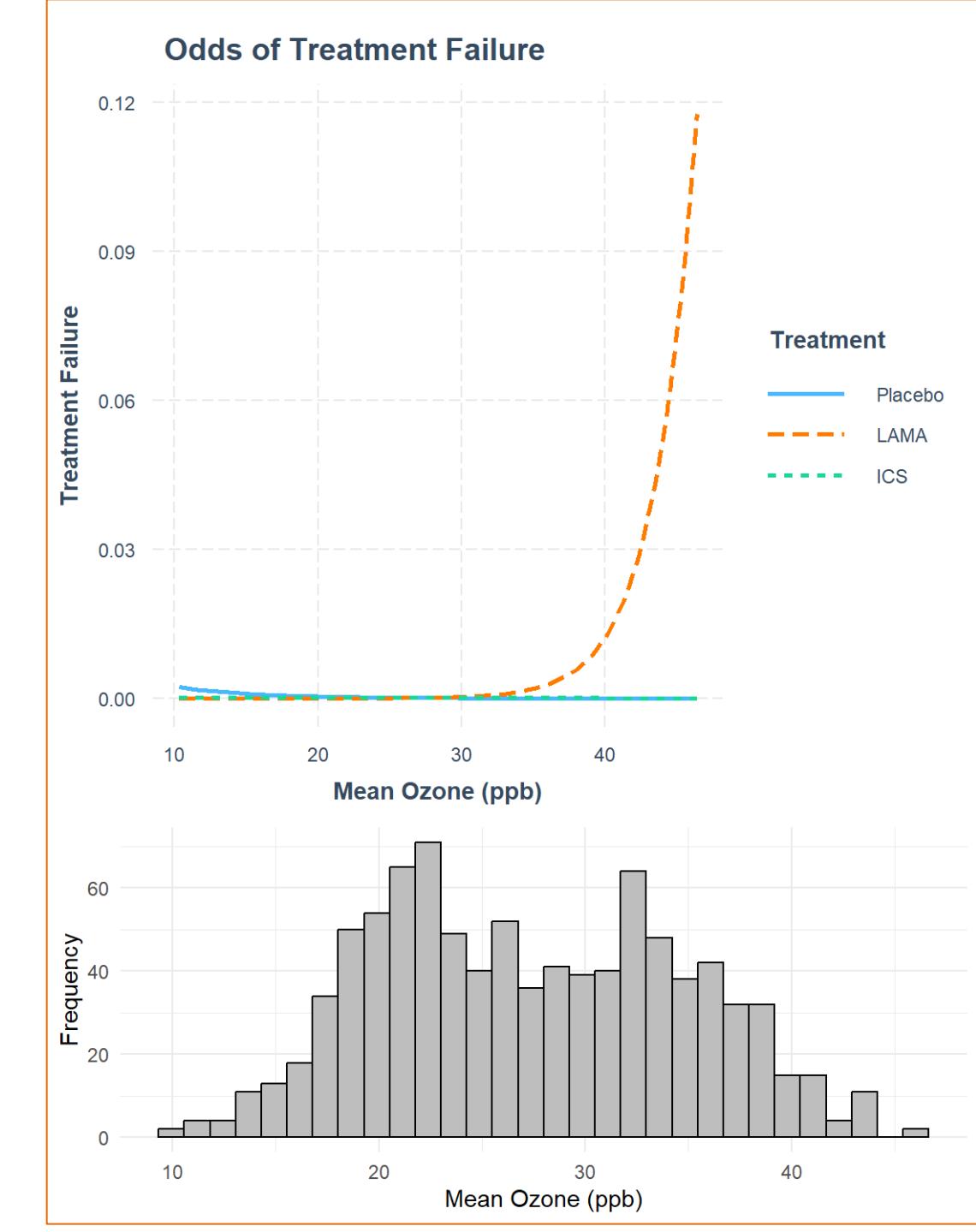
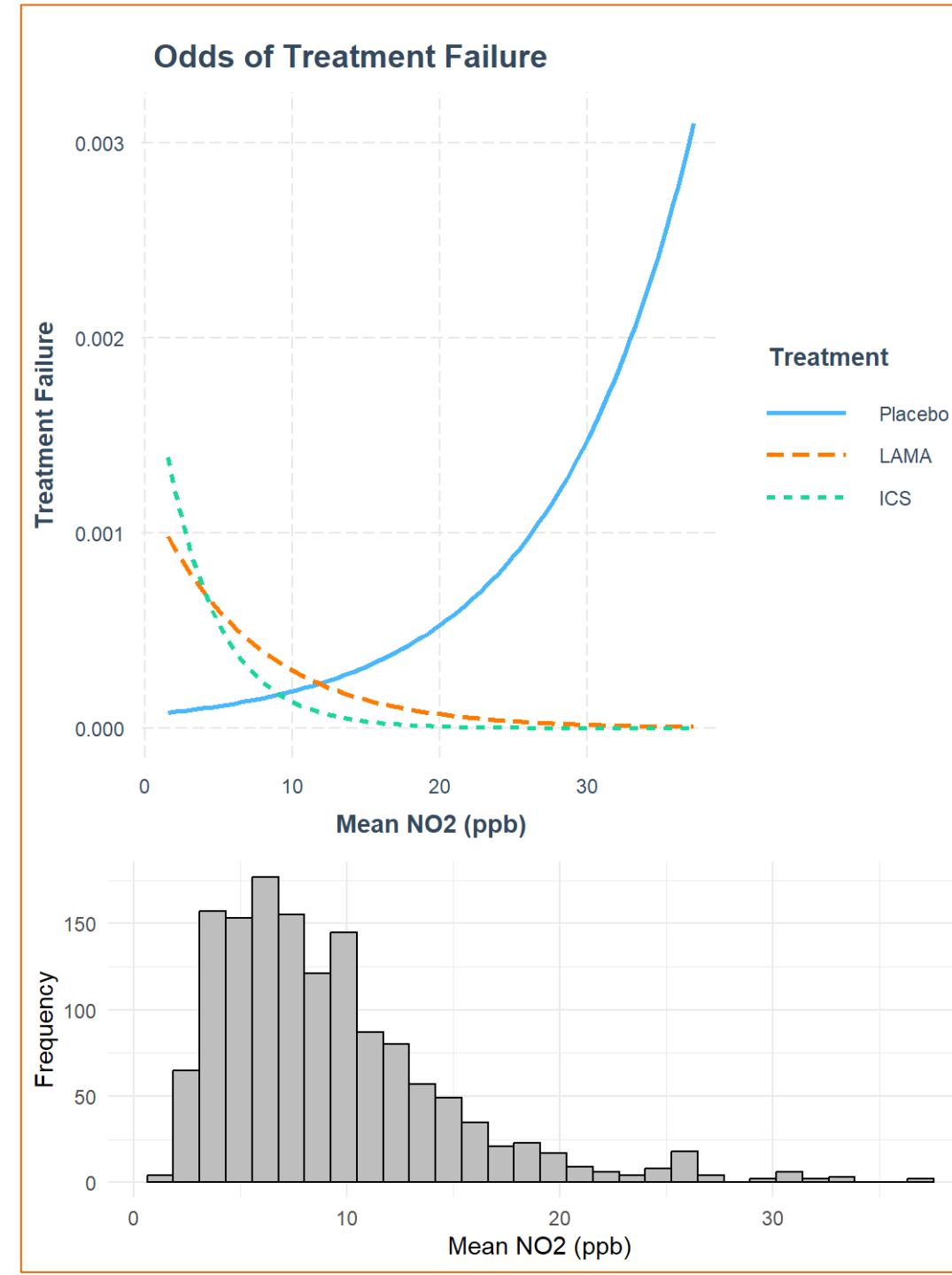
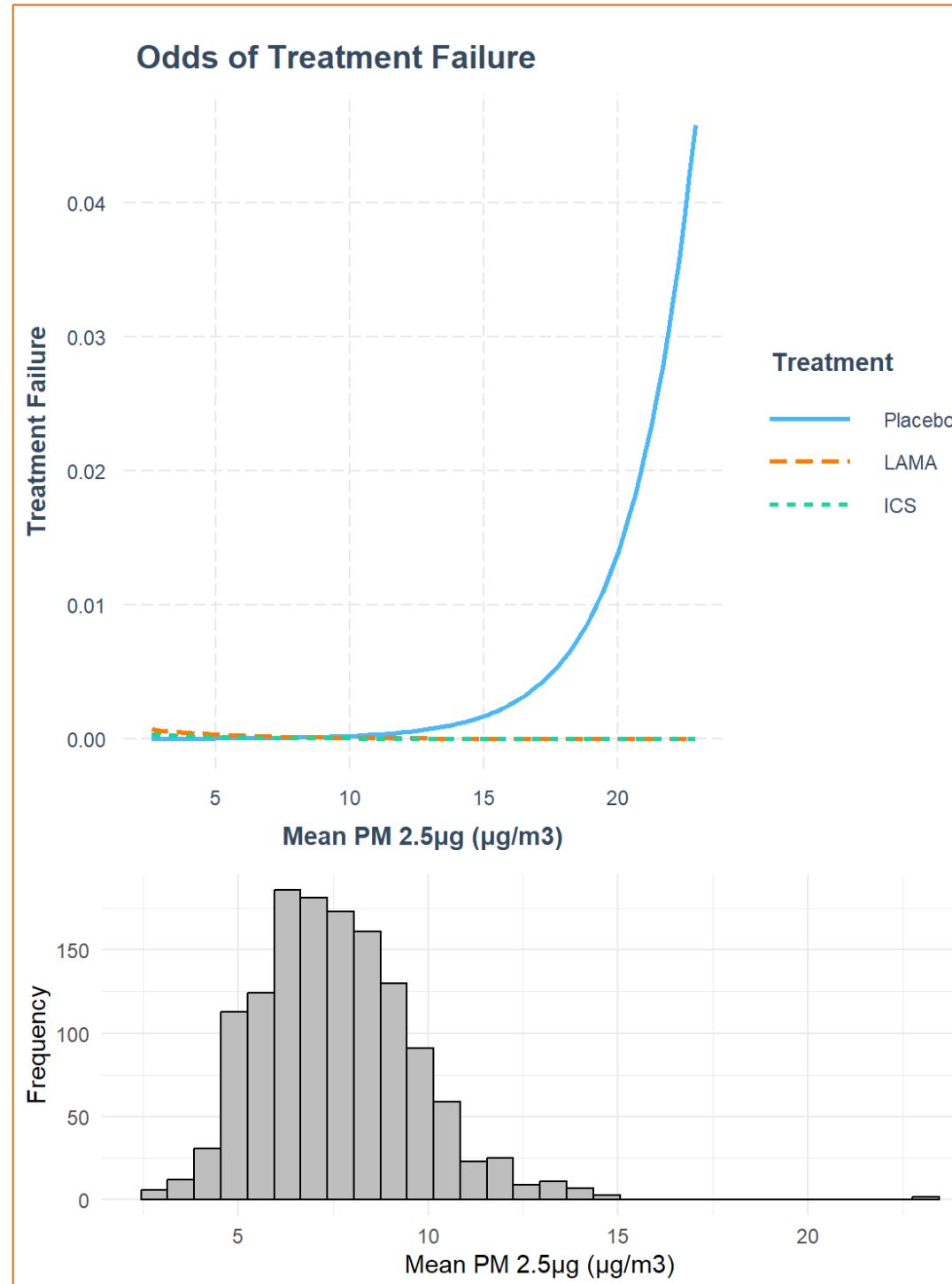
What is the effect of exposure to air pollution exposure on Asthma Treatment Failure as modified by treatment with ICS and LAMA compared to placebo?

Generalized Linear Mixed Models random intercept for each individual

$$E[Y_{ij}] = \beta_0 + \beta_1 \text{Air Pollutant}_{ij} + \\ \beta_2 \text{Phenotype}_i + \beta_3 \text{Air Pollutant}_{ij} * \text{Phenotype}_i + \\ \beta_4 \text{Covs} + b_{0i}$$

$$E[Y_{ij}] = \beta_0 + \beta_1 \text{Air Pollutant}_{ij} + \\ \beta_2 \text{Treatment}_{ij} + \beta_3 \text{Air Pollutant}_{ij} * \text{Treatment}_{ij} + \\ \beta_4 \text{Covs} + b_{0i}$$

Results



Models adjusted for baseline provocative concentration of inhaled methacholine (PC₂₀),
Median fraction of exhaled nitric oxide, eczema or atopic dermatitis

SIENA Findings

- **Asthma phenotypes may modify the association between PM_{2.5} and treatment failure.**
- **Treatment Observations:** Treatment significantly modified the association between PM_{2.5} NO₂ and O₃ and the odds of treatment failure

Limitations

- Post Hoc Analyses
- Participant retention
- Applicability of Findings

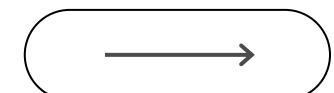
Strengths

- Data richness
- Innovative approach
- Focus on vulnerable populations



Implications

- Holistic Treatment Plans
- Efficacy and Effectiveness gap
- Contribution to the field



FUTURE

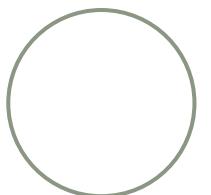
Methodological Developments

- Effectiveness
- Populations
- Representativeness
- Move away from exploratory approach

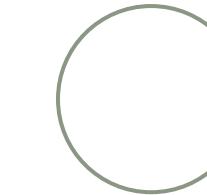
DIRECTIONS



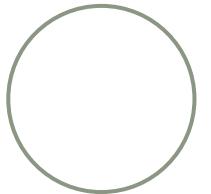
Acknowledgments



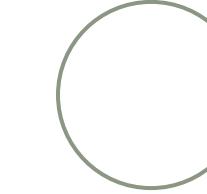
Jane E. Clougherty, ScD,
MSc



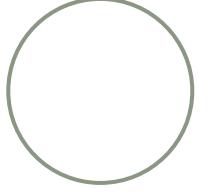
Ellen Kinnee, MS



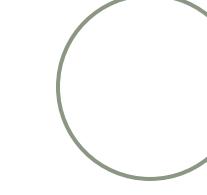
Fernando Holguin, MD,
MPH



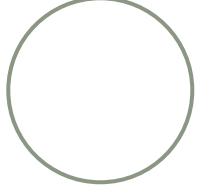
Joel Kaufman MD, MPH &
Michael T. Young, PhD



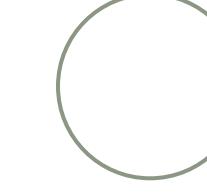
Usama Bilal, MD, PhD,
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Research Coordinators



Leslie McClure, PhD



Funding
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Questions?



Questions?

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