

DATE
6/04/2024

Modification in Responses to Asthma Treatment by Environmental and Social Exposures

A Secondary Analysis of AsthmaNet Clinical Trials

DISSERTATION DEFENSE

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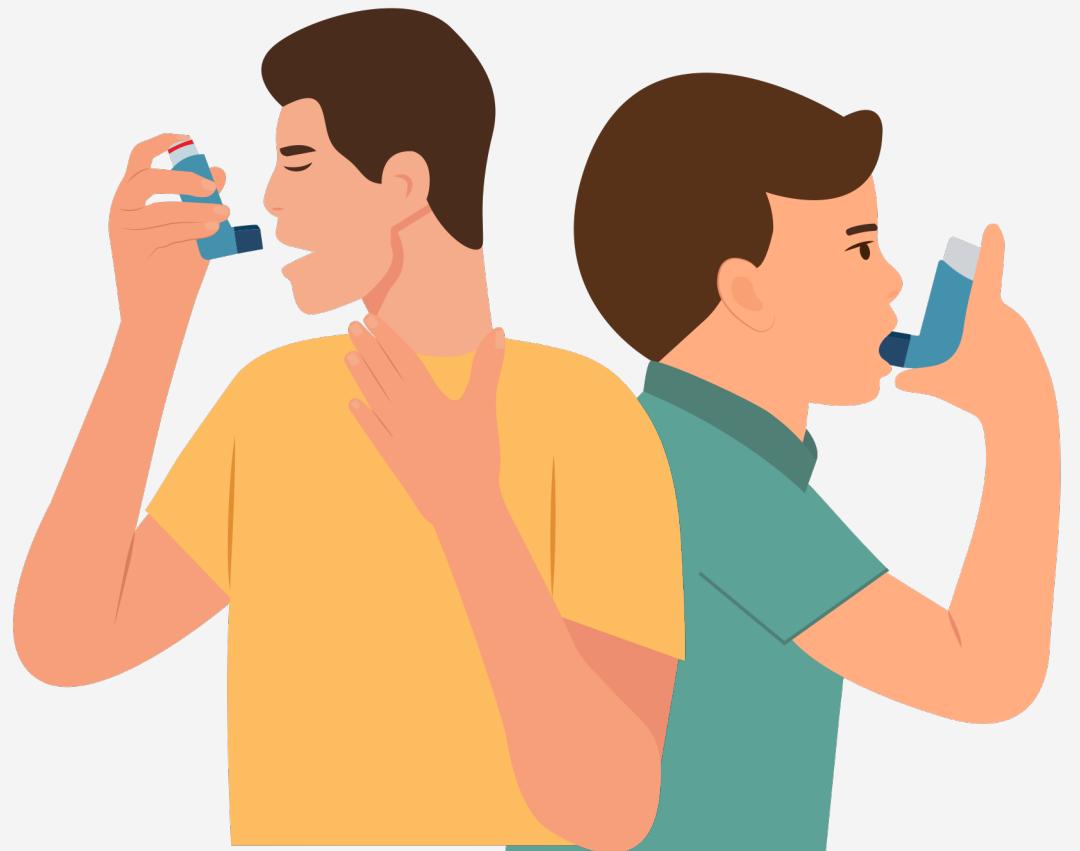
ACKNOWLEDGEMENTS

67

Q&A

Background

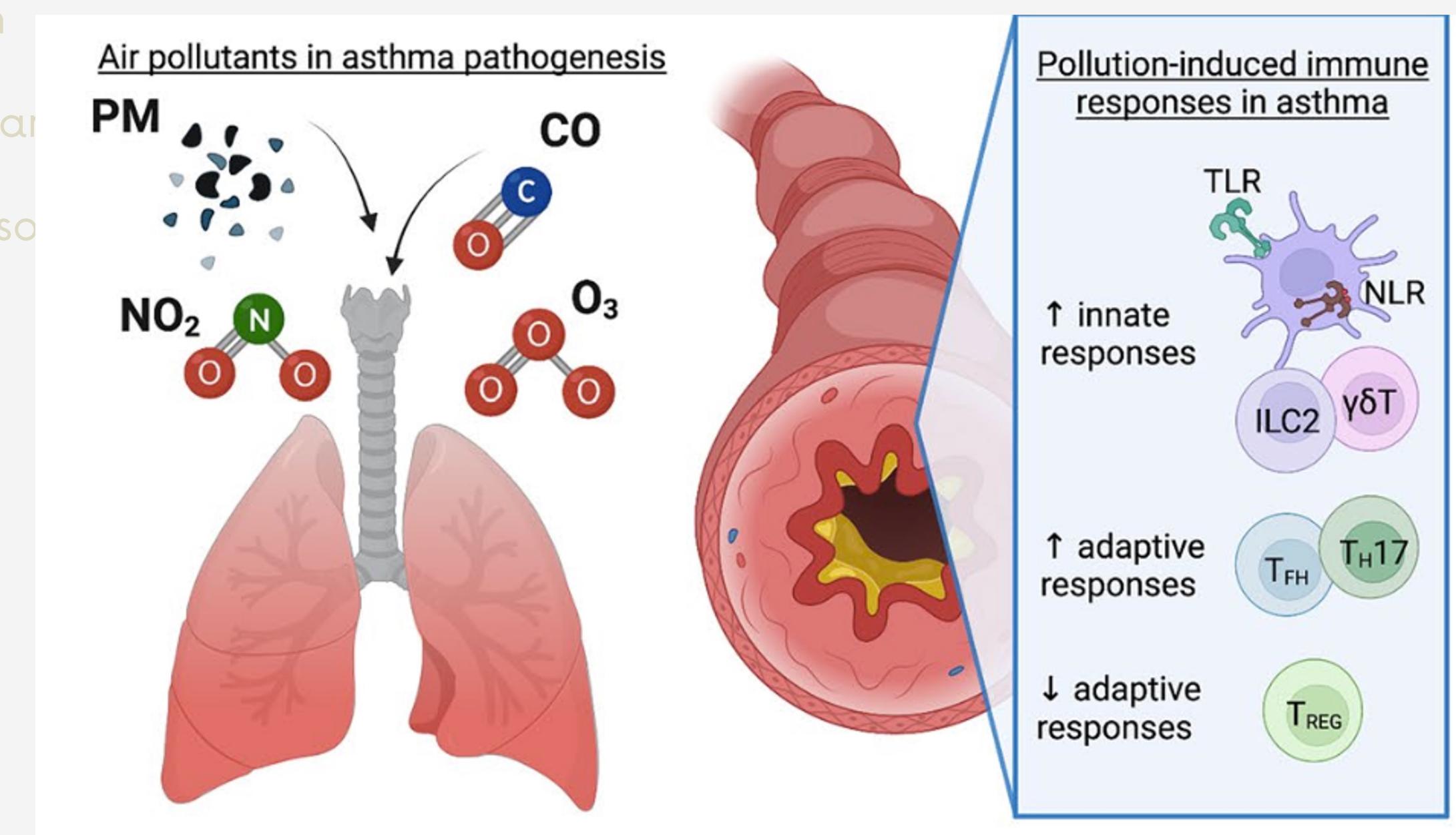
- Health impacts of air pollution
- Vast research on air pollution (and socio-environmental) exposures and asthma
- Mechanisms by which air pollution and social context act on asthma



Background

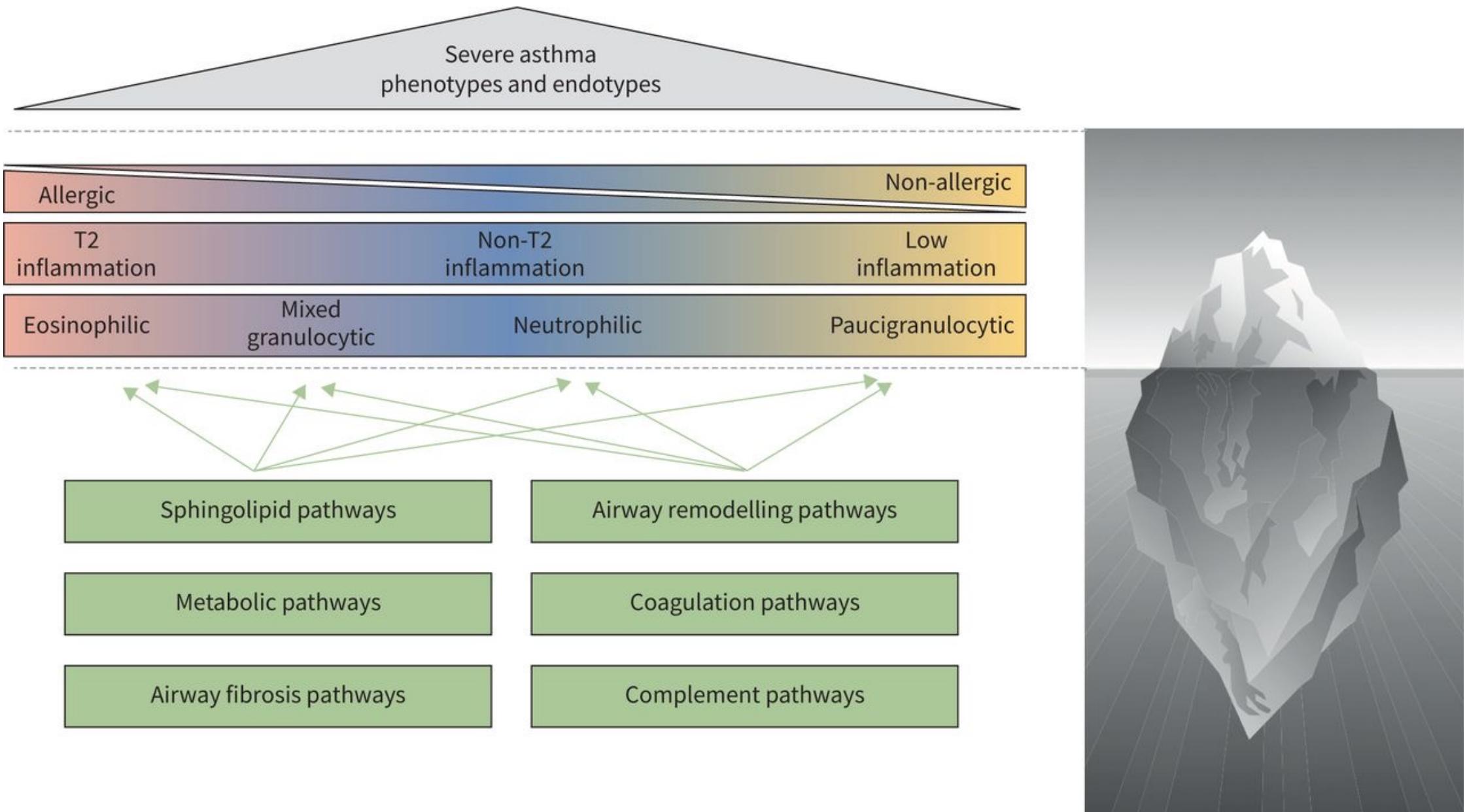
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- Vast research on air pollution and health
- Mechanisms by which AP and so

Air Pollution and Asthma Pathogenesis



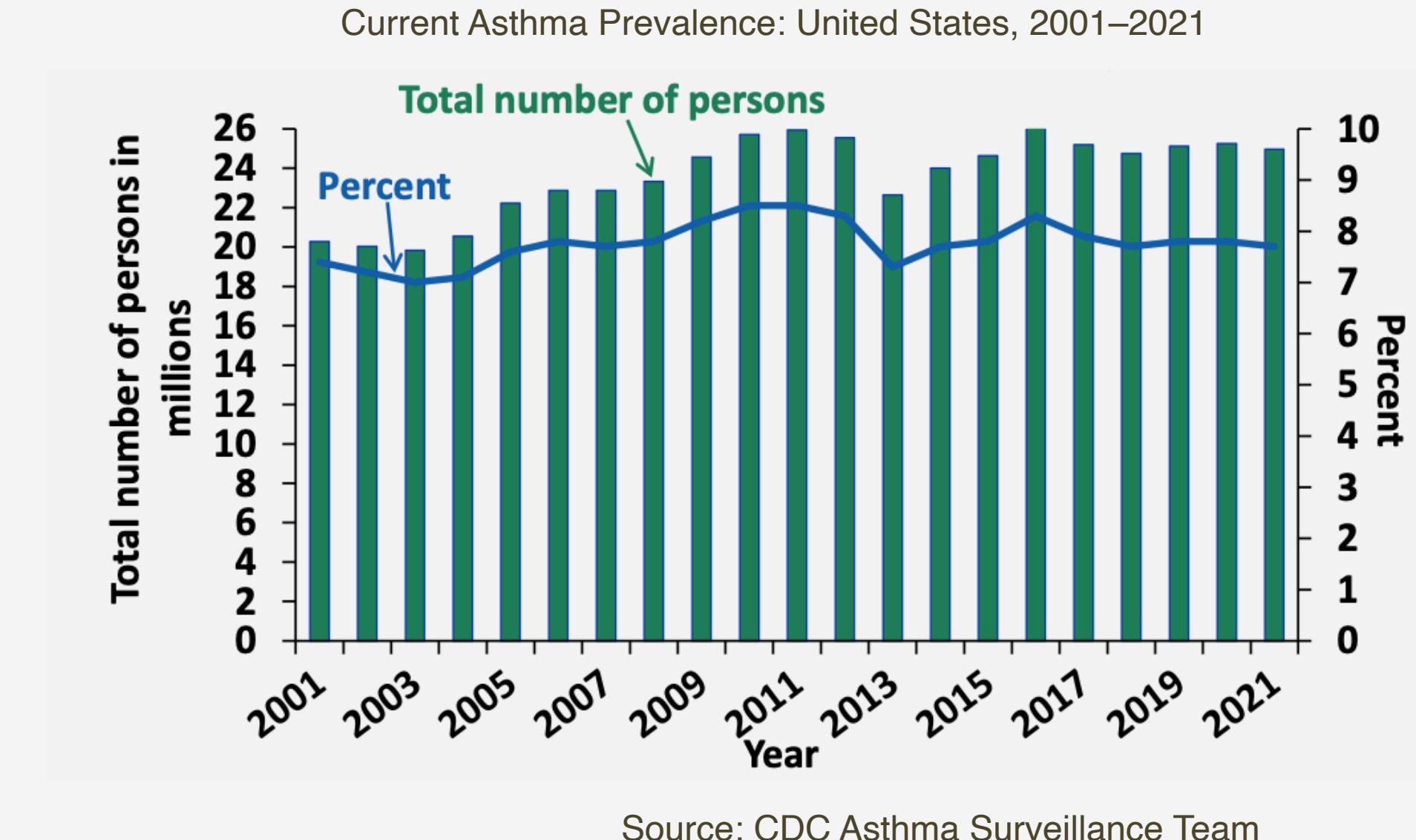
Asthma

- Heterogeneous disease (s)
- Characteristics
 - Reversible airway obstruction
 - Hyperresponsiveness
 - Inflammation



Asthma

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



Randomized Controlled Trials for Asthma

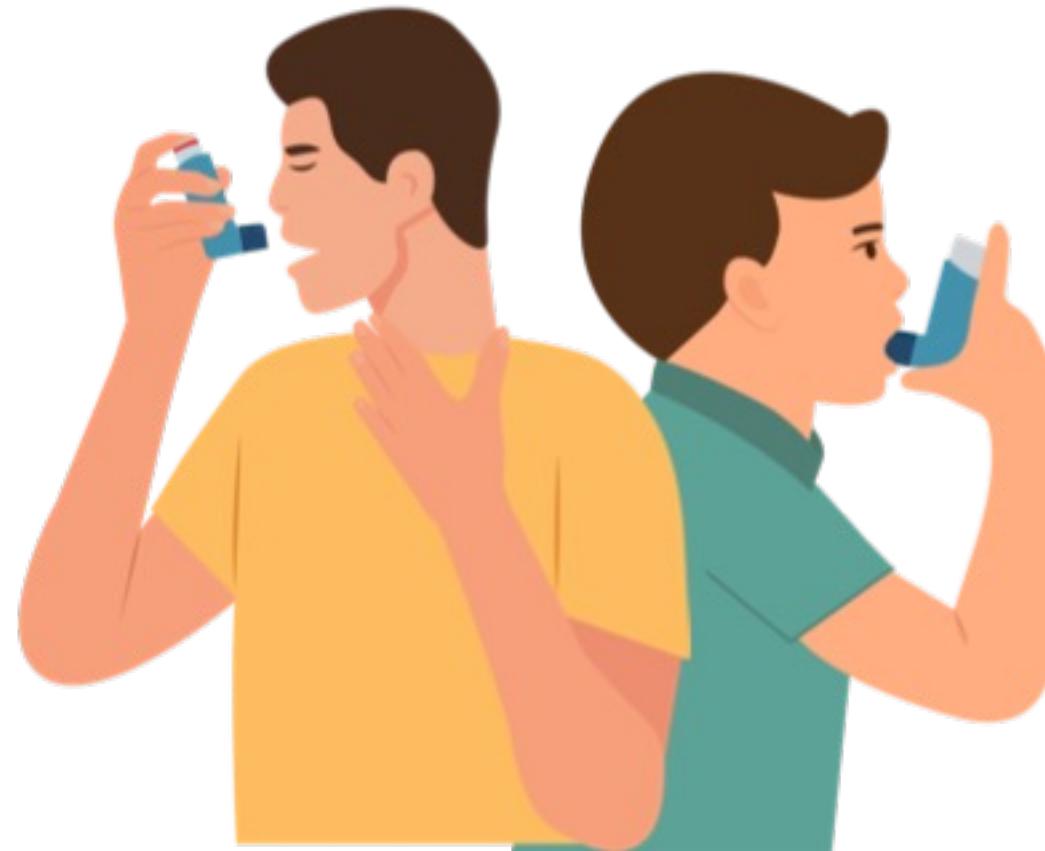
The gold standard for clinical recommendations:

- Internally valid findings
- High-quality data
- Longitudinal

Issues with RCTs:

- Enrollment often biased by proximity to clinical sites leading to geographical biases.
- Many RCTs don't represent the full population at risk.
- Clinical guidelines may rely on RCTs that may not be representative.

Recommended Treatments for Asthma



Glucocorticosteroids

- First-line therapy for controlling airway inflammation in asthma.
- Increased expression of anti-inflammatory genes
- Suppression of pro-inflammatory gene activation

Recommended Treatments for Asthma

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

		Management of Persistent Asthma in Individuals Ages 5-11 Years					
		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
5-11 years of age	Intermittent Asthma	Persistent Asthma: Daily Medication					
	Preferred Treatment [†]	SABA* as needed	low-dose ICS*	low-dose ICS* + either LABA,* LTRA,* or theophylline ^(b)	medium-dose ICS* + LABA*	high-dose ICS* + LABA*	high-dose ICS* + LABA* + oral corticosteroids
	Alternative Treatment ^{†,‡}	cromolyn, LTRA,* or theophylline [§]	OR medium-dose ICS	medium-dose ICS* + either LTRA* or theophylline [§]	high-dose ICS* + either LTRA* or theophylline [§]	high-dose ICS* + either LTRA* or theophylline [§] + oral corticosteroids	
	Quick-Relief Medication	Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma. ^{**}					
<ul style="list-style-type: none"> ▪ SABA* as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments every 20 minutes as needed. Short course of oral systemic corticosteroids may be needed. ▪ Caution: Increasing use of SABA or use >2 days/week for symptom relief (not to prevent EIB*) generally indicates inadequate control and the need to step up treatment. 							

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.

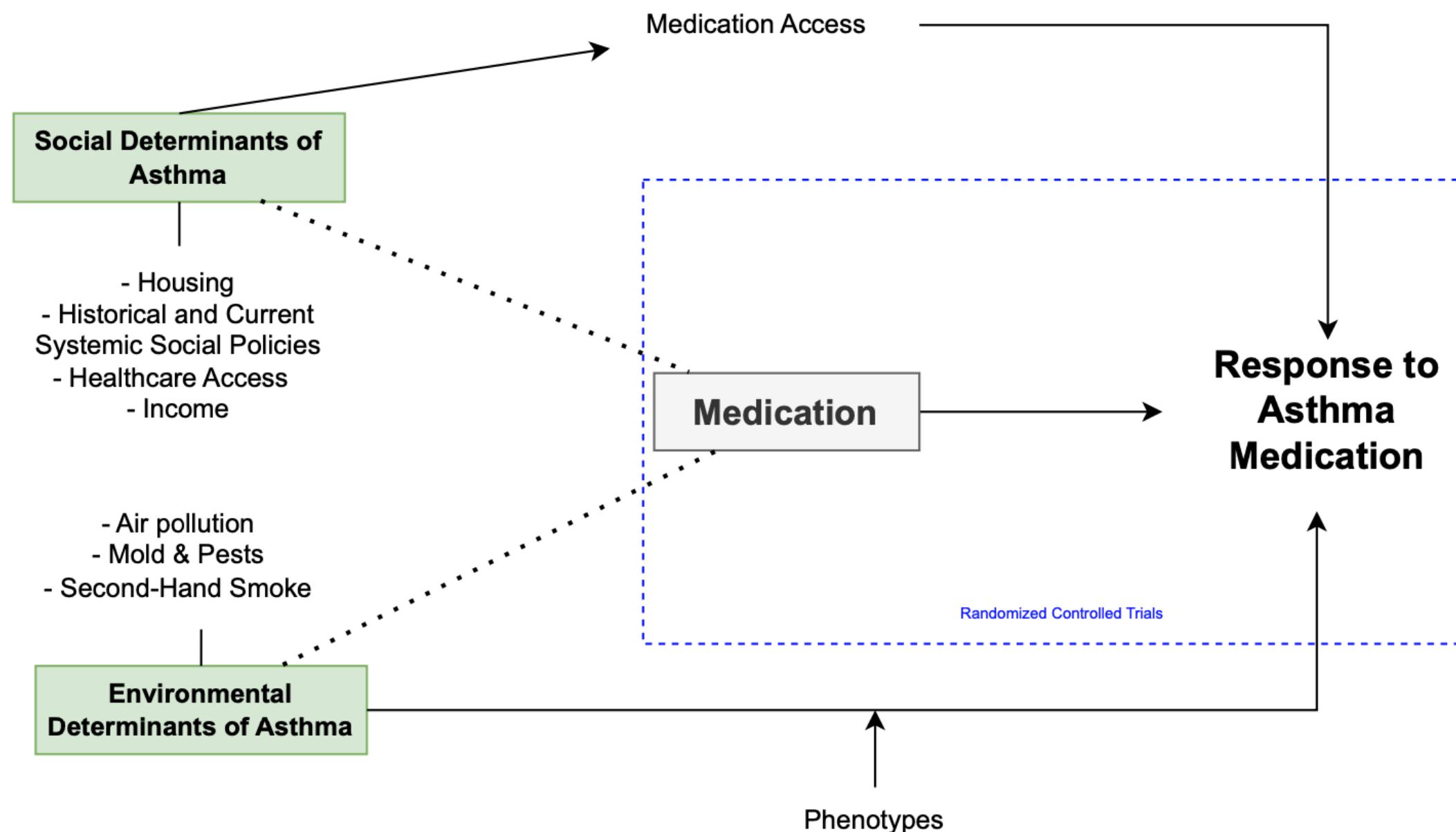
However, distinct societal-level patterns exist.

The Thesis

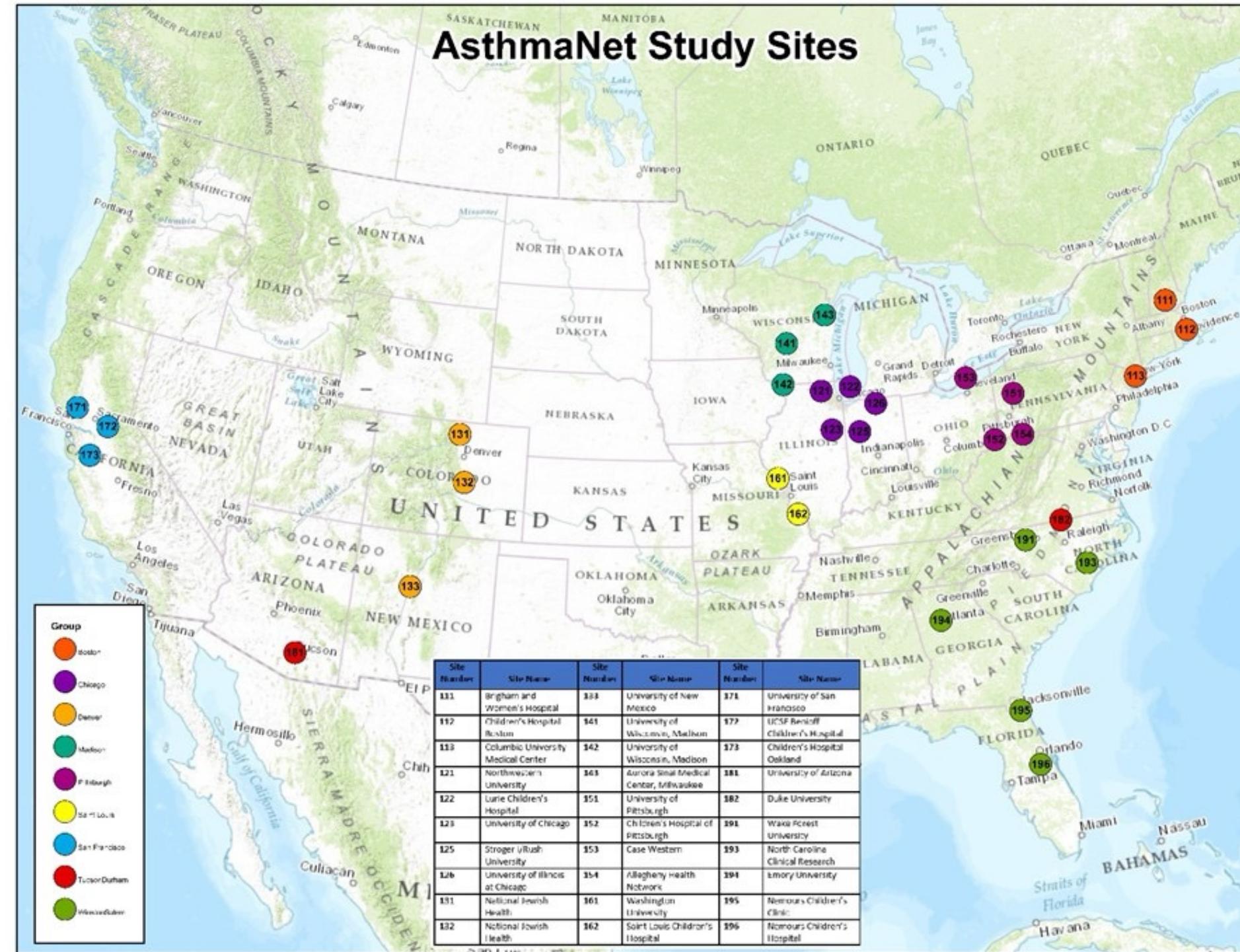
Few studies have evaluated the potential for air pollution and social context to modify the association between treatment and asthma outcomes.

Overall Research Framework

How do socio-environmental exposures modify the association between receiving asthma medication and asthma symptoms?

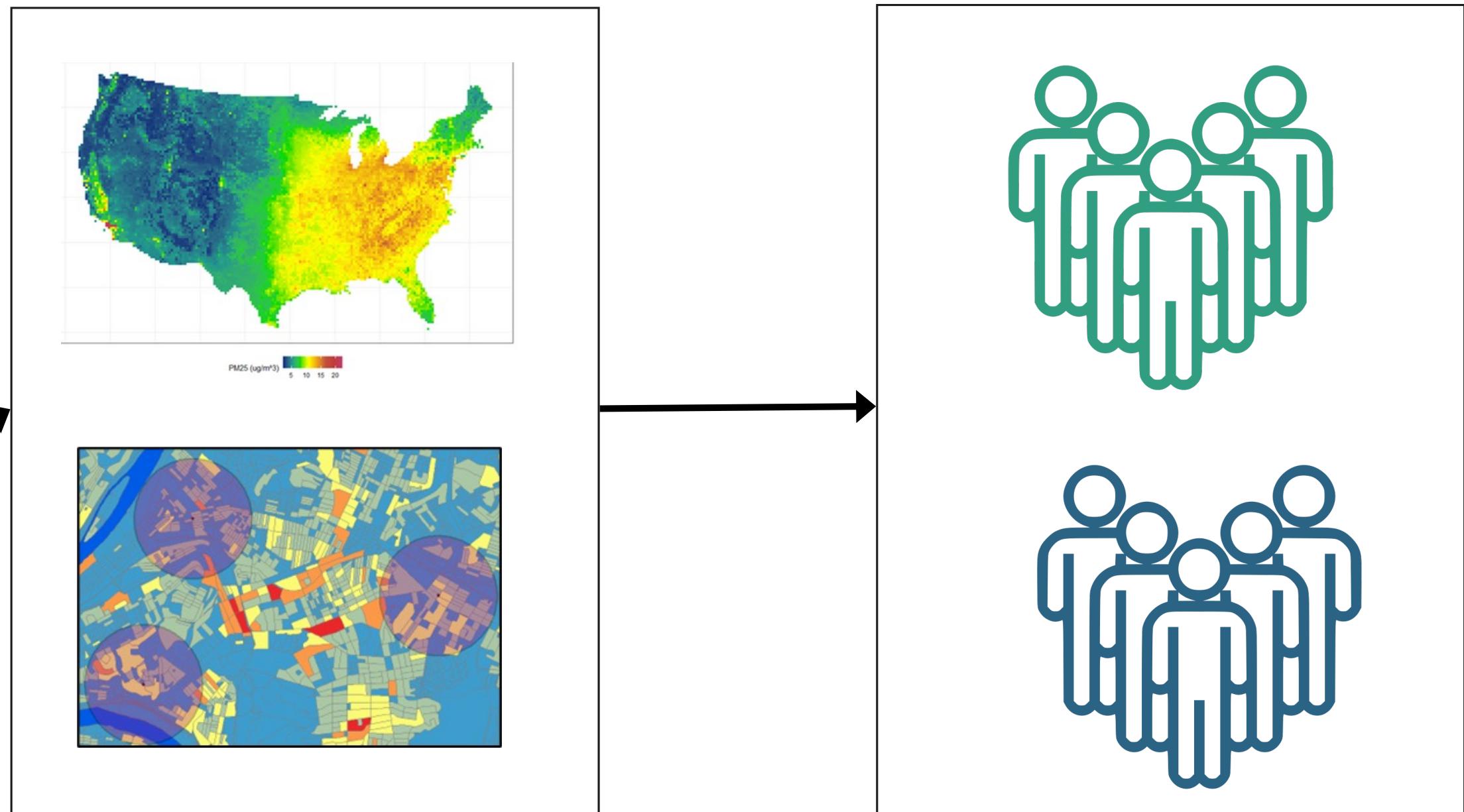
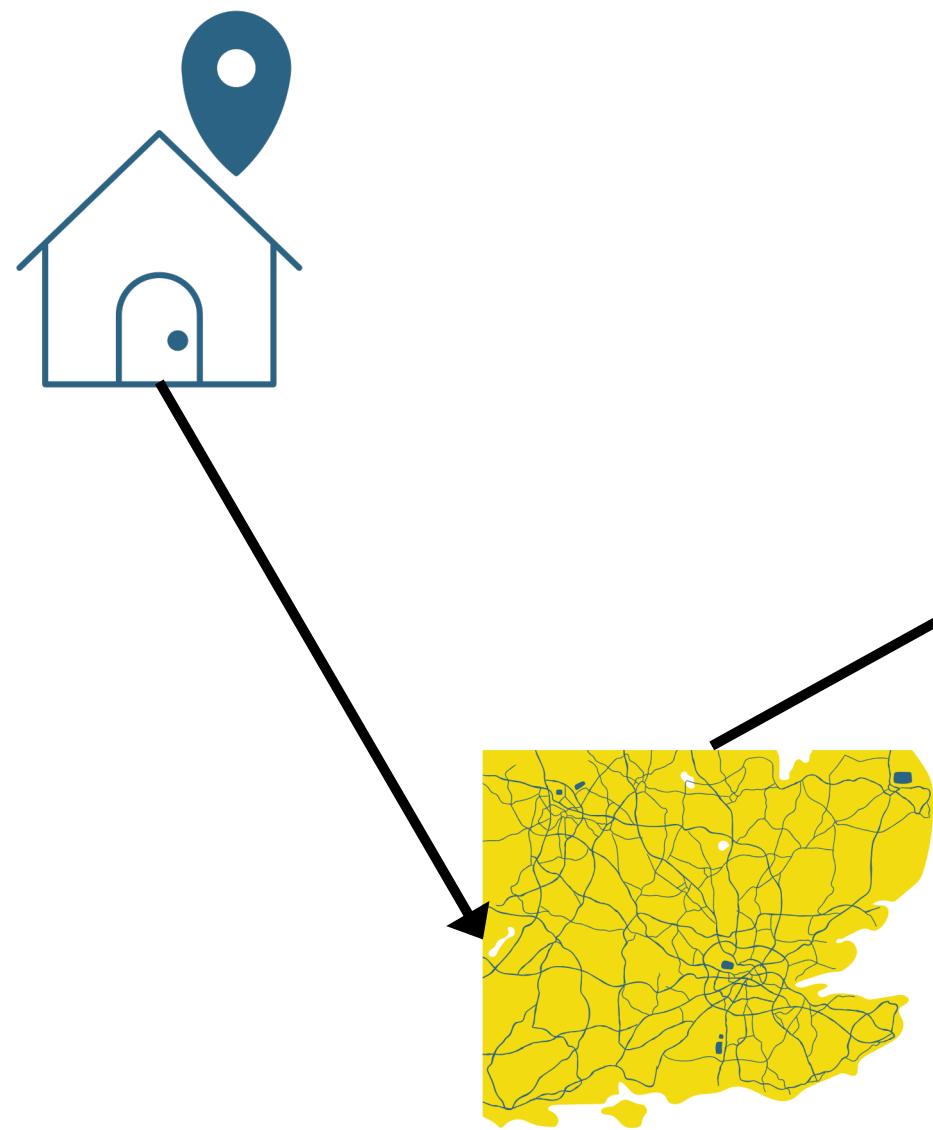


AsthmaNet

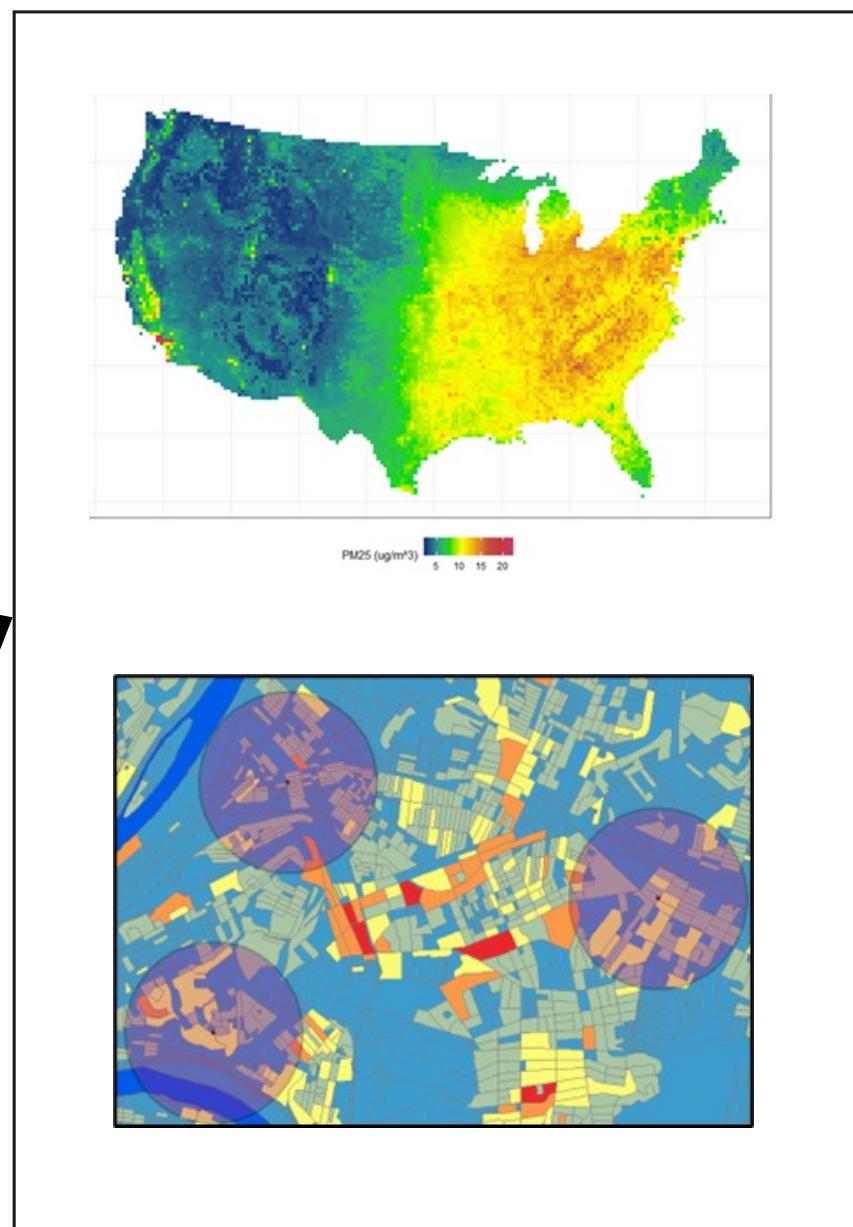
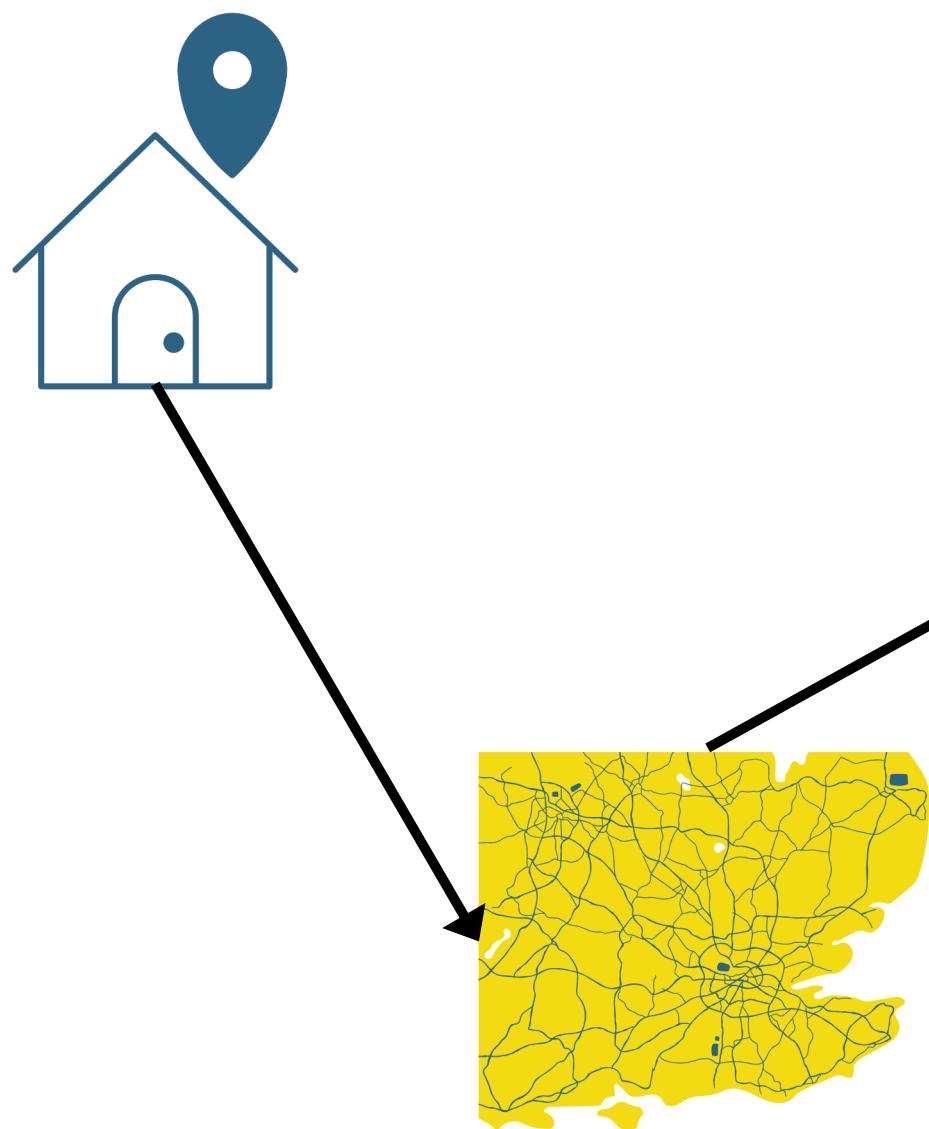


Same protocols across 17 US cities

GIS-Based Methods

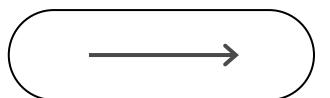


GIS-Based Methods



- Modeled air pollution in 2-week concentration resolution
 - Averaged pollutant estimates from a national universal kriging model
- Estimated for individual's geocoded residence census block
 - ACS 5-year summary (2012-16), block group level.
 - U.S. Health Resources and Services Administration

AIM 1



How do social and environmental co-exposures modify the association between receiving stepped-up asthma treatment and asthma symptoms in children?

AsthmaNet Trials

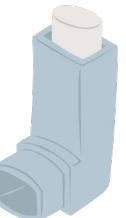
STICS

- Children (5-11)
- 2014 – 2017
- N = 254
- Parallel Design
- Step up
 - LOW vs HIGH ICS DOSE

STICS Trial



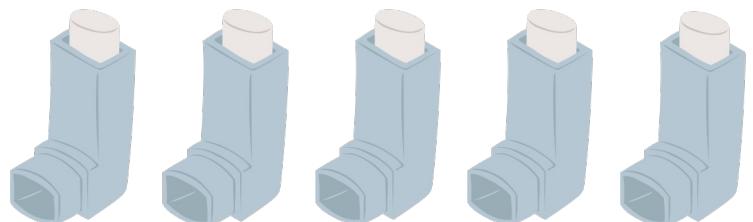
Low Dose



44 ug of Fluticasone



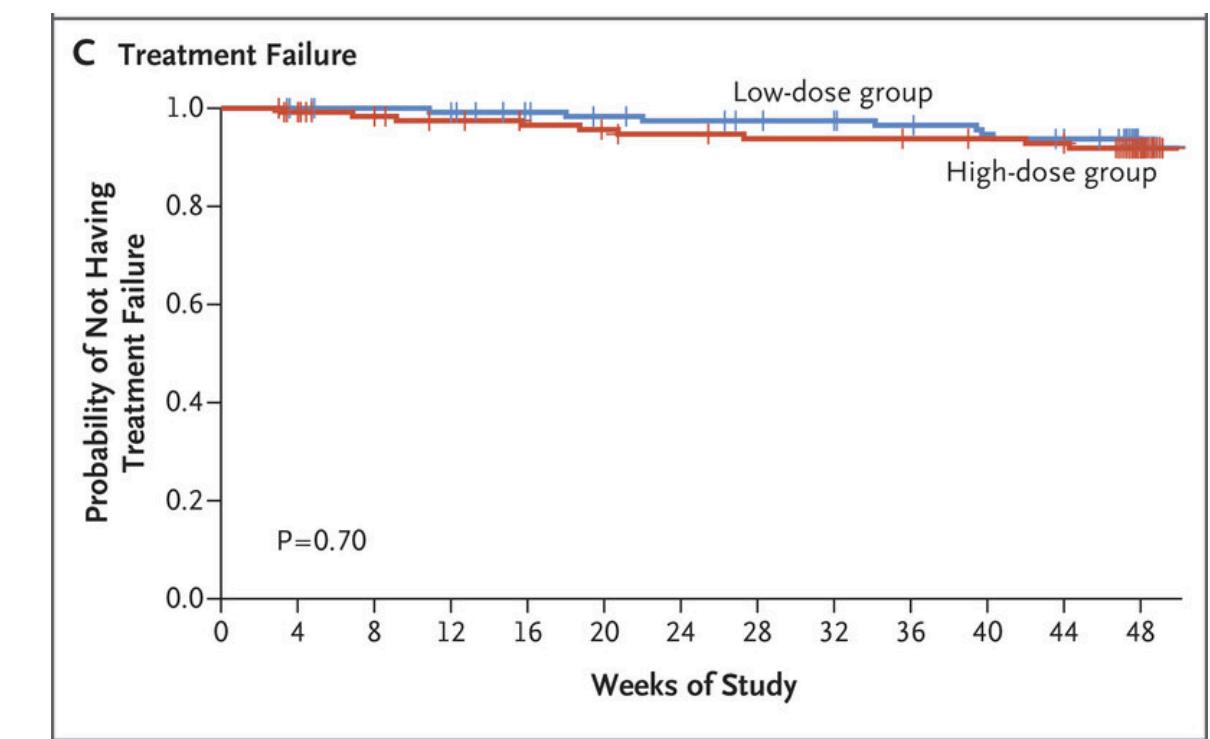
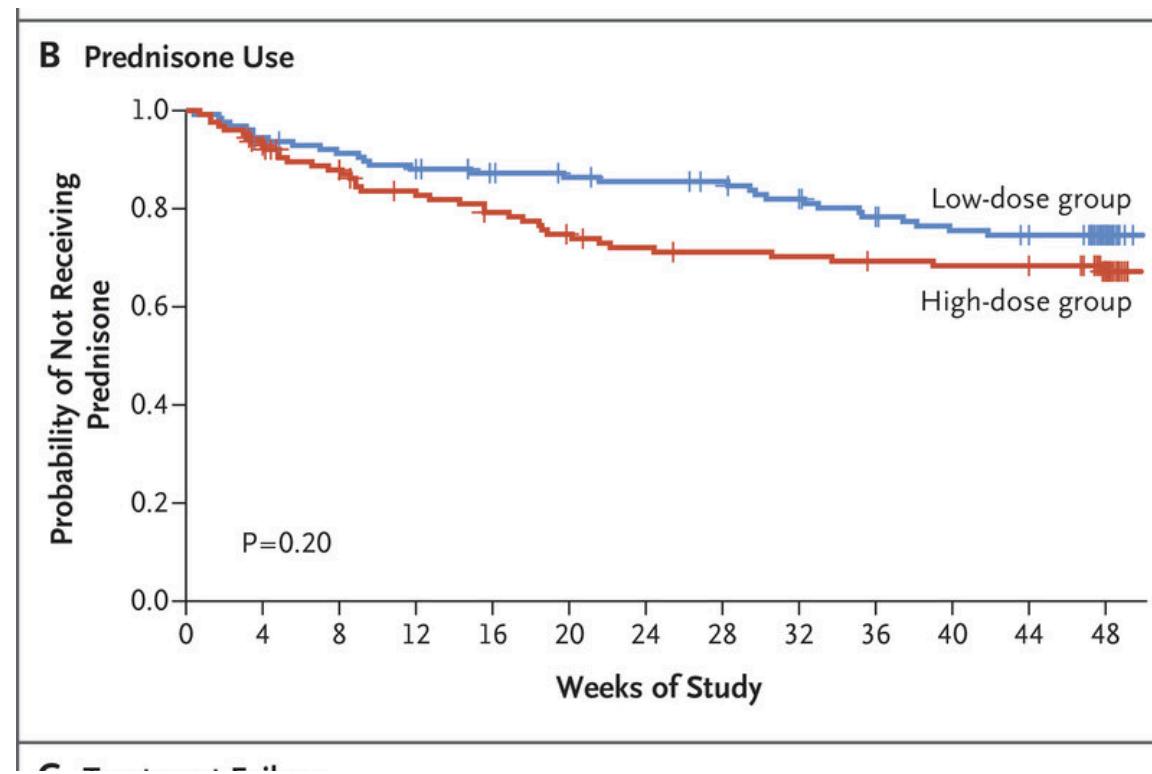
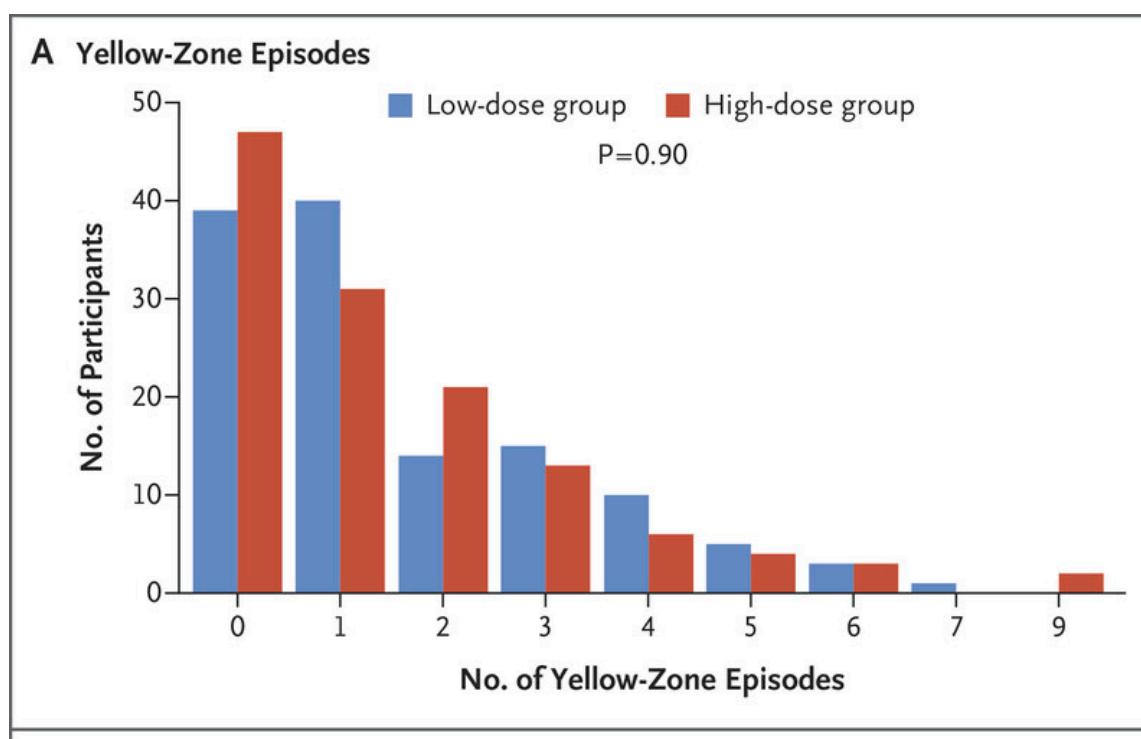
High Dose



220 ug of Fluticasone



STICS Trial Findings



Outcomes	Low-Dose Group (N=127)	High-Dose Group (N=127)	Treatment Effect (95% CI) \pm	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

Recommended Treatments for Asthma

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
5-11 years of age	Intermittent Asthma	Persistent Asthma: Daily Medication Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.					
	Preferred Treatment [†]	SABA* as needed	low-dose ICS*	low-dose ICS* + either LABA,* LTRA,* or theophylline ^(b)	medium-dose ICS* + LABA*	high-dose ICS* + LABA*	high-dose ICS* + LABA* + oral corticosteroids
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STICS Ancillary: Methods

ASTHMA MEDICATION

- 1xICS
- 5xICS

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

- PM_{2.5}, NO₂ and O₃
- % Below FPL, age, race, sex

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, age, race, sex, BMI, HPSA & MUA

HPSA & MUA

- HPSA: Health Provider Shortage Area
 - Geographic designation
- MUA: Medically Underserved Areas
 - Metric of healthcare access
 - Provider: population

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

MODELS

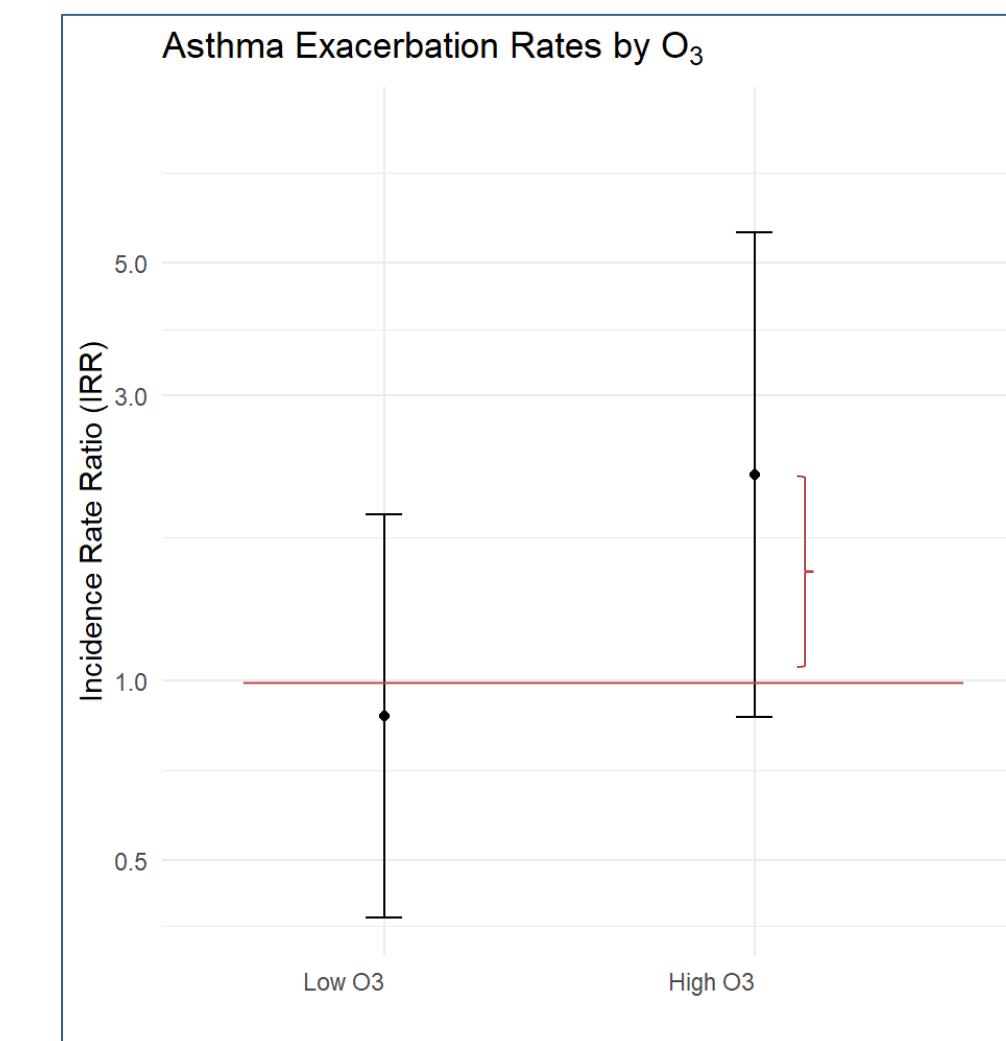
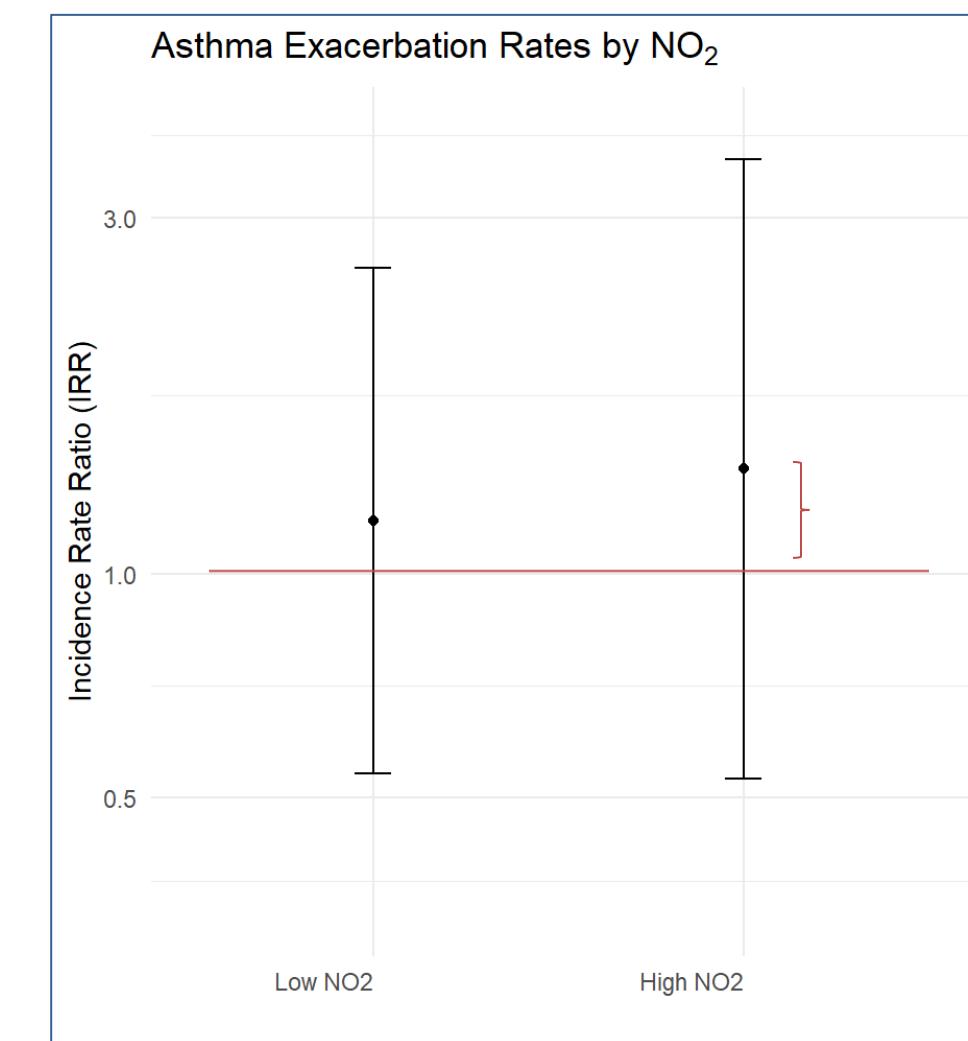
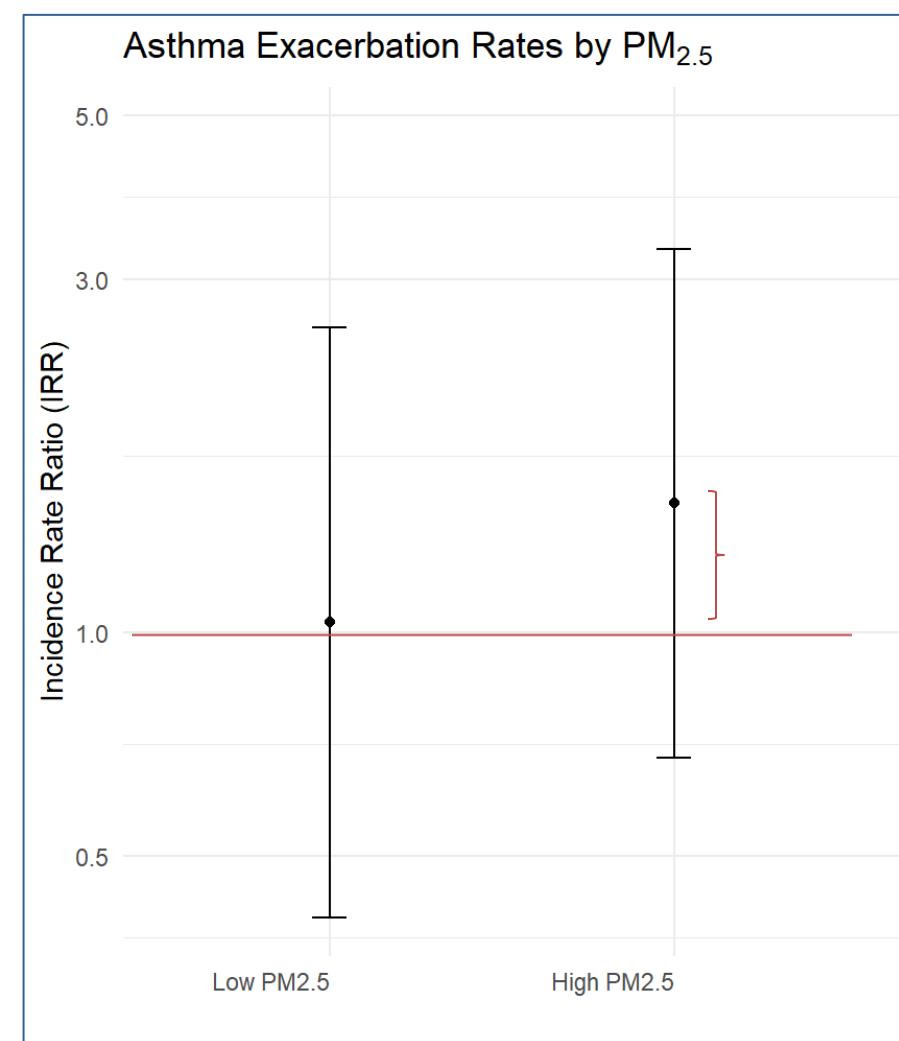
- Generalized linear model
 - log link function and response following a negative binomial distribution.
- Stratified Cox Proportional Hazards regression extension for time-to-event outcomes.

MEDIAN DICHOTOMIZED

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

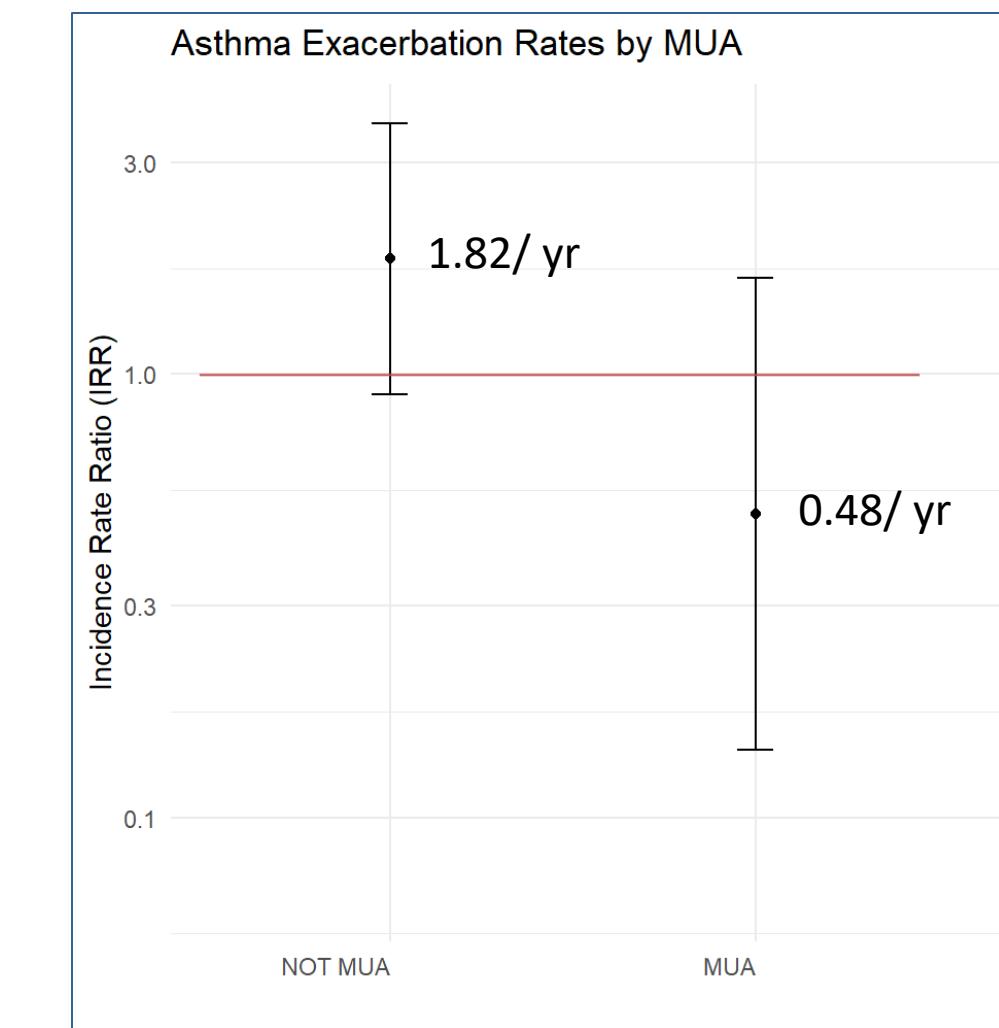
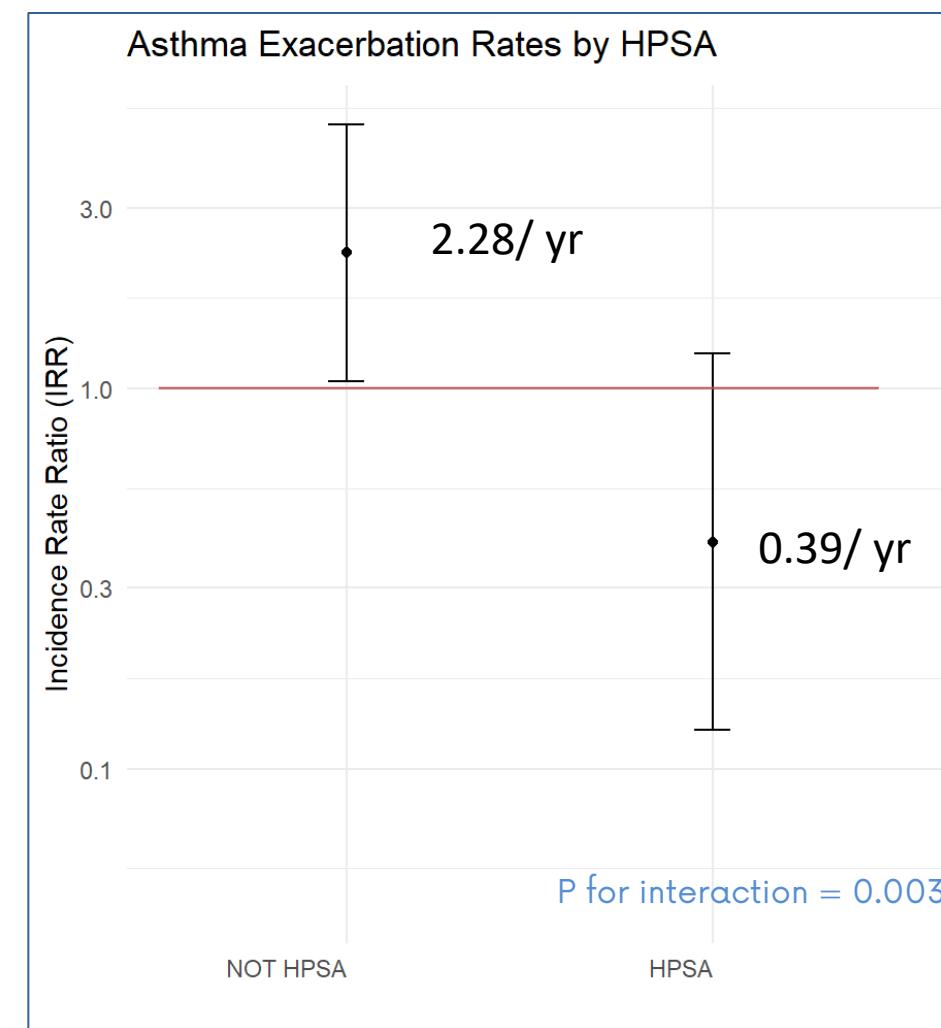
STICS Ancillary Findings

Exacerbations as Modified by Air Pollution Exposure



STICS Ancillary Findings

Exacerbations as Modified by Healthcare Access



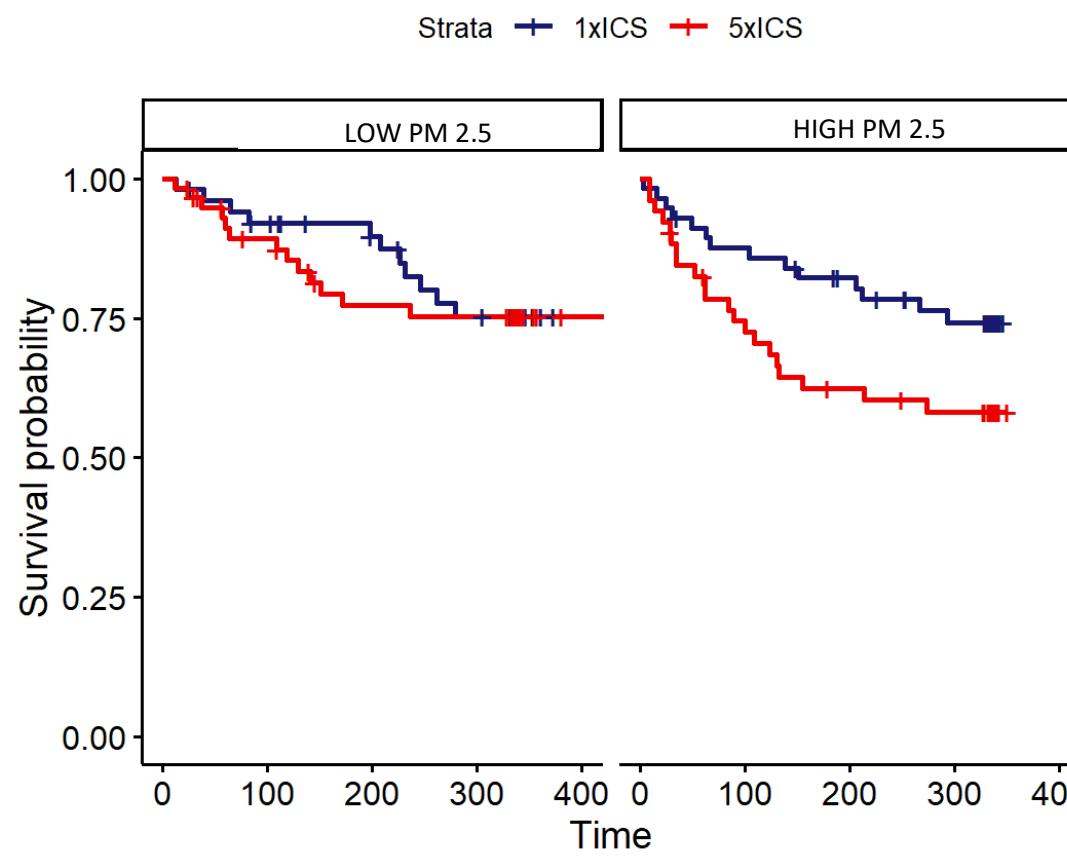
Models adjusted for sex, race, age, pets, percent below poverty level

STICS Ancillary Findings: PM_{2.5}, NO₂ & O₃

AIM 1

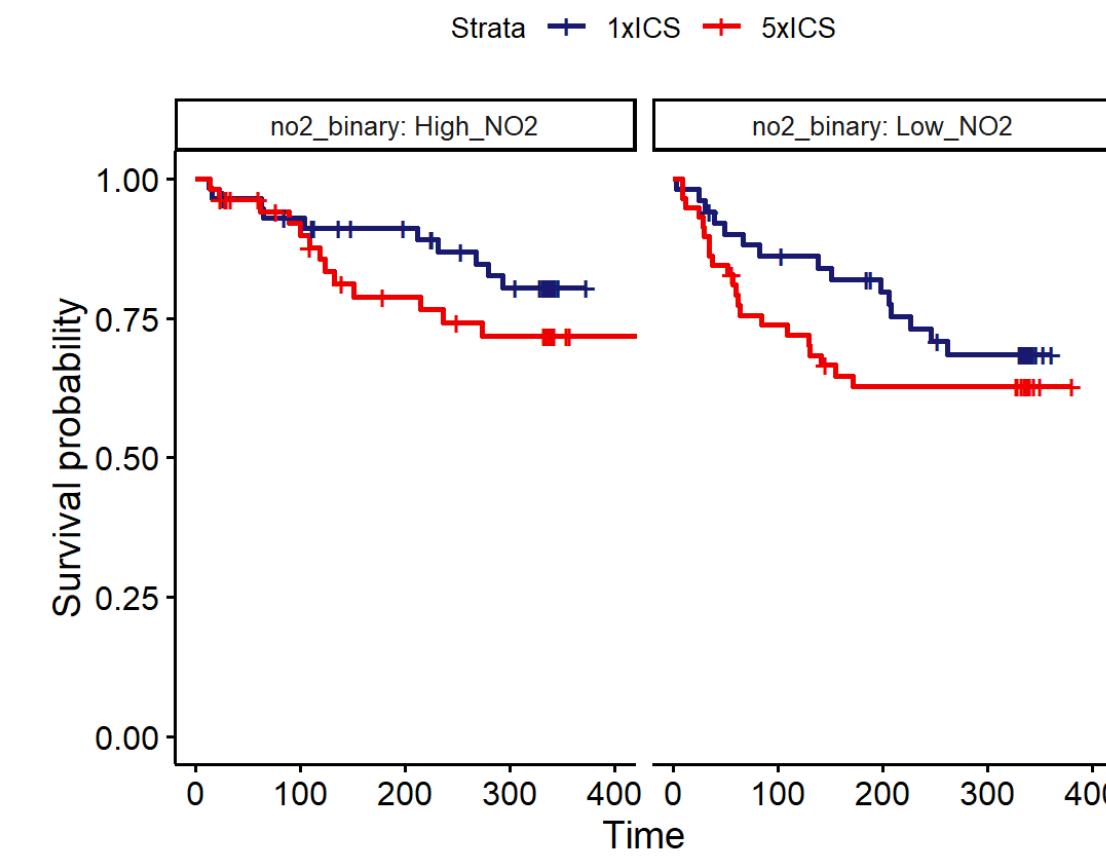
Survival Curves

Time to First Exacerbation Treated with Prednisone



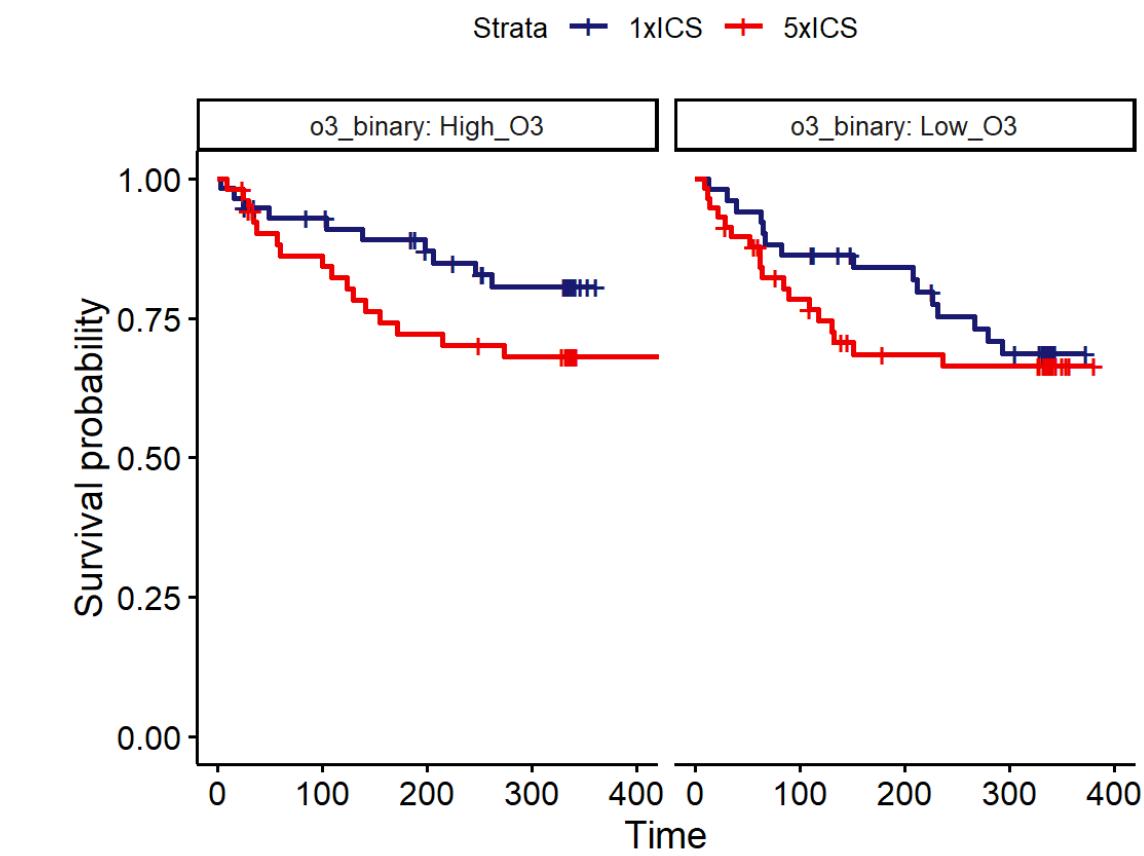
Survival Curves

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Survival Curves

Time to First Exacerbation Treated with Prednisone



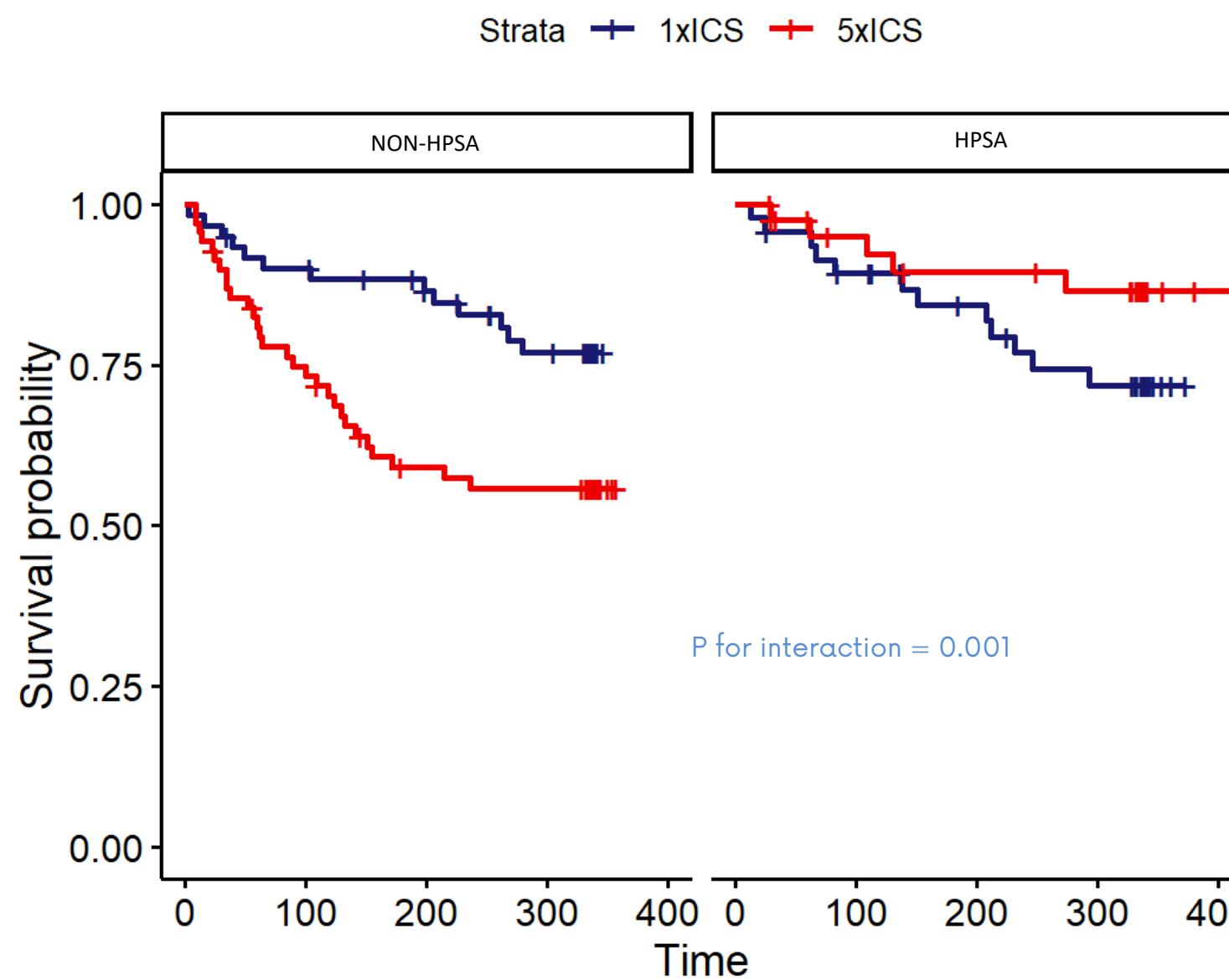
Models adjusted for sex, race, age, pets, percent below poverty level

STICS Ancillary Findings: Health Provider Shortage Areas

AIM 1

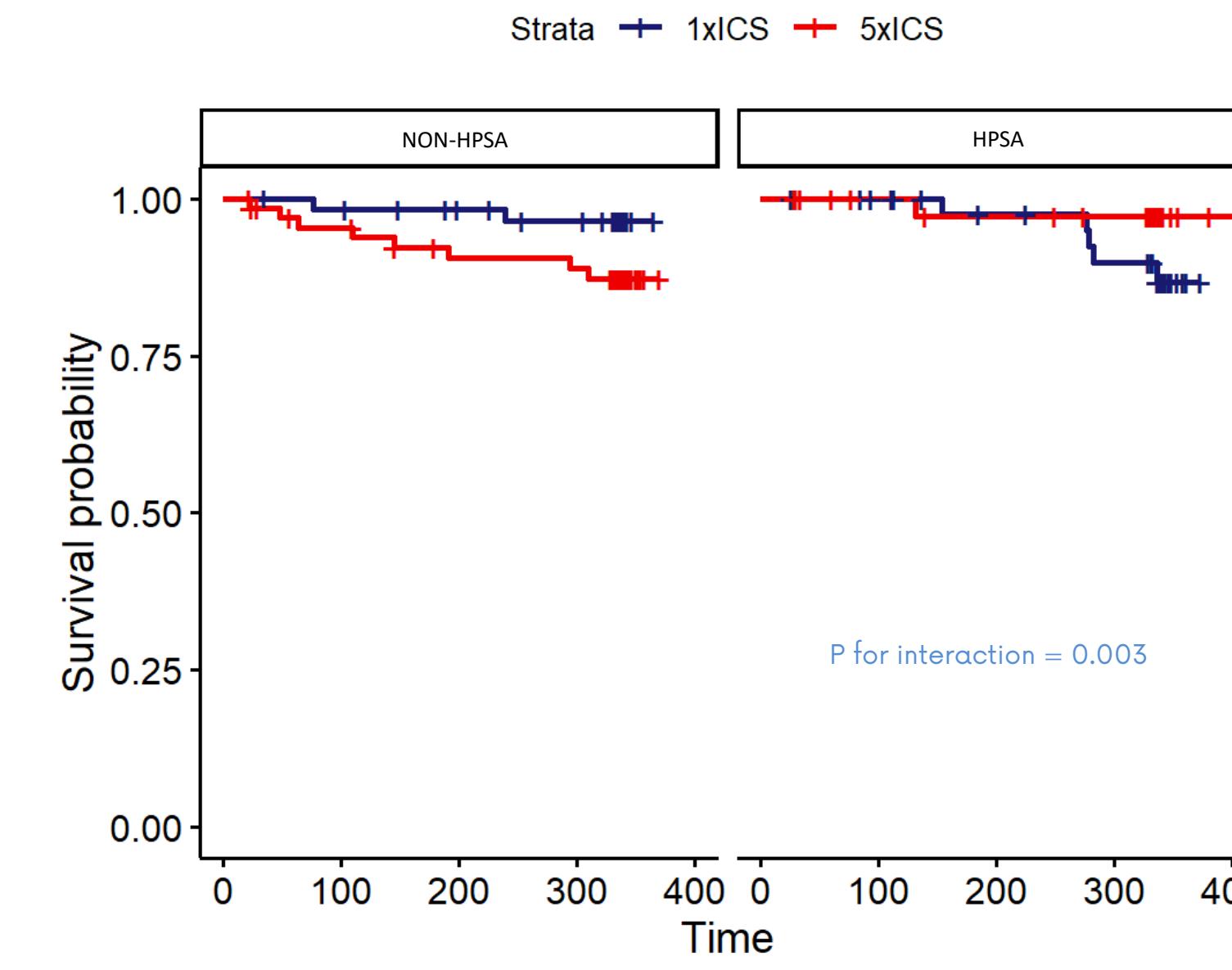
Survival Curves

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Survival Curves

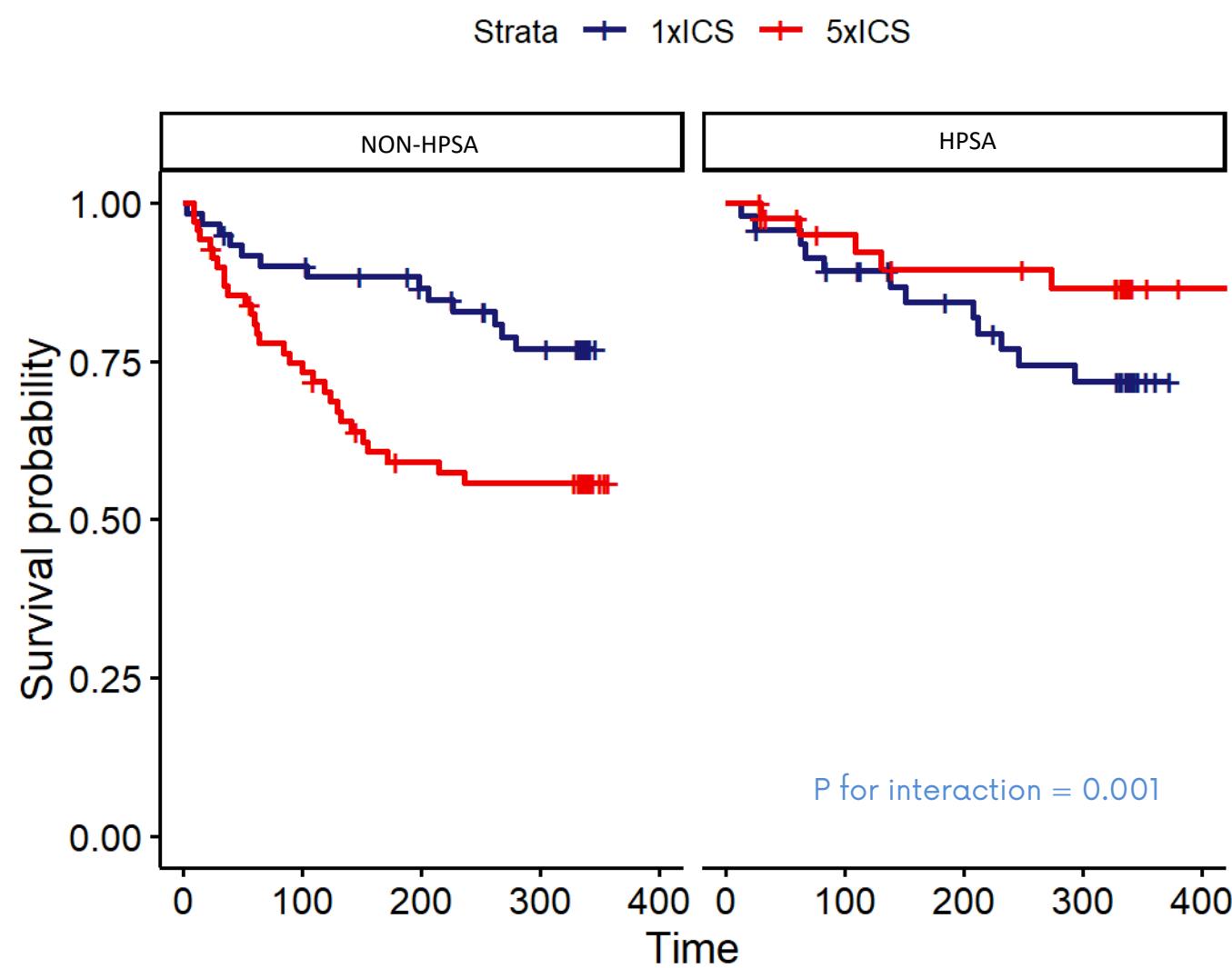
Time to Treatment Failure



STICS Ancillary Findings: Healthcare Access

Survival Curves

Time to First Exacerbation Treated with Prednisone



- Receiving a high dose of inhaled corticosteroid (vs low dose) while also living in areas with higher SES resulted in:

Taking prednisone sooner

AIM 2

How does air pollution exposure modify the association between receiving treatment and asthma in an underrepresented pediatric population?



AsthmaNet Trials

BARD

- Children (5-11) & Adults (>12+)
- African American
- 2014 – 2016
- N = 280
- Crossover Design
- Step up combination
 - Adding LABA to LOW vs HIGH ICS DOSE

AIM 2

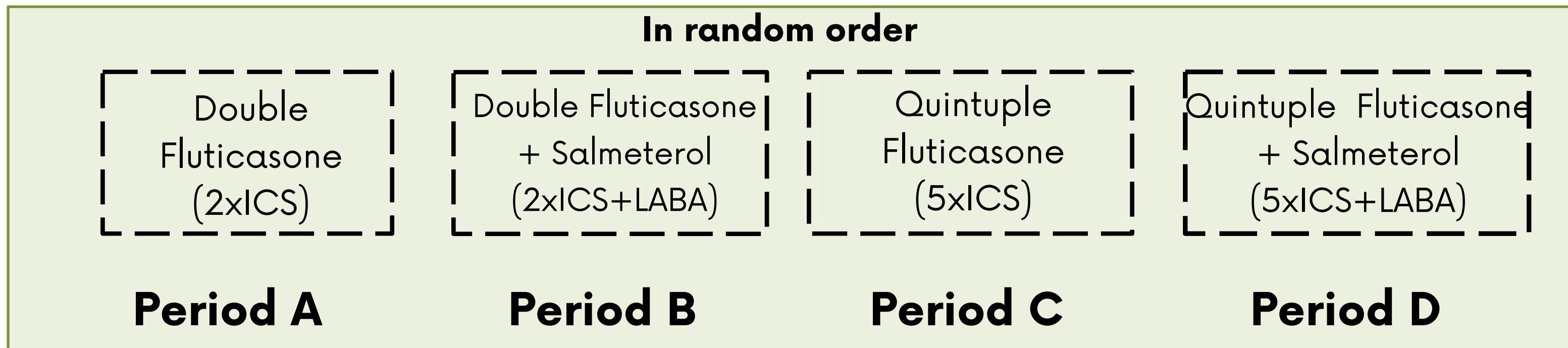
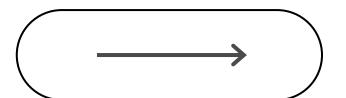
AGES 5-11 YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA



		Management of Persistent Asthma in Individuals Ages 5-11 Years						
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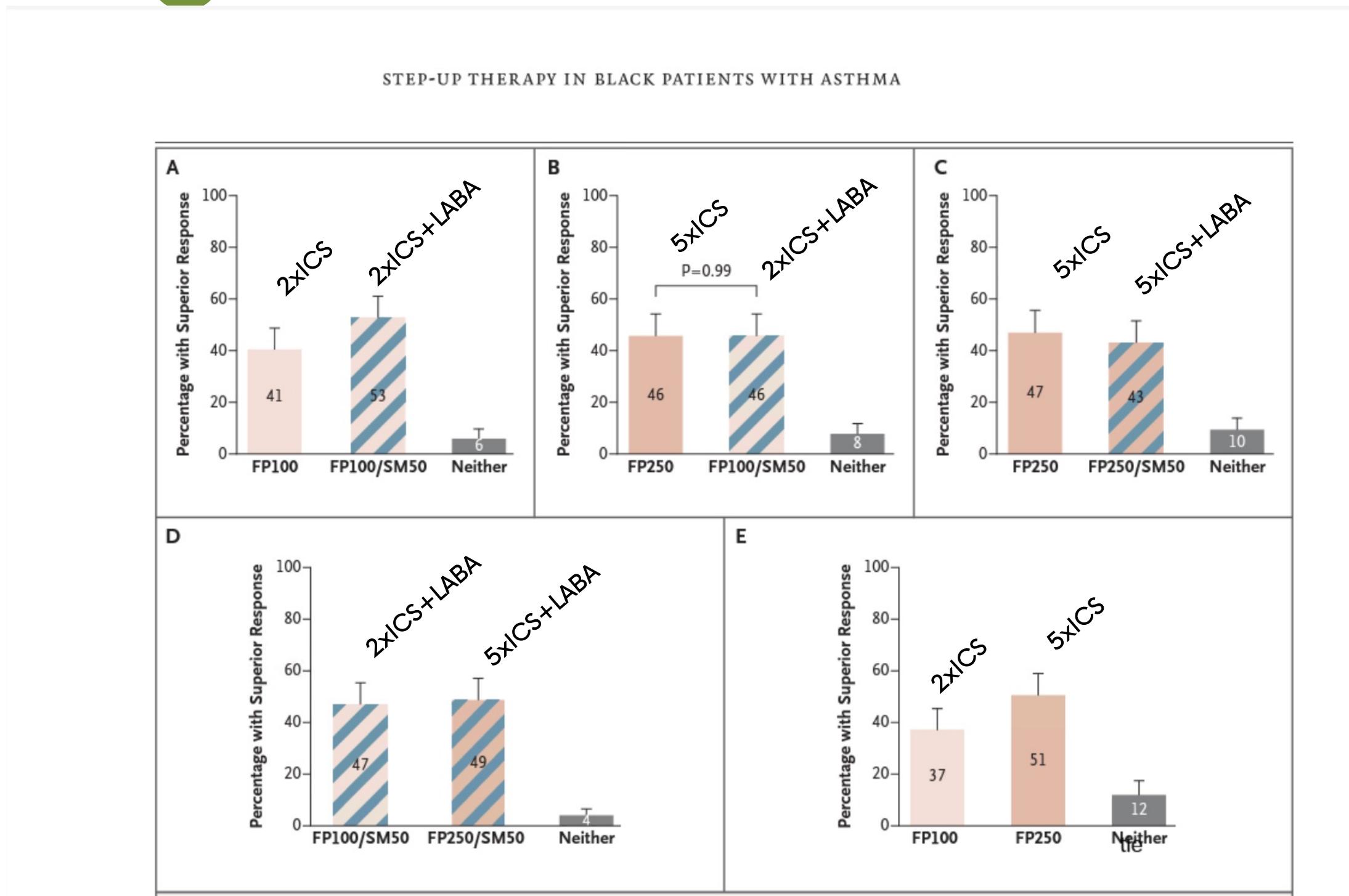
BARD Trial

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).

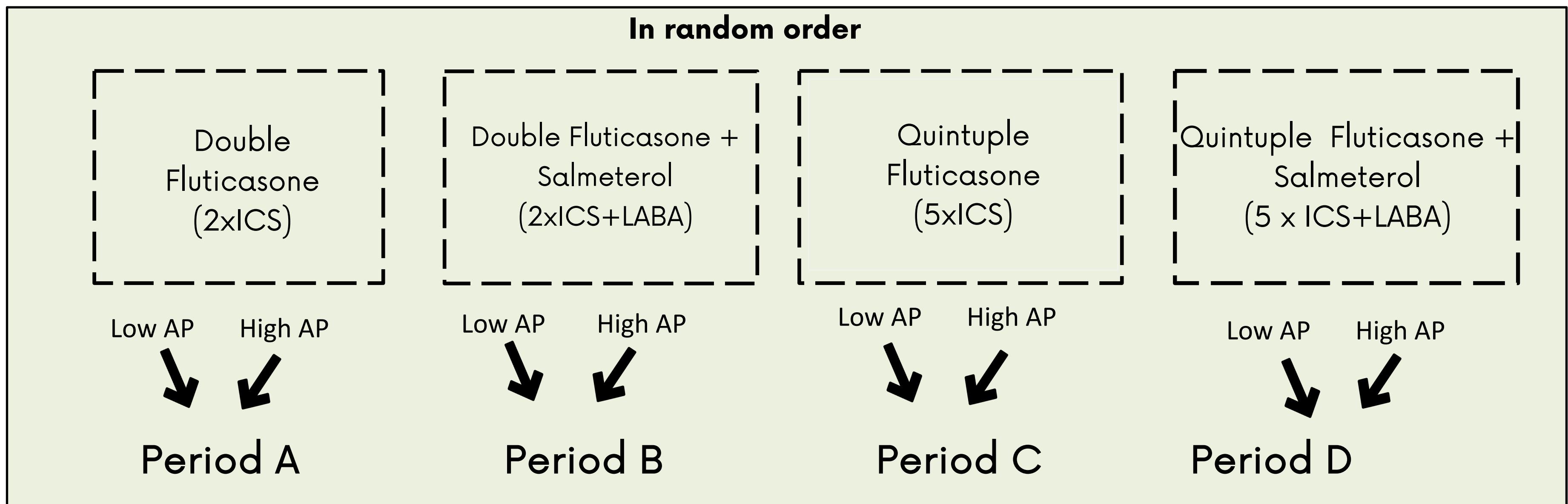
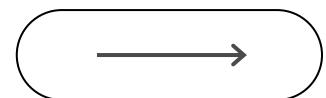
Original BARD Trial Findings



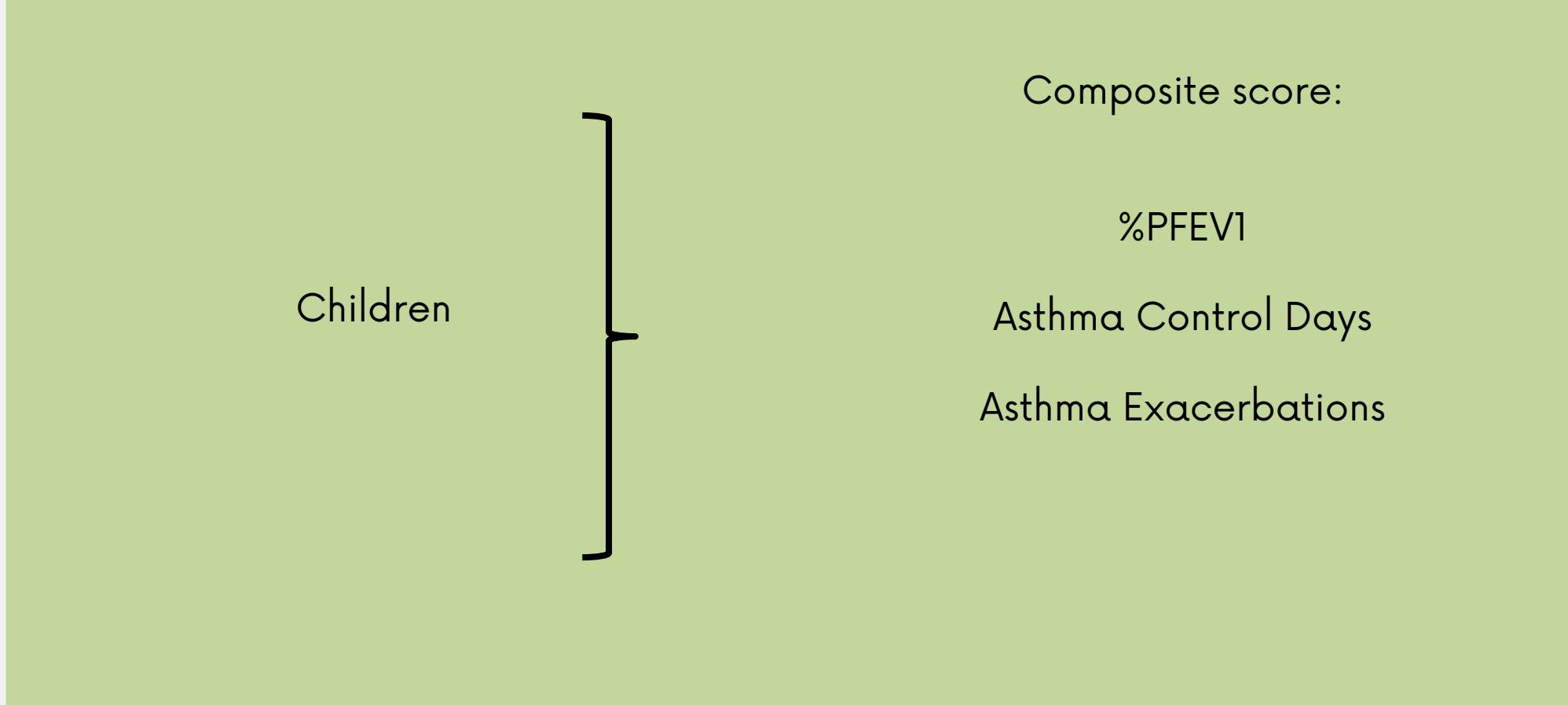
DOI: 10.1056/NEJMoa1905560

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



BARD Trial Reanalysis

Children

Composite score:
%PFEV1

Asthma Control Days

Asthma Exacerbations

Median Dichotomized Air Pollution Exposure

Treatment Period Specific

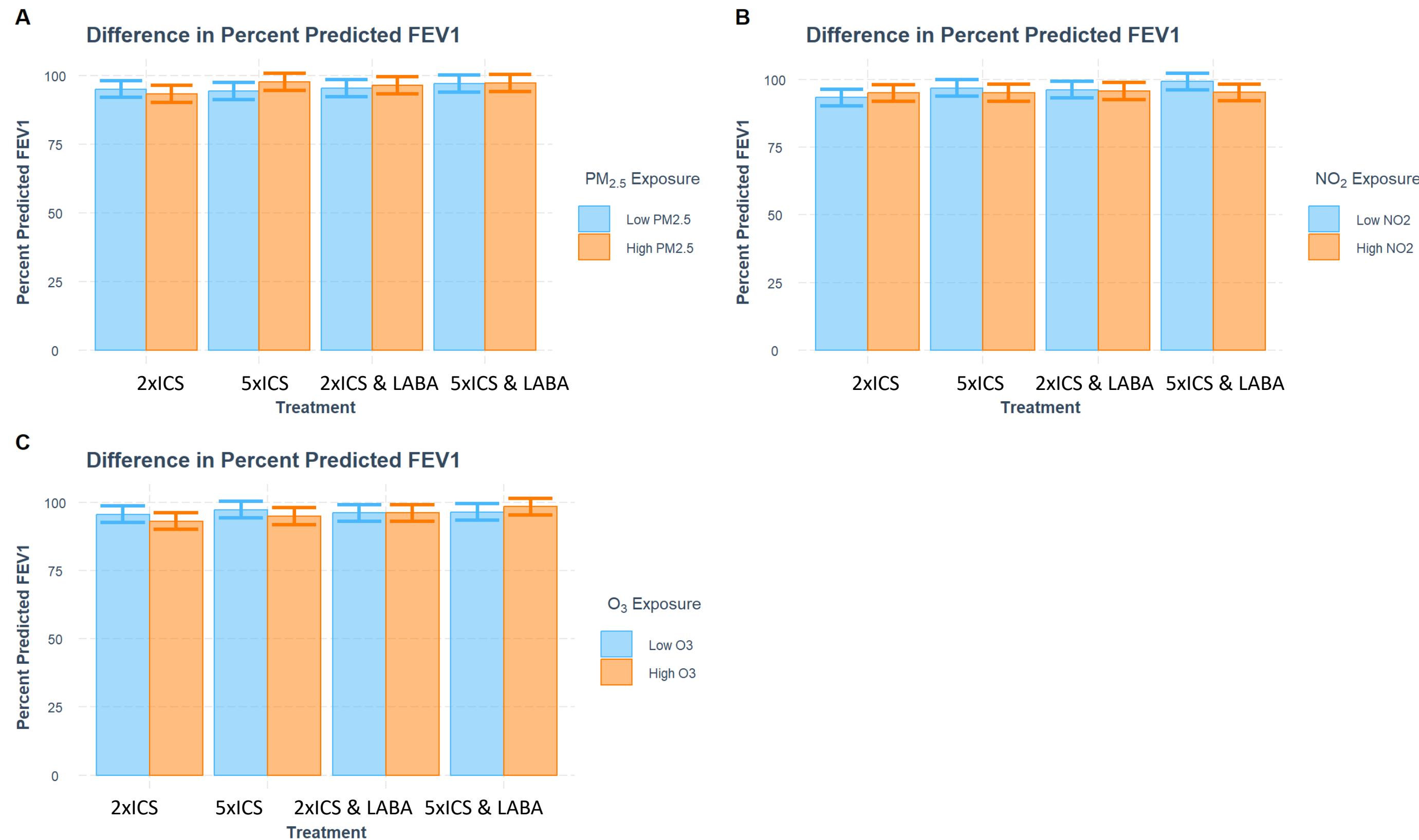
- $\text{PM}_{2.5}$
- NO_2
- O_3

Statistical Methods

Linear Mixed Models with Random Intercepts for
each individual

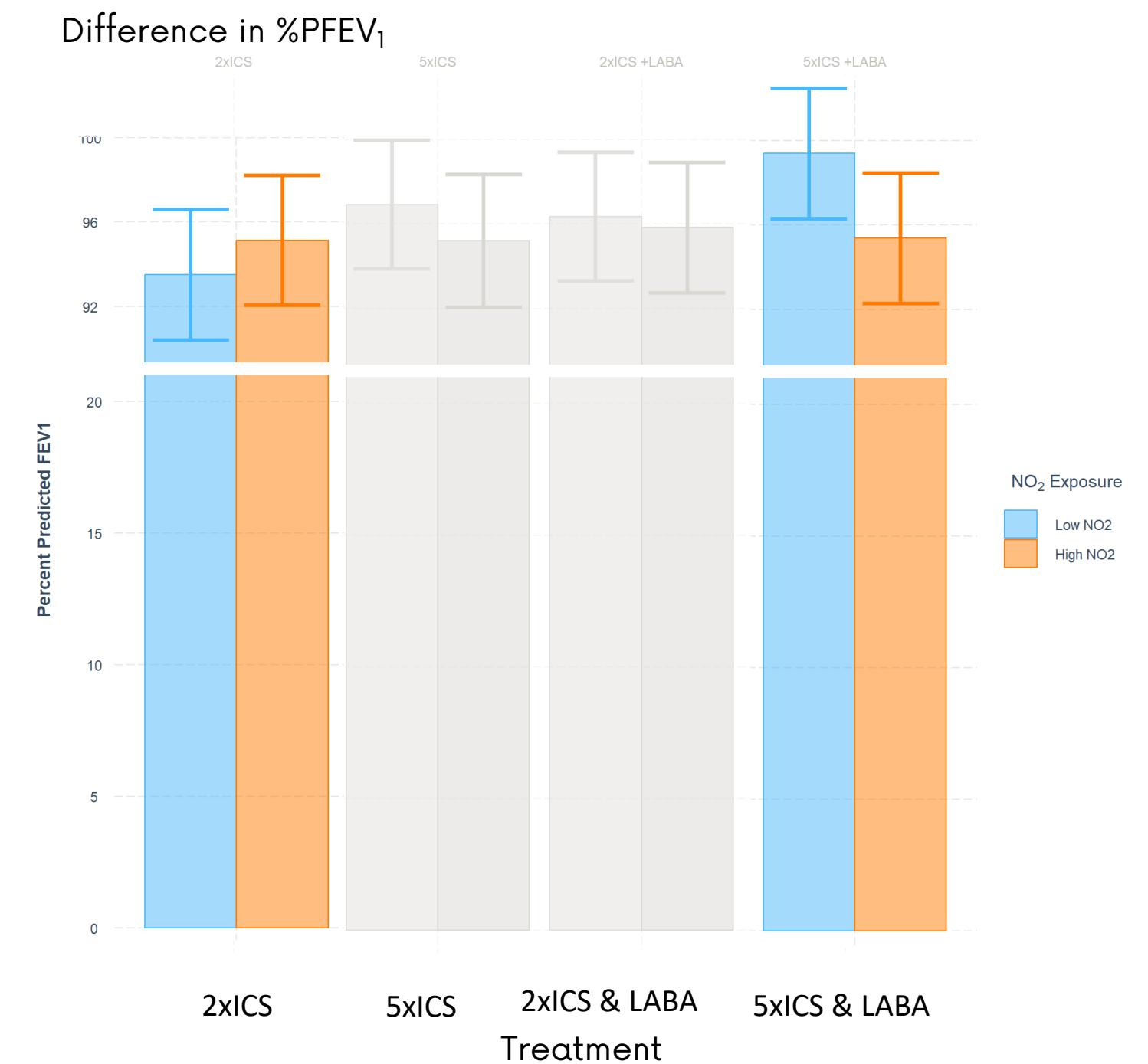
Poisson link function for asthma exacerbation
rate outcome

BARD Trial Ancillary Findings



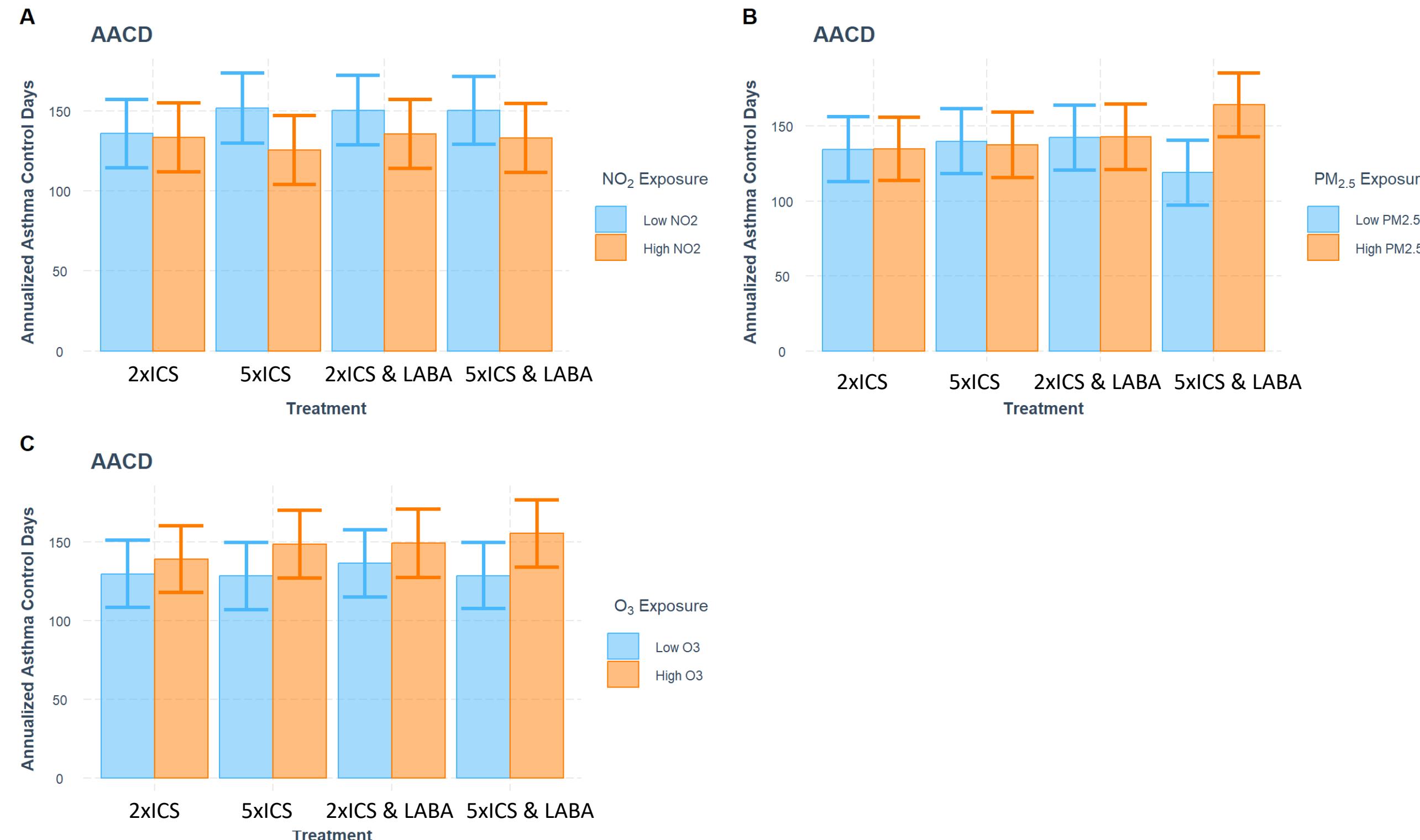
BARD Trial Ancillary Findings

- Compared to treatment with the lowest ICS dose, treatment with the 5xICS & LABA results in:
Increase in %PFEV₁ only among low NO₂
No benefits of the 5xICS & LABA among those exposed to High NO₂



p for interaction = 0.05

BARD Trial Ancillary Findings

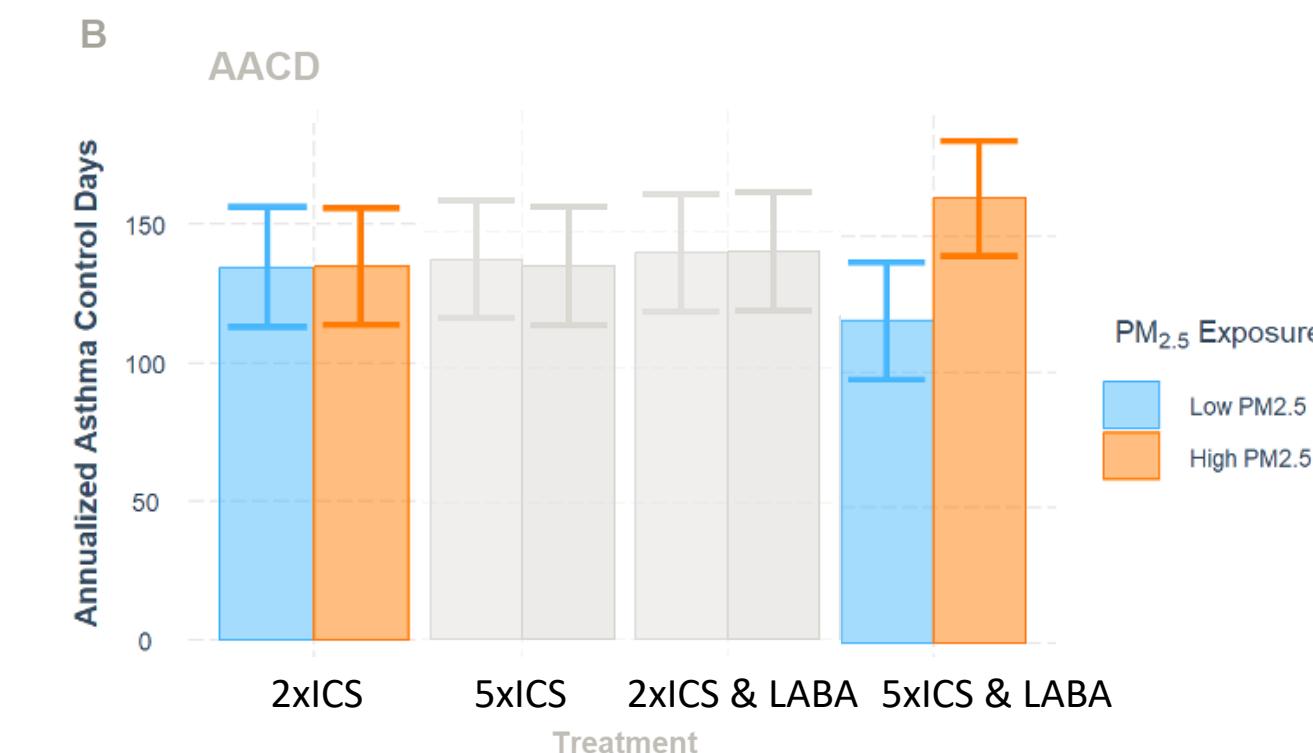


BARD Trial Ancillary Findings

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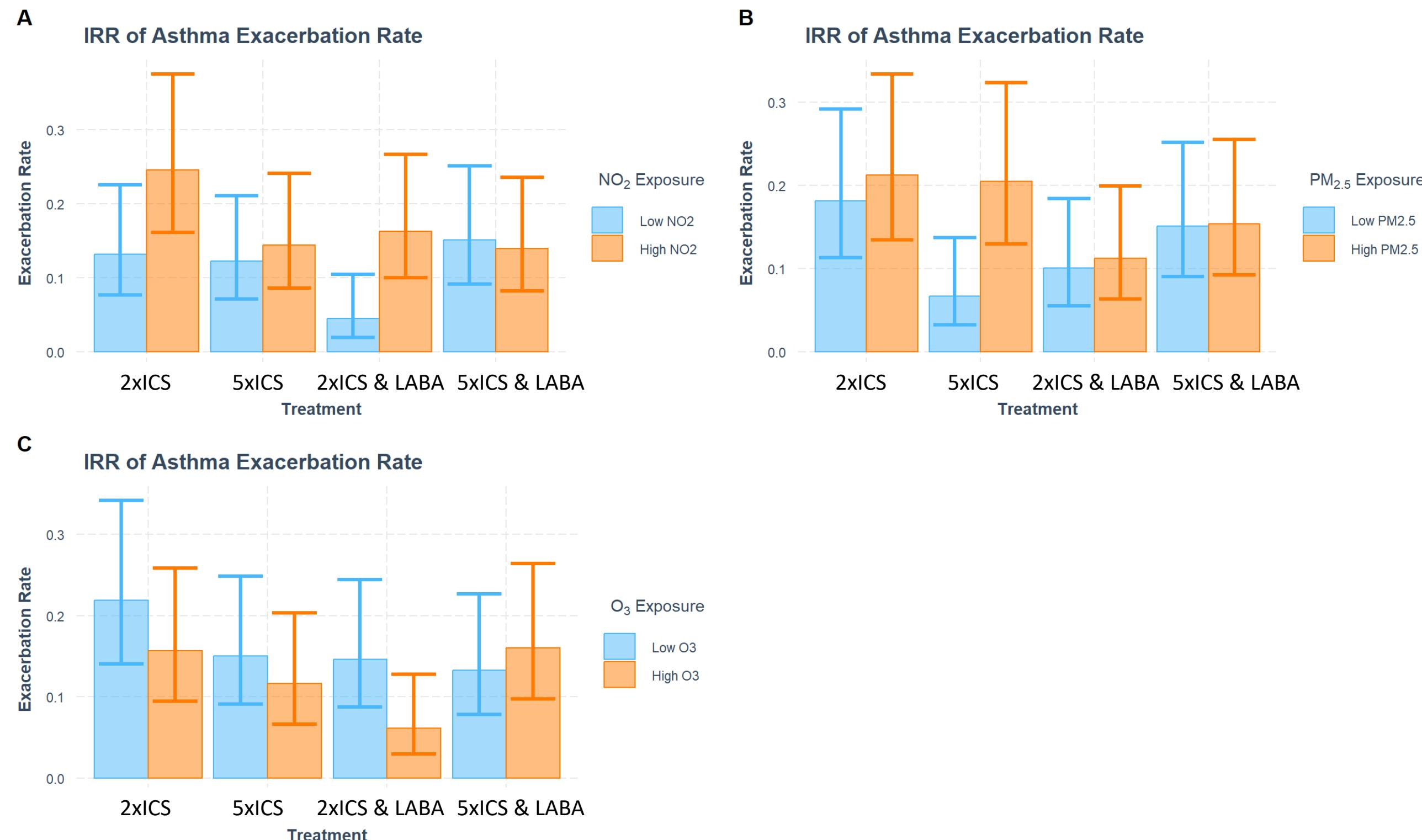
Increase asthma control only among high PM_{2.5}

Decreased control in the 5xICS & LABA among those exposed to Low PM_{2.5}



p for interaction = 0.01

BARD Trial Ancillary Findings



BARD Ancillary Findings: Takeaways

Effect Modification: Treatment efficacy varied based on air pollution levels.

Treatment Observations:

- Compared to the lowest ICS dose:
 - 5xICS+LABA improved lung function mainly in Low-NO₂ areas
 - 5xICS+LABA yielded more asthma control in High-PM_{2.5} areas

AIM 3

How do asthma phenotypes and medication modify the association between air pollution exposure and asthma symptoms in adults with persistent asthma?



AsthmaNet Trials

SIENA

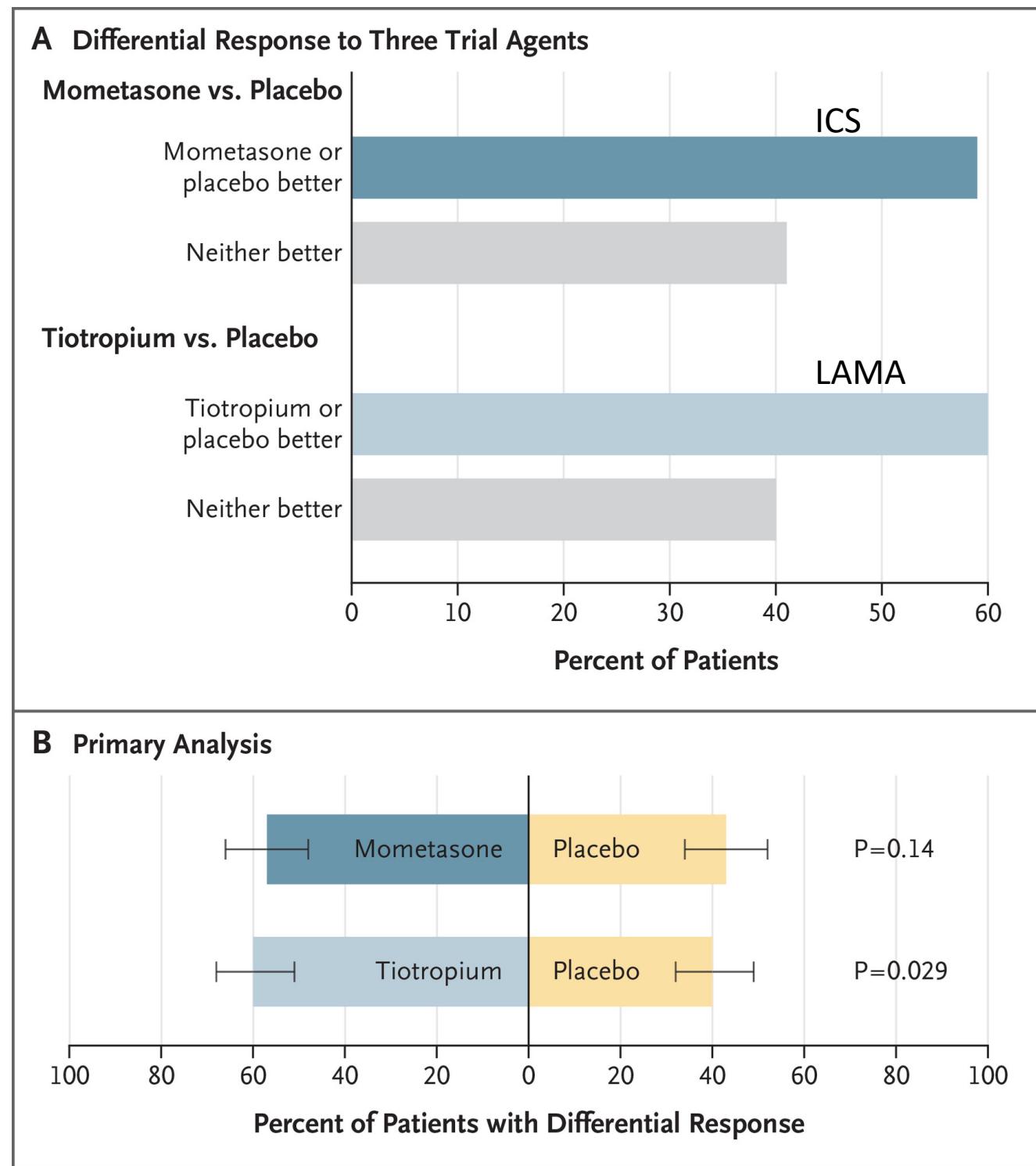
- Adolescents and Adults
- Asthma Phenotype
- 2014 – 2018
- N = 295
- Crossover Design
 - Treatment with ICS or LAMA vs Placebo

Recommended Treatments for Asthma

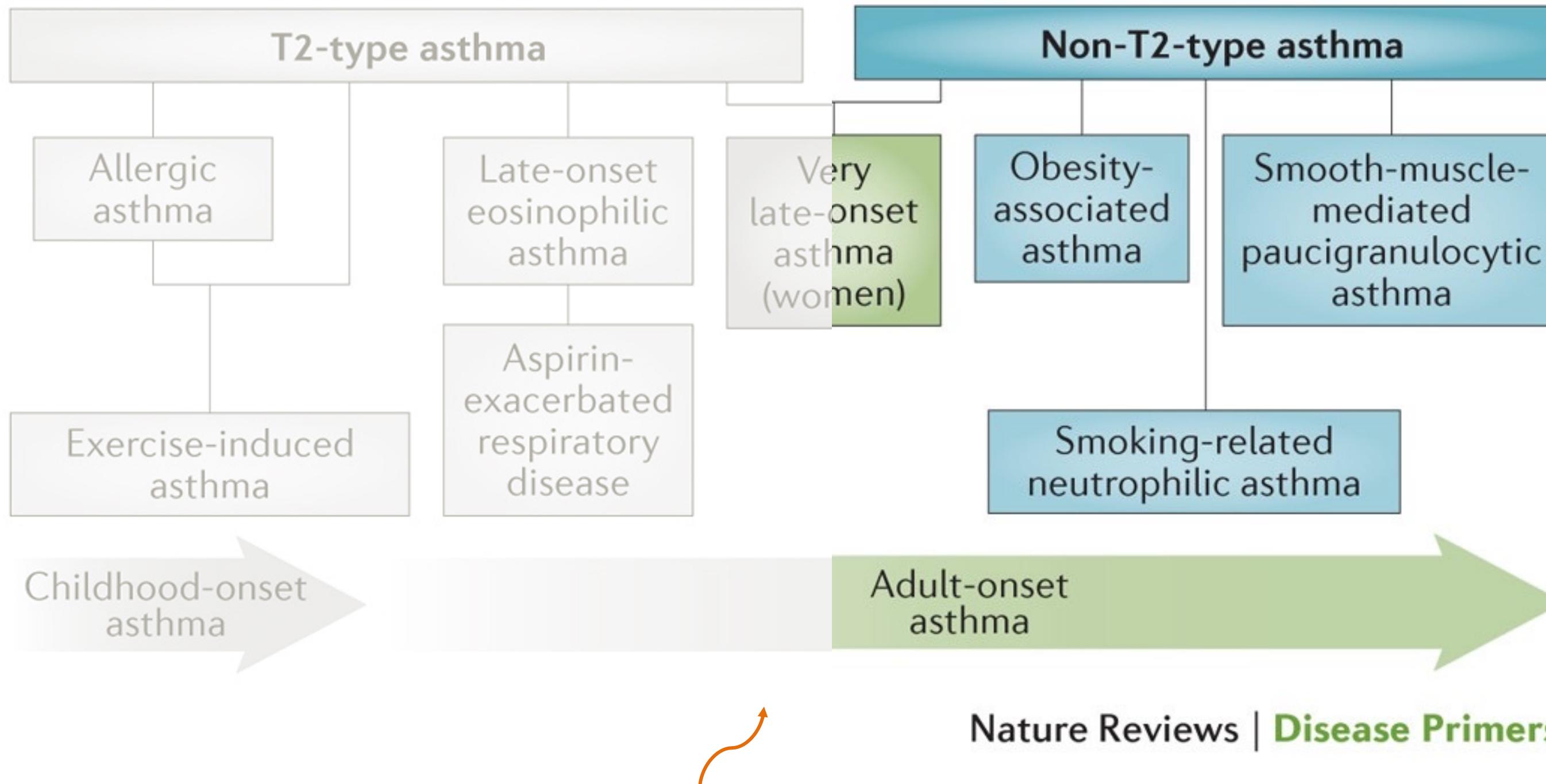
AIM 3

Intermittent Asthma		Management of Persistent Asthma in Individuals Ages 12+ Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* 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 adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**					

SIENA Trial

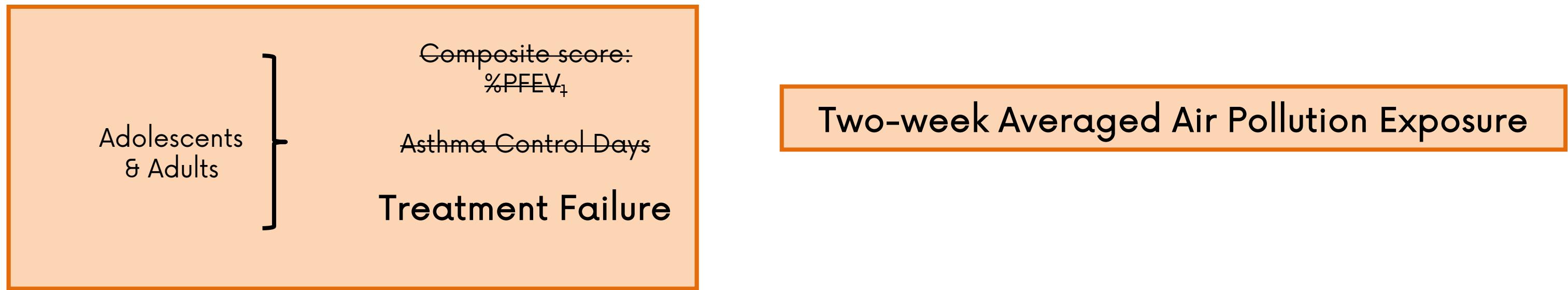


Asthma phenotypes and endotypes



Our Approach

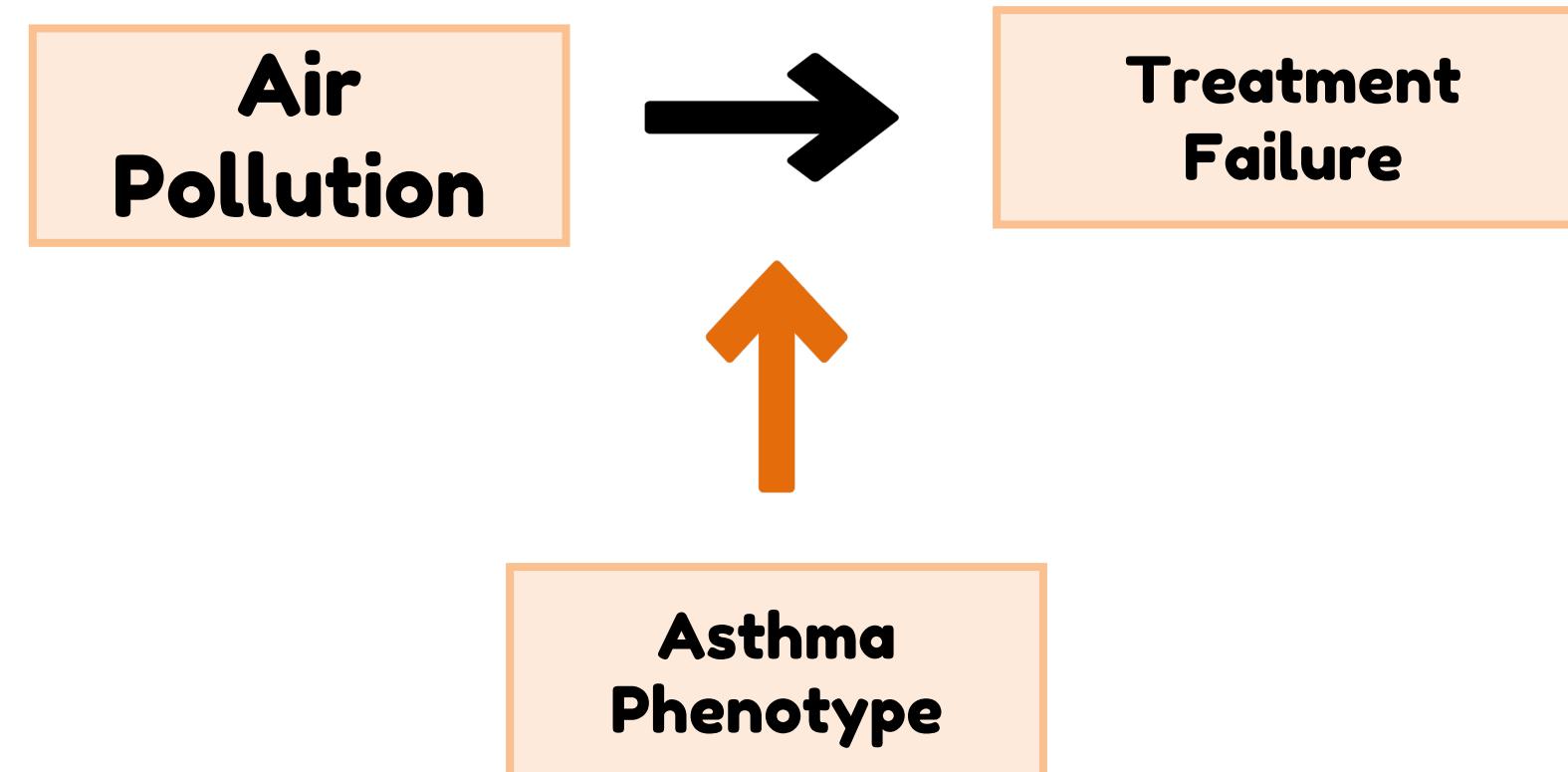
Is there a difference in the effect of air pollution exposure on Asthma Treatment Failure by eosinophilic status?



Generalized Linear Mixed Models random intercept for each individual

Questions

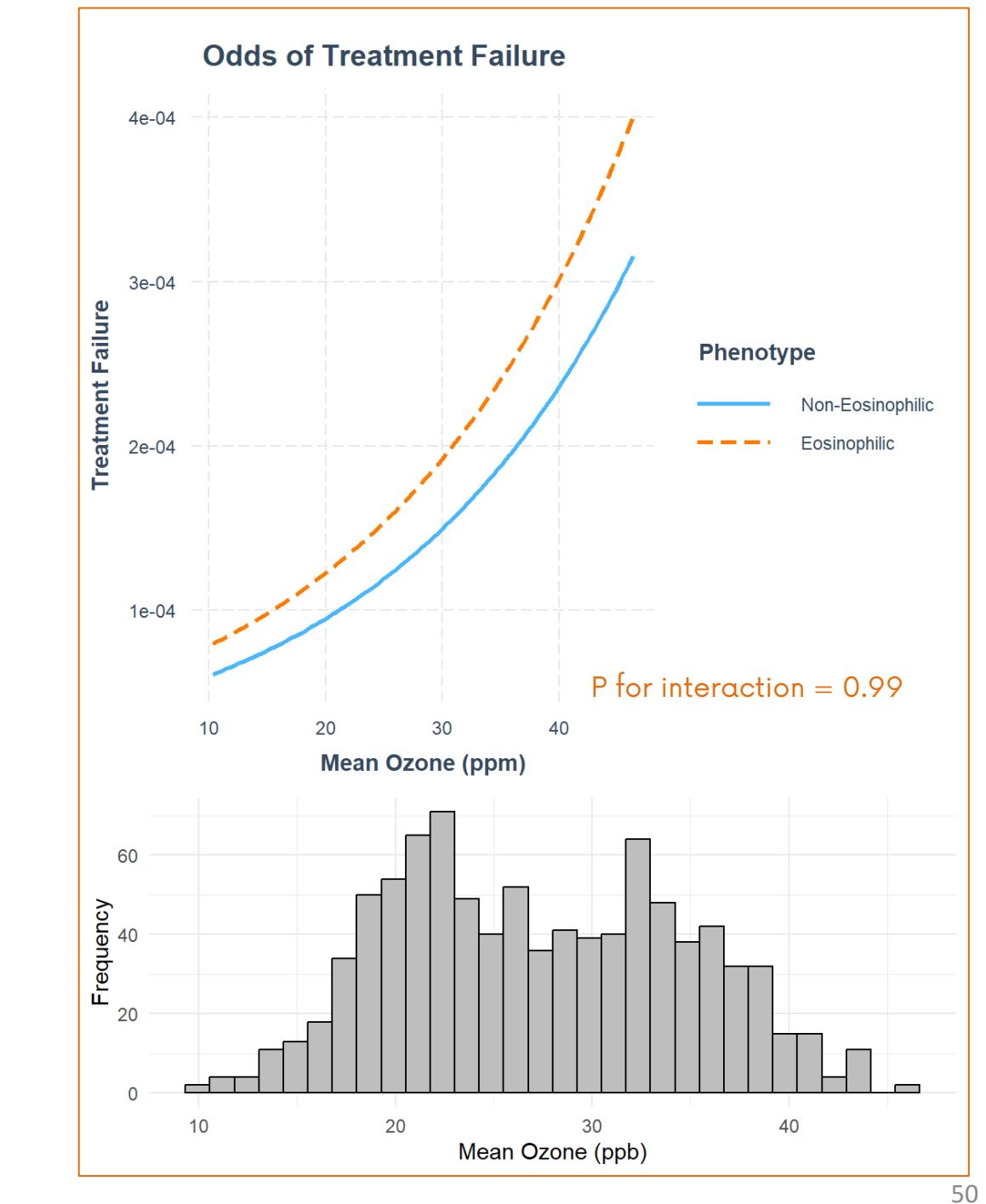
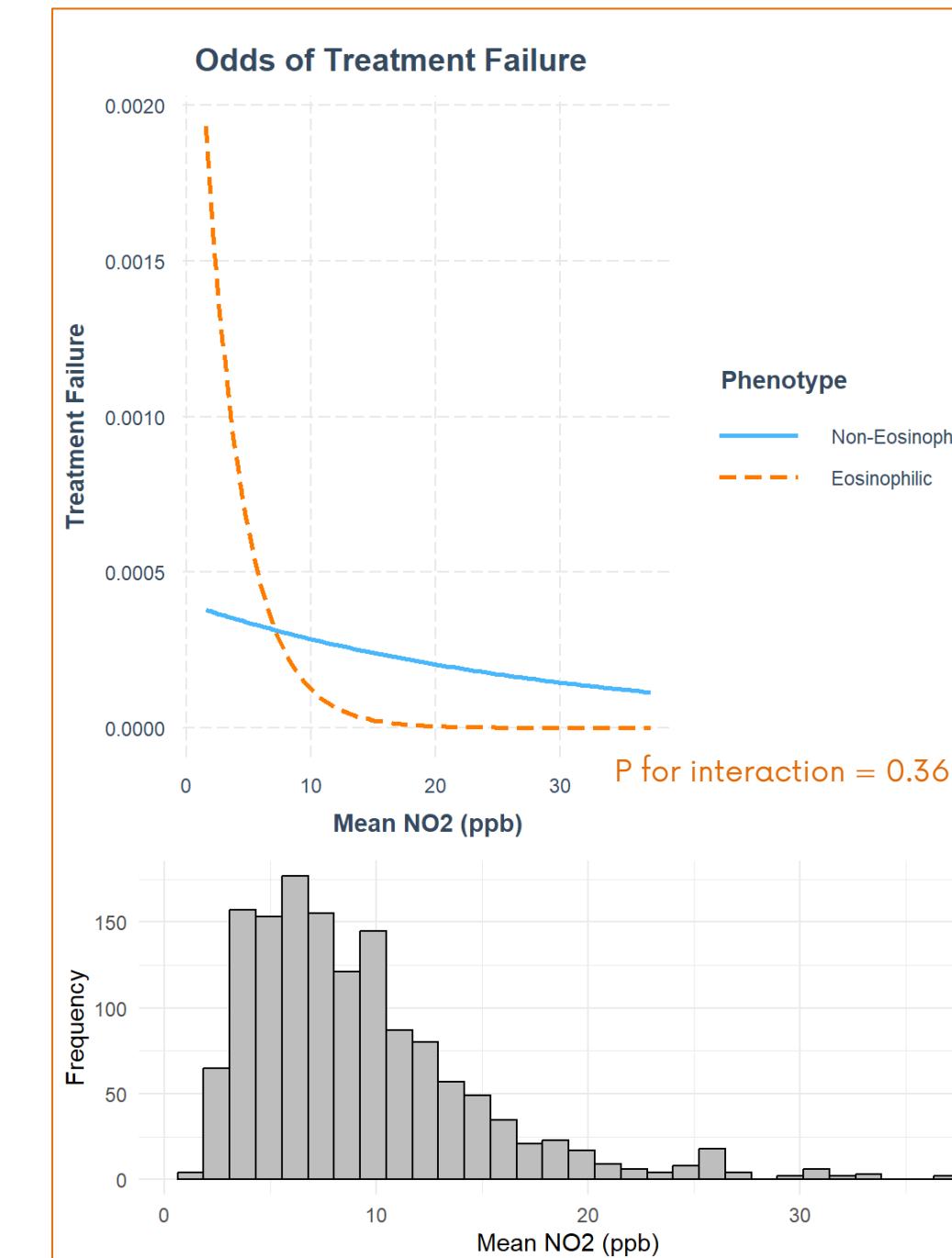
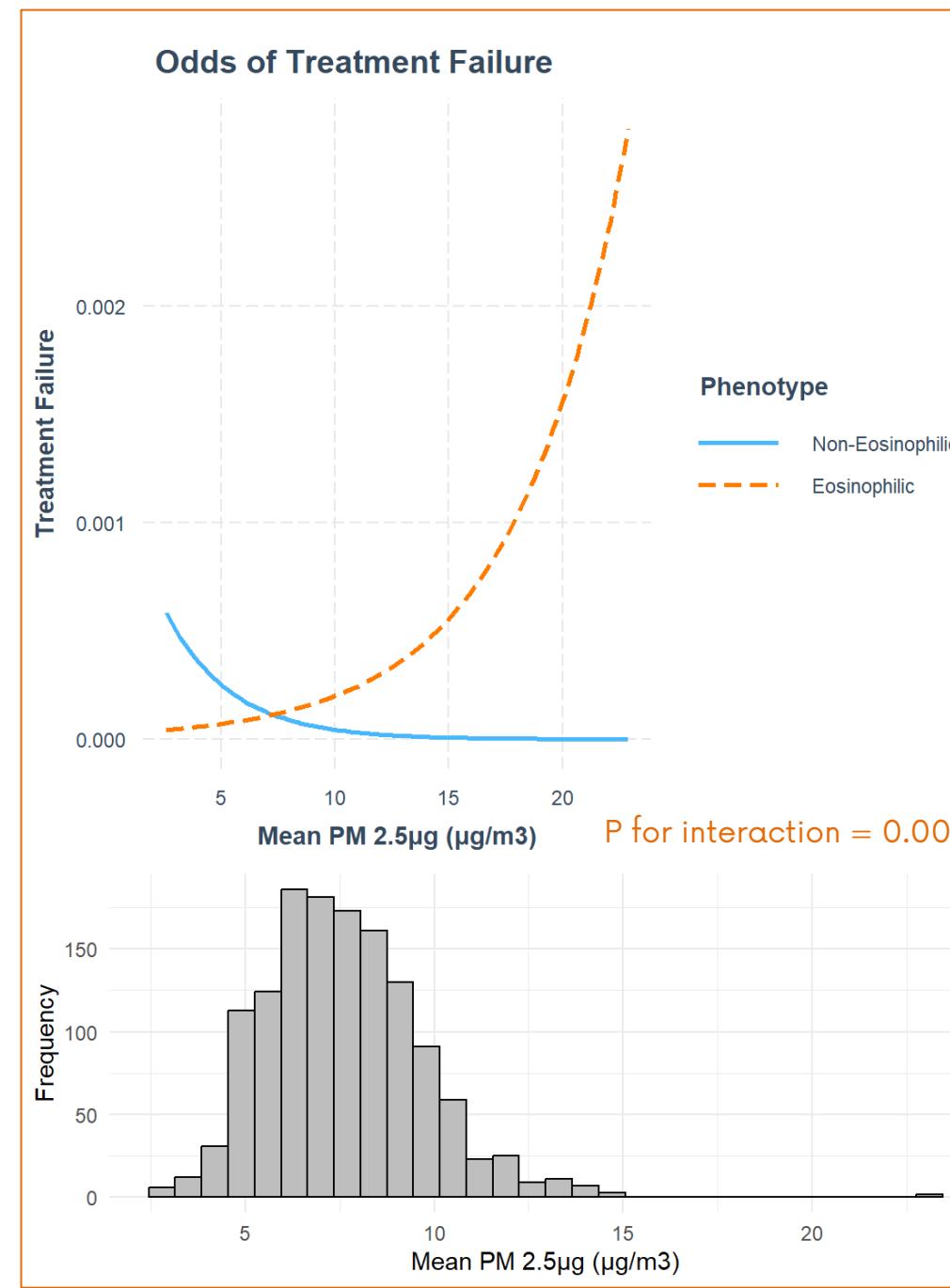
Is there a difference in the effect of air pollution exposure on Asthma Treatment Failure by eosinophilic status?



SIENA Ancillary Findings

Effect Modification by Phenotype

AIM 3

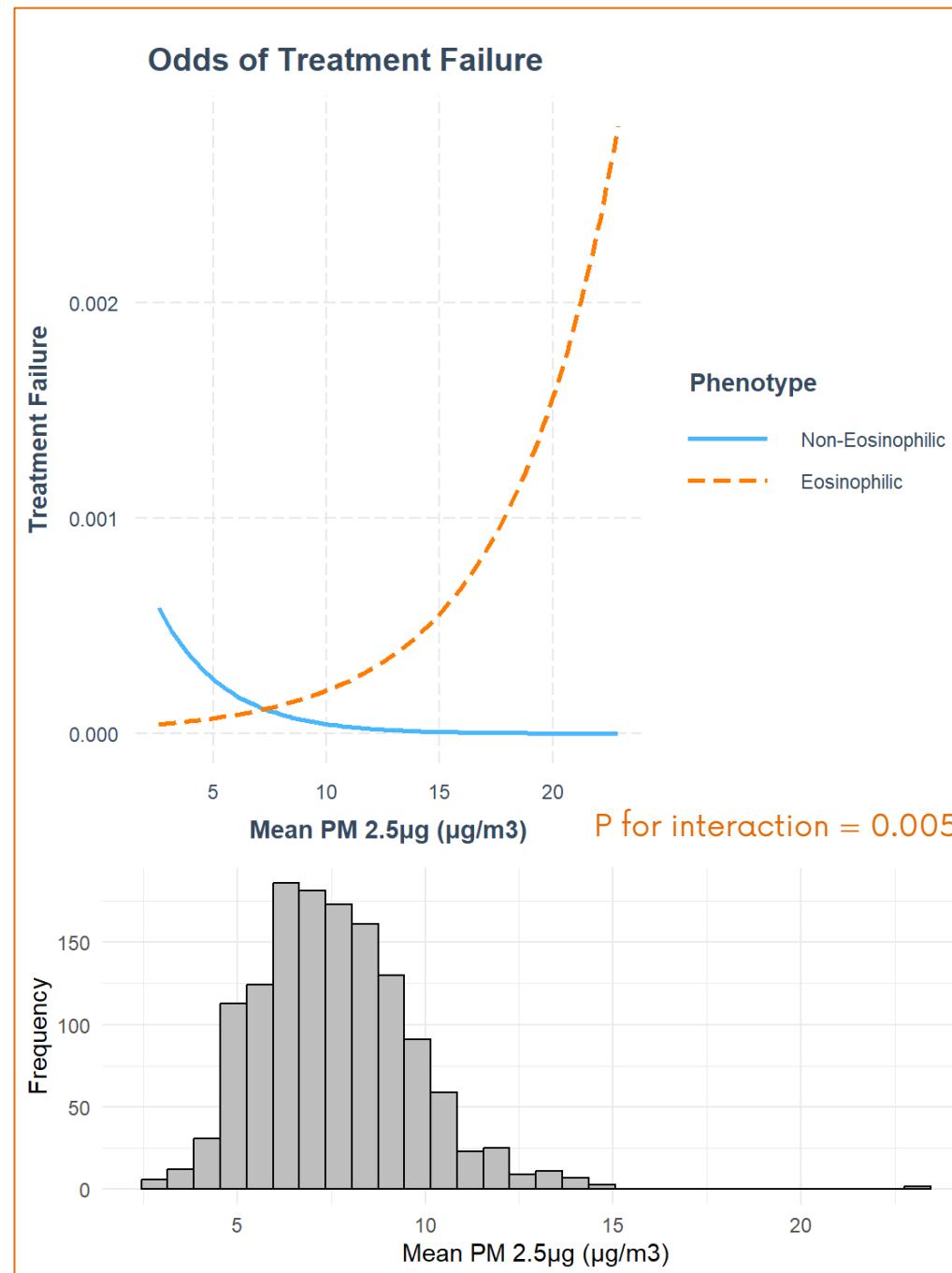


Models adjusted for baseline provocative concentration of inhaled methacholine (PC20), Median fraction of exhaled nitric oxide, eczema or atopic dermatitis, HPSA, MUA, % Below Poverty Line

SIENA Ancillary Findings

Effect Modification by Phenotype

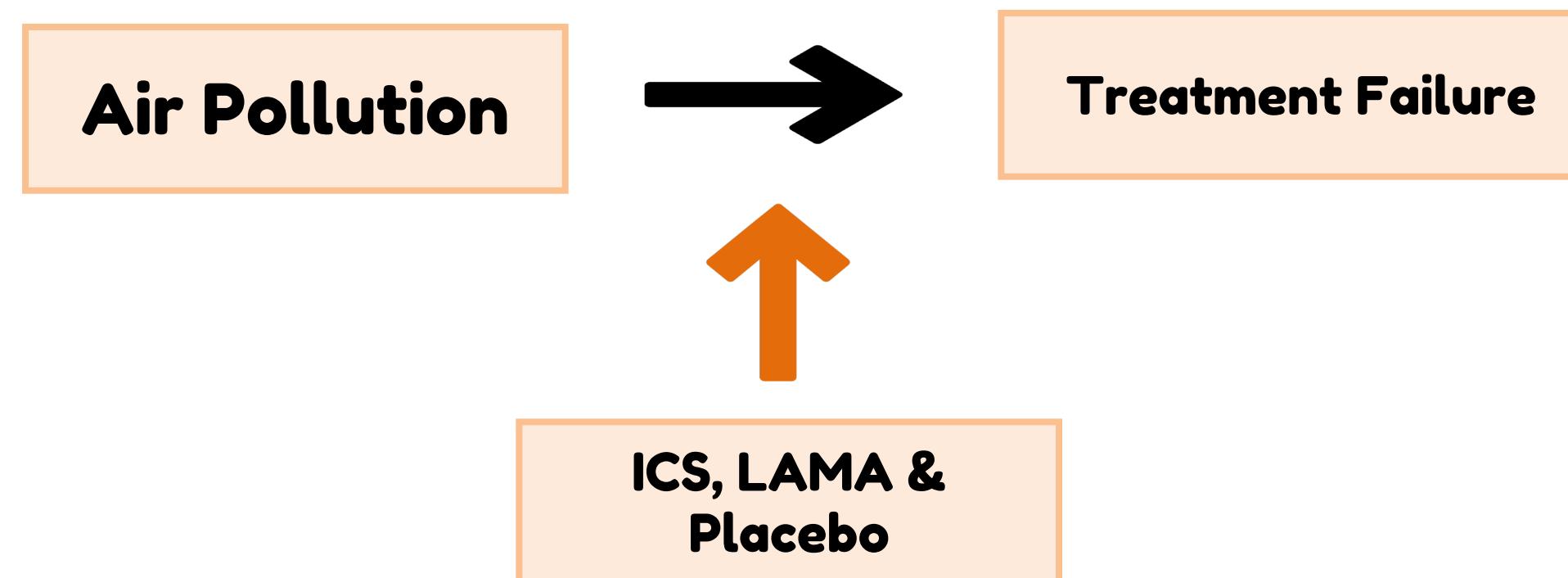
AIM 3



- Compared to eosinophilic asthma participants, non-eos participants had:
Decrease in the odds of treatment failure as PM_{2.5} increased

Research Question

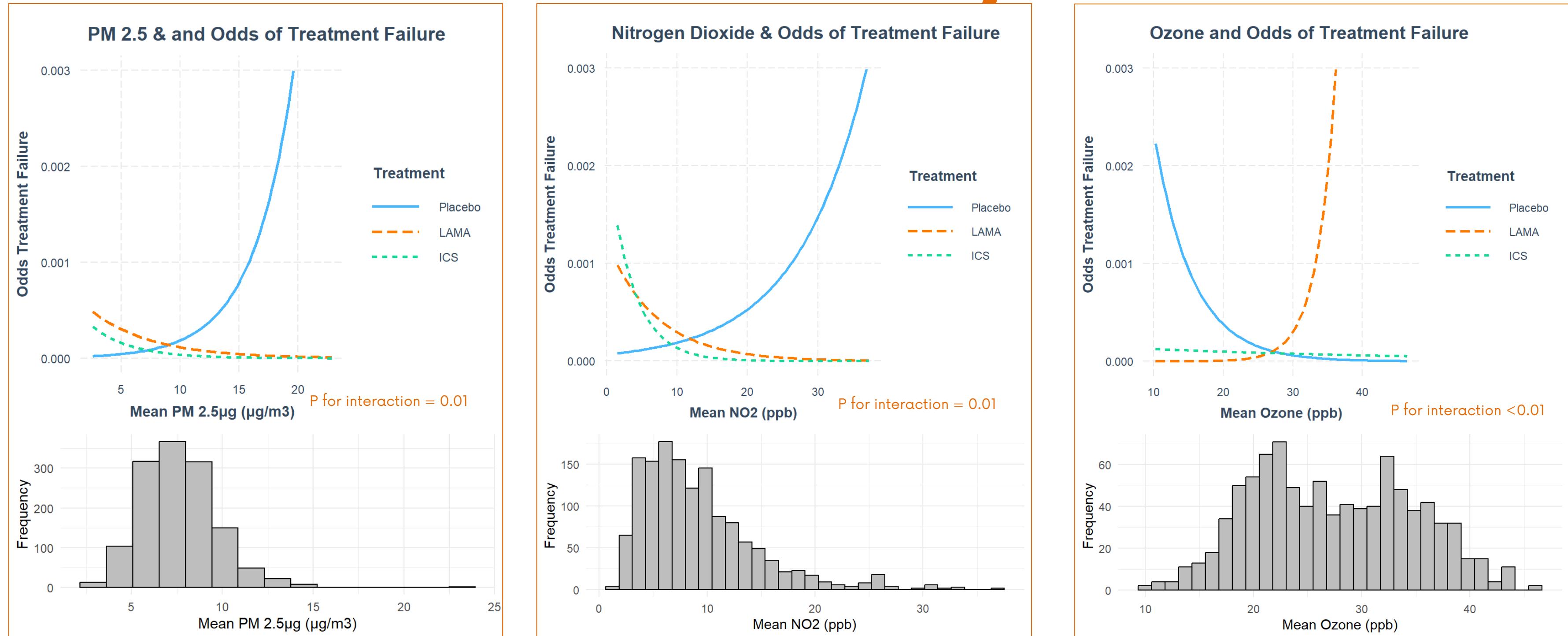
What is the effect of exposure to air pollution on Treatment Failure as modified by medication with ICS and LAMA compared to placebo?



SIENA Ancillary Findings

Effect Modification by Medication

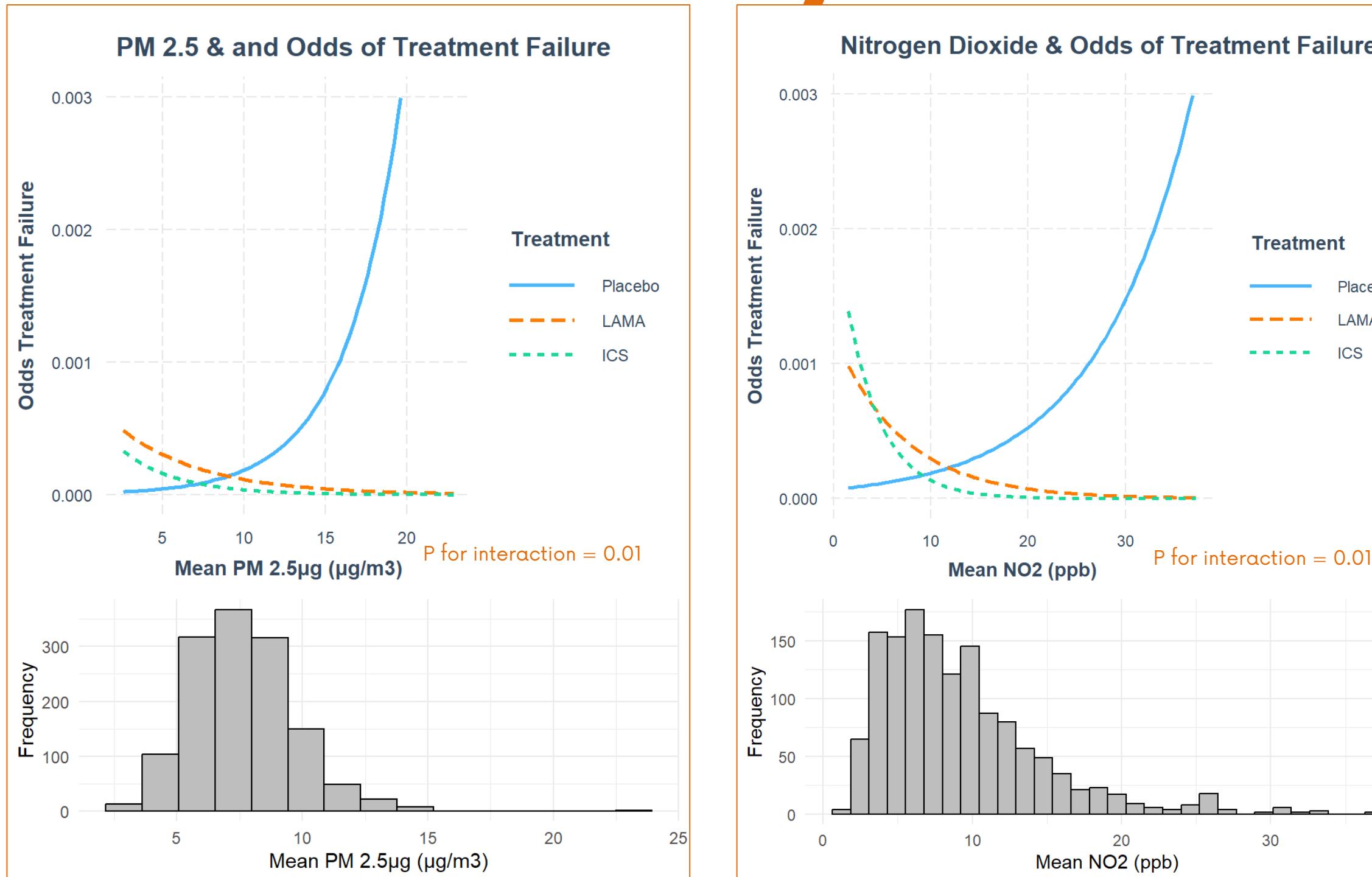
AIM 3



Models adjusted for baseline provocative concentration of inhaled methacholine (PC₂₀), Median fraction of exhaled nitric oxide, eczema or atopic dermatitis, HPSA, MUA, % Below Poverty Line

Results: Effect Modification by Medication

AIM 3



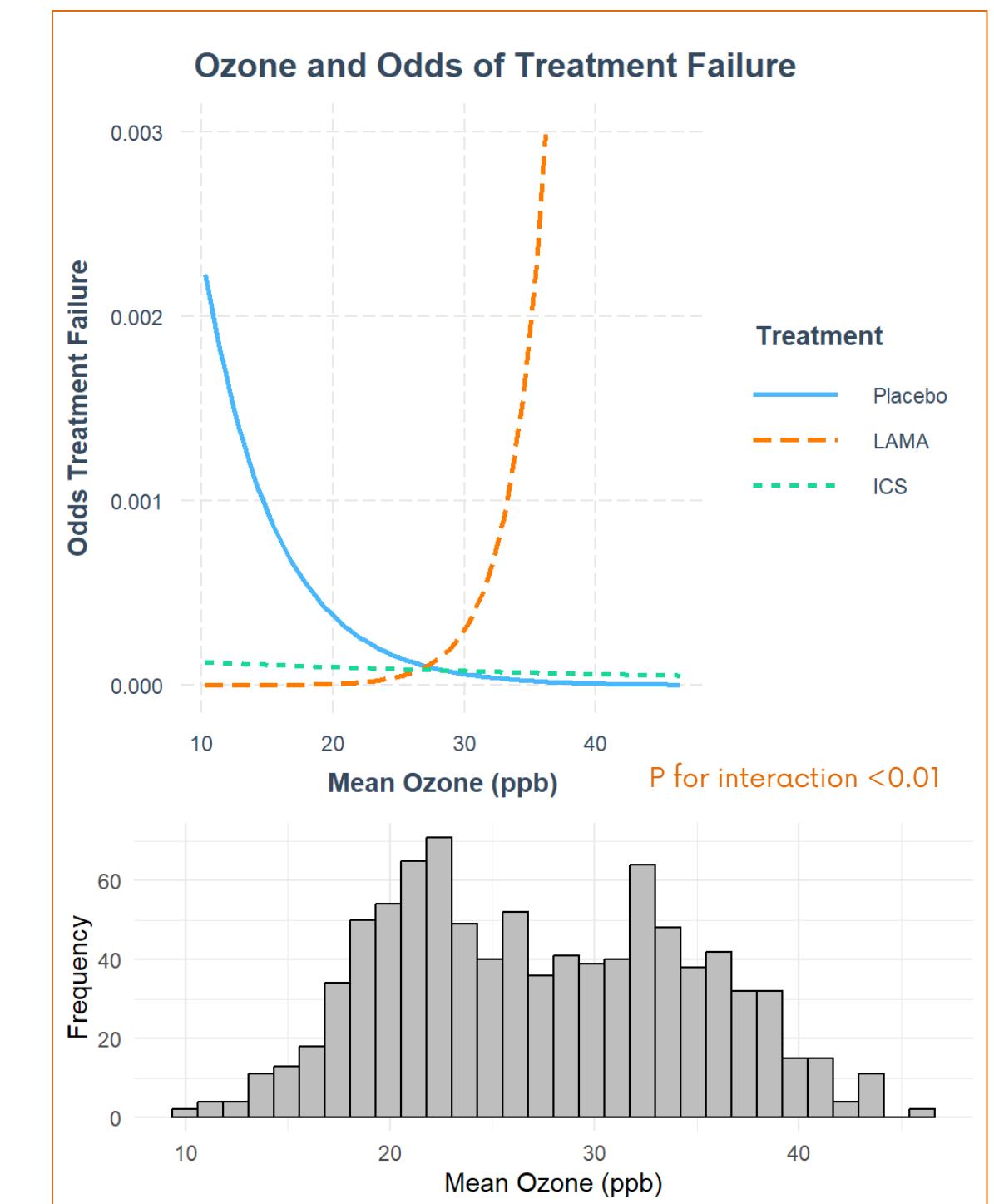
- As $\text{PM}_{2.5}$ and NO_2 increased:
 - Treatment with ICS and LAMA, (compared to Placebo) resulted in a **decrease in the odds of treatment failure**

Models adjusted for baseline provocative concentration of inhaled methacholine (PC20), Median fraction of exhaled nitric oxide, eczema or atopic dermatitis, HPSA, MUA, % Below Poverty Line

Results: Effect Modification by Medication

AIM 3

- As O_3 increased:
 - Treatment with LAMA, (compared to Placebo) resulted in a increase in the odds of treatment failure



Models adjusted for baseline provocative concentration of inhaled methacholine (PC₂₀), Median fraction of exhaled nitric oxide, eczema or atopic dermatitis, HPSA, MUA, % Below Poverty Line

SIENA Ancillary Findings

Takeaways

- Asthma phenotypes modified the association between PM_{2.5} and treatment failure.
 - ↑PM_{2.5} Worse for people with eosinophilic asthma, compared to non-eosinophilic
- Treatment significantly modified the association between PM_{2.5}, NO₂ and O₃ exposure and the odds of treatment failure

Overall Findings

- Evidence that underscores socio-environmental influence on treatment response in children
- In adults, we show increased exposure to PM_{2.5} differentially impacts asthma depending on eosinophilic status
- Identify a gap in asthma treatment and management



Limitations

- Post hoc analyses
- Participant retention
- Applicability of findings

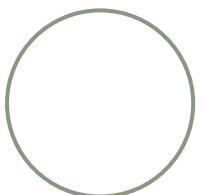
Strengths

- Focus on vulnerable populations
- Data richness & integration
- Innovative approach

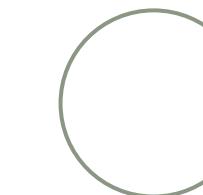
Implications

- Comprehensive treatment plans
- Contribution to the field of environmental health and clinical practice
 - Concurrent public health and clinical practices
 - Efficacy and effectiveness gap

Acknowledgments



Jane E. Clougherty, ScD, MSc

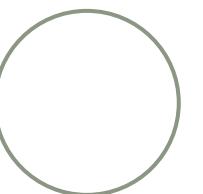


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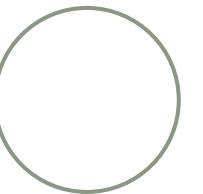
Fernando Holguin, MD, MPH

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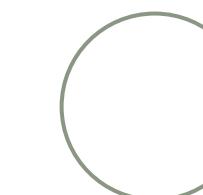


Joel Kaufman MD, MPH &
Michael T. Young, PhD

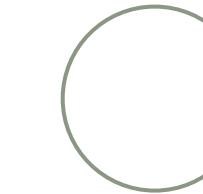


AsthmaNet Participants &
Research Coordinators

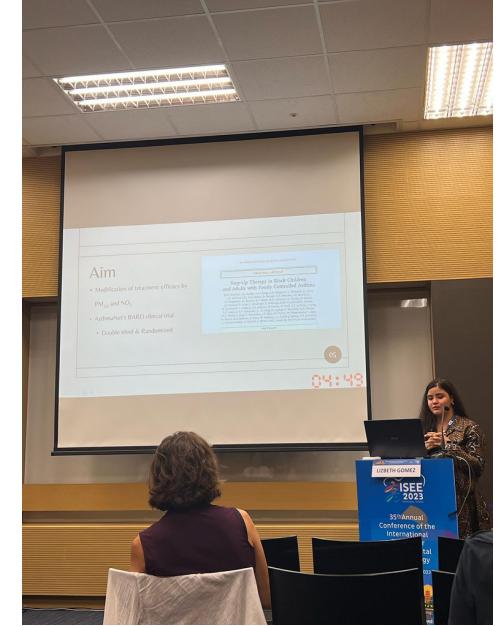
Funding
EOH Department



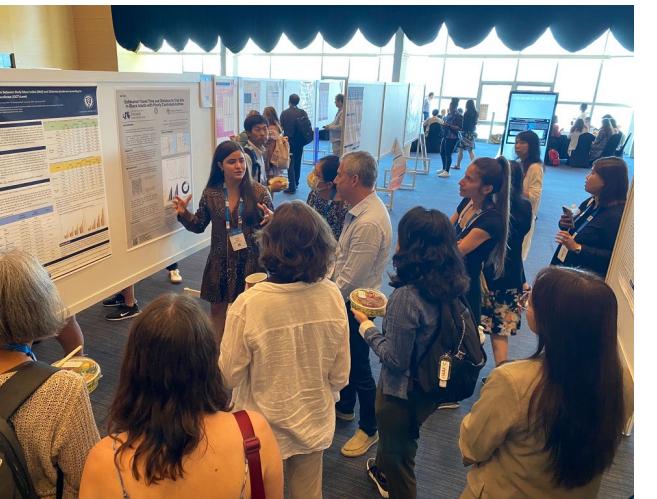
Mentors (Past & Present)
GATHER Training
PrIMER Training



Peers and Colleagues
Family
Friends



THANK YOU



Questions?



More Questions?

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