Drivers of Asthma in School Children

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March 22, 2024 11:55-12:30

Severe Asthma Update

S. Jean Emans, MD, Professor of Pediatrics
Harvard Medical School
Director, Clinical Research Center
Asthma, Allergy, & Immunology
Dermatology & Rheumatology
Boston Children's Hospital

HARVARD
MEDICAL SCHOOL

Disclosures

- ABAI Board of Directors, Secretary, and CAP-Co-Chair and MOC Co-Chair
- AAAAI Board of Directors
- Consulting GSK, Genentech, Novartis, Sanofi, Regeneron, Teva, Astra Zeneca- asthma therapies
- NIH funding

Objective

1. To understand the relevance of home and school exposures and other drivers and social determinants of asthma in school children
2. To identify interventions targeting the environment and supporting policies and change in support of schools
3. To take what we learned in schools to personalized strategies for difficult to control asthma

Case

- 7-year old Puerto Rican boy with frequent wheezing episodes.
- Referred to A/I/P specialist but has “no showed” to these two scheduled visits.
- Parents are divorced and mother immigrated 18 months ago
- Lapse in Medicaid coverage after family evicted from apt as landlord didn’t pay mortgage
- Lives in a shelter near a major expressway
- Flovent 110mcg 2puffs twice daily – w/o spacer (no access)
- Allergen skin testing demonstrates positives to mouse allergen and dust mite
- He attends an urban school and notices his asthma symptoms are more pronounced at school

What are some of the drivers of asthma to consider in this scenario?

- **Social determinants** of health (SDOH) defined by WHO as "conditions in which people are born, grow up, live, work and age.
- Influence health, risk of illness and life expectancy.
- Social inequities in health–the unfair and avoidable differences in health status across groups in society– due to uneven distribution of social determinants.

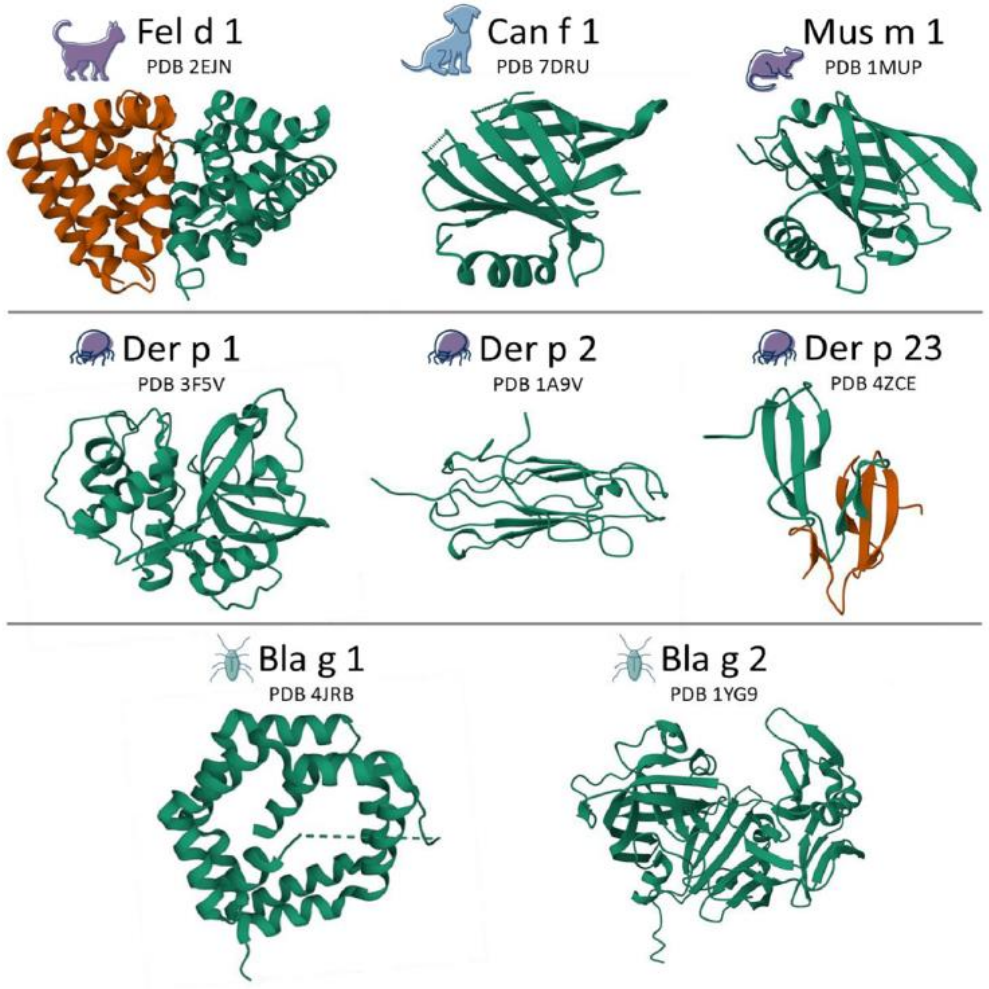
Davis et al JACI 2021, https://health.gov/healthypeople/objectives-and-data/social-determinants-health, https://www.cdc.gov/healthyyouth/disparities/index.htm

Addressing Drivers of Asthma by Focusing on Children's Environments

For the past 20 Dr. Wanda Phipatanakul has been asking why asthma hits so hard in urban and lower-income areas. (Image: AdobeStock/Illustration: Sebastian Stankiewicz, Boston Children's Hospital)

https://answers.childrenshospital.org/asthma-inequities/

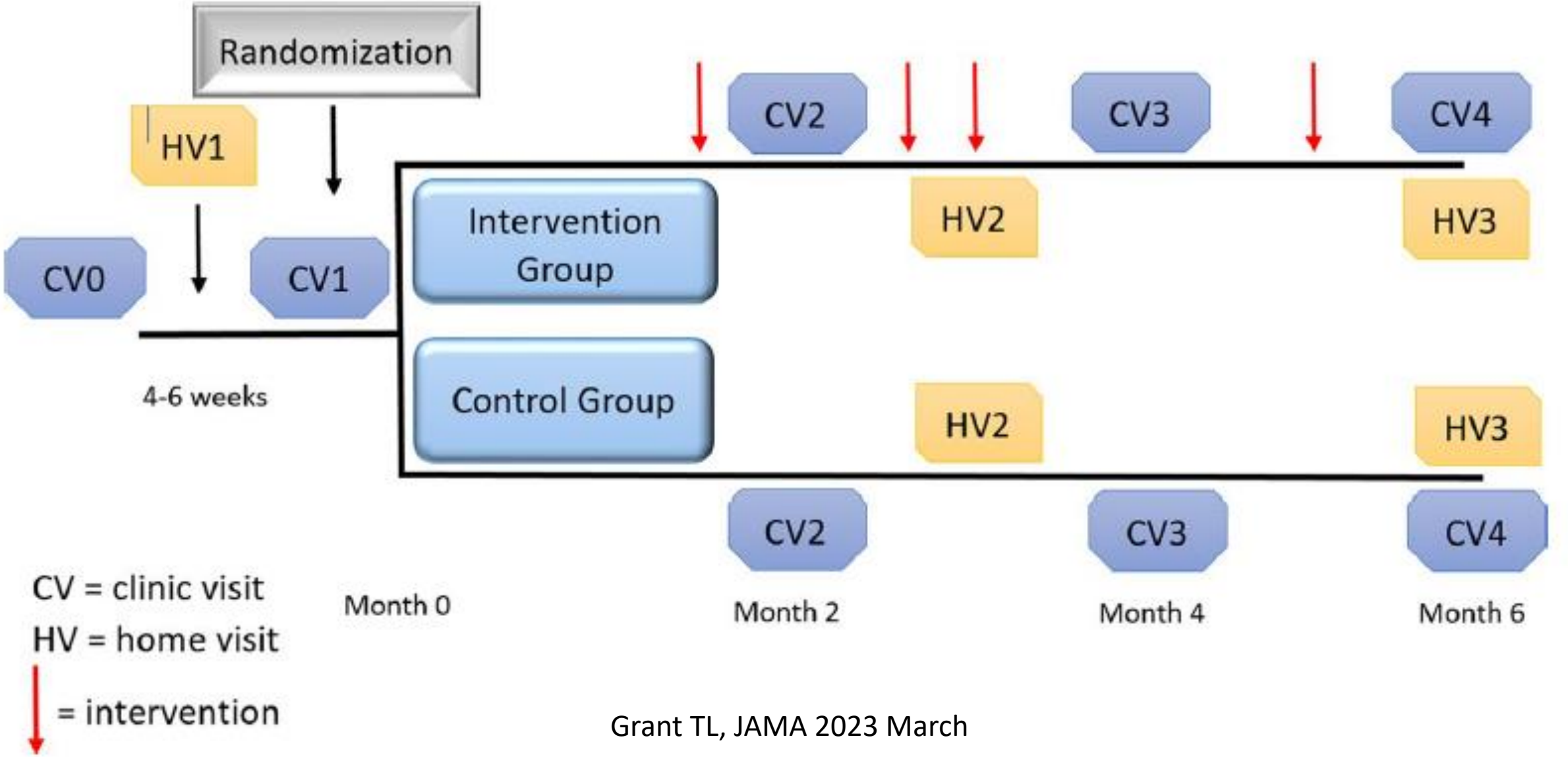
Exposure Thresholds that Predictably Result in Allergic Response



DOSE in dust µg/g	
Mite	1-50
Cat	0.5-25
Roach	0.1-16
Mouse	2-30
Dose (airborne)	10-200 ng/m3
Annual exposure	1-1000 µg

Grant T, JACI 2023

Comprehensive Home Environmental Intervention and Step Controller Titration



Grant TL, JAMA 2023 March

Indoor environmental exposures and obstructive lung disease phenotypes amoung asthmatic children living in poor, urban neighborhoods

Air trapping was defined as an FVC z score of less than 21.64 or a change in FVC with bronchodilation of >_10% predicted.

Baltimore City

Mouse-sensitized Children with Asthma

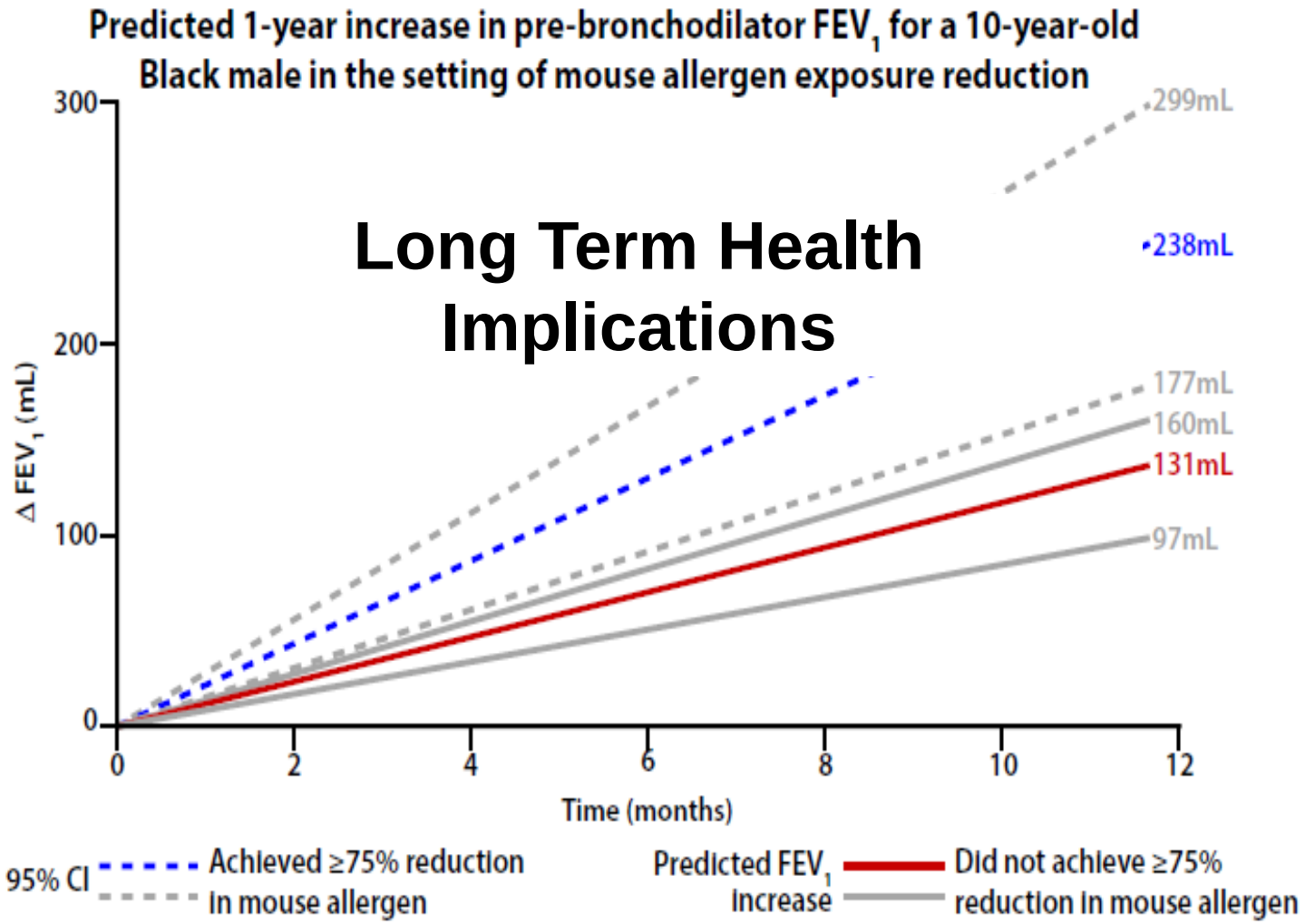
↑ Mouse Allergen Exposure

23%↑ Odds of Air Trapping per 2-fold↑ in Mouse Allergen

Cockroach, dog, cat, PM, and air nicotine exposures were not associated with air trapping

Grant T, JACI 2022

Reducing Allergen Exposure Increase Lung Growth



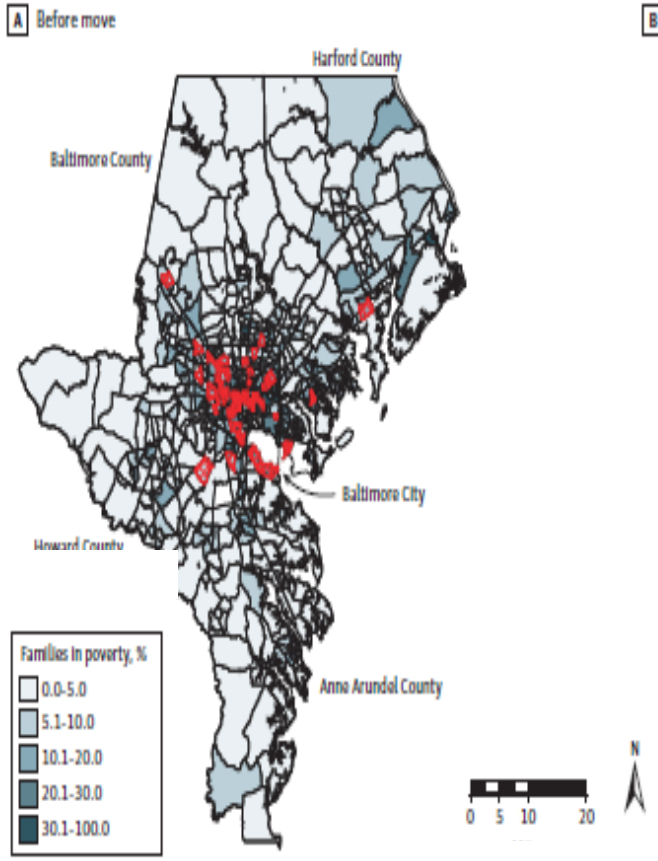
Grant, T et al JACI 2020

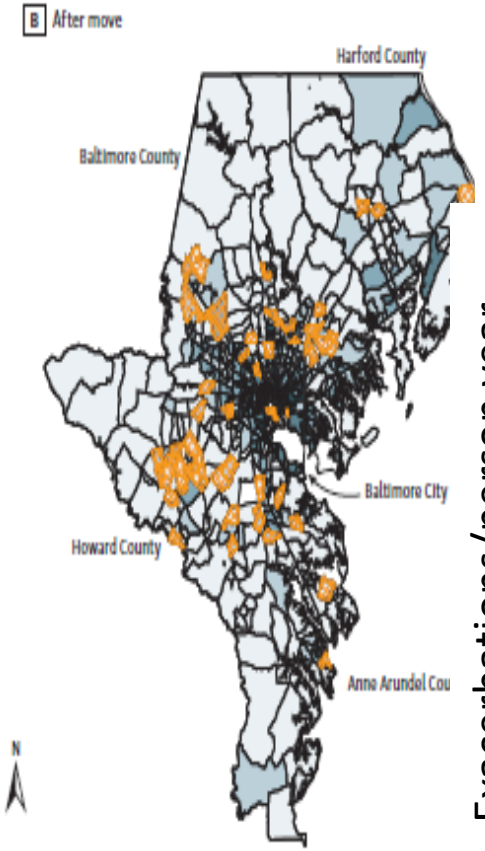
JAMA | Original Investigation

Association of a Housing Mobility Program With Childhood Asthma Symptoms and Exacerbations

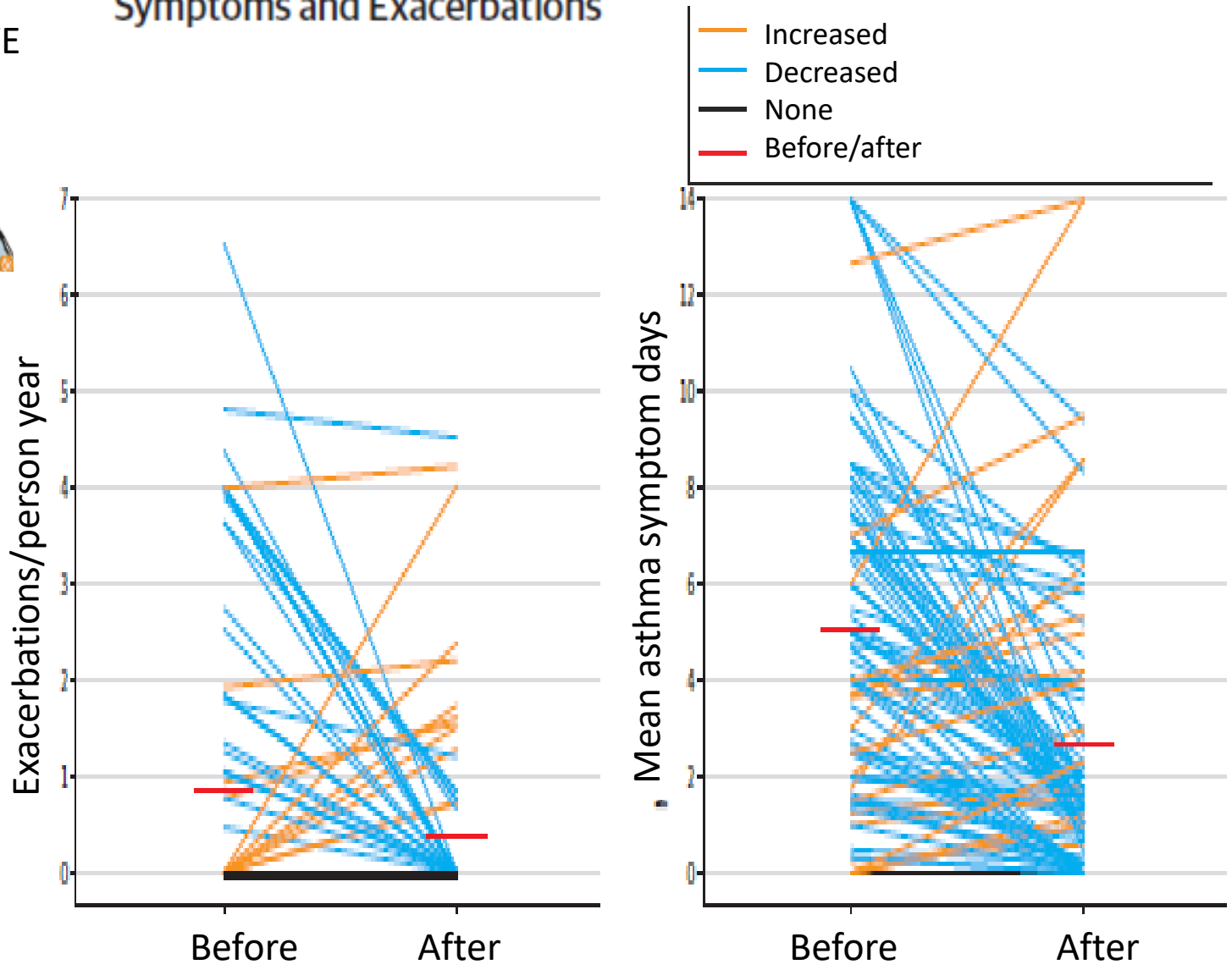
BEFORE MOVE

AFTER MOVE





Families in poverty %

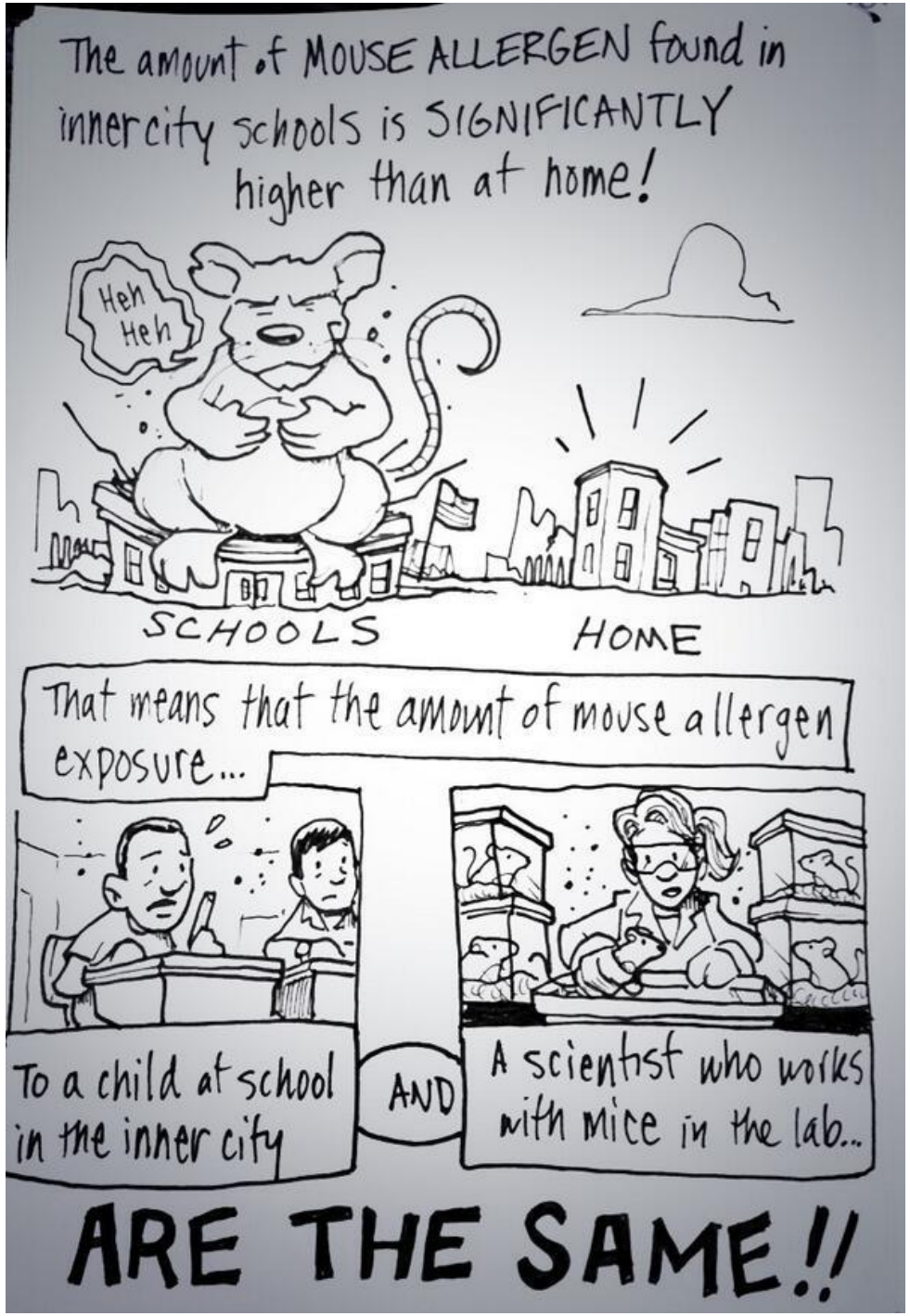


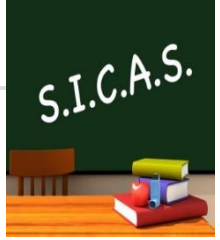
Pollack, C, et al JAMA 2023

We know home environments are key drivers of asthma- what about schools?

Twitter:
Booster Shot Comics
@BoosterShotCmx

What did Dr. Phipatanakul find in her study on inner city schools? Spoiler: its totally mice #AAAAI #graphicmedicine





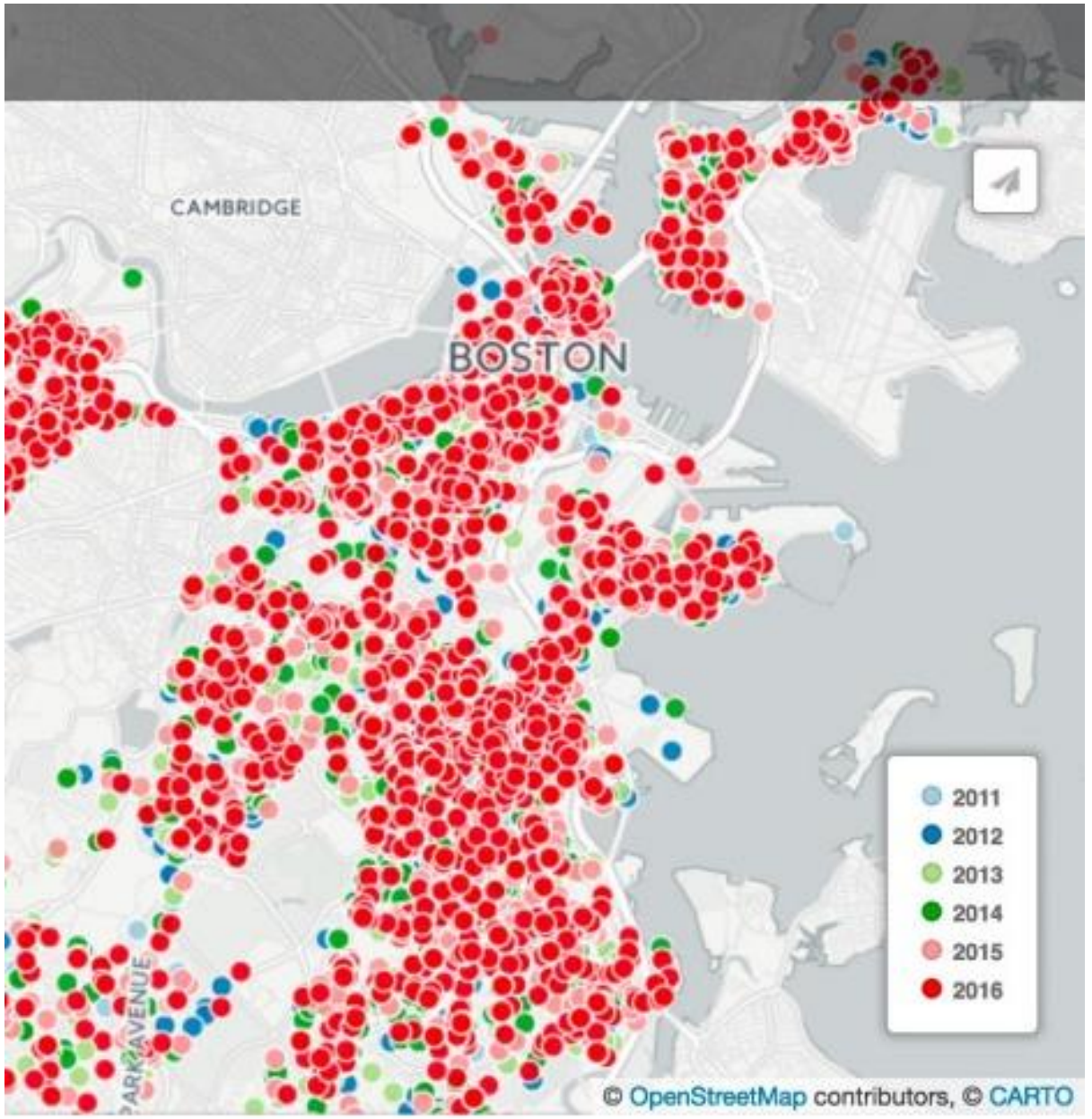
Sheehan WJ, et al JAMA Peds 2017

America Is on the Verge of Ratpocalypse

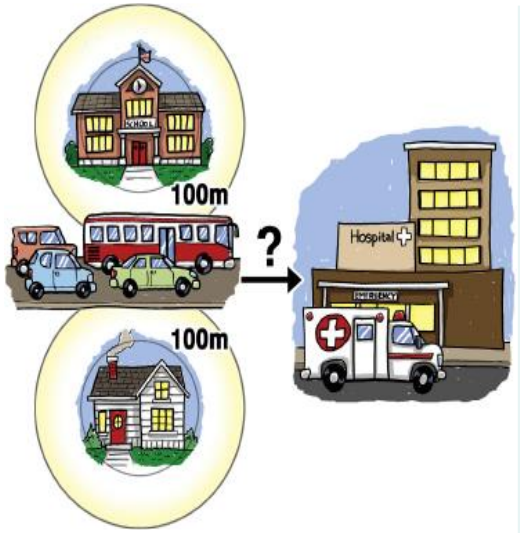
Warmer weather is fueling a rodent surge, straining public health systems and the economy. It's time for the federal government to step in.

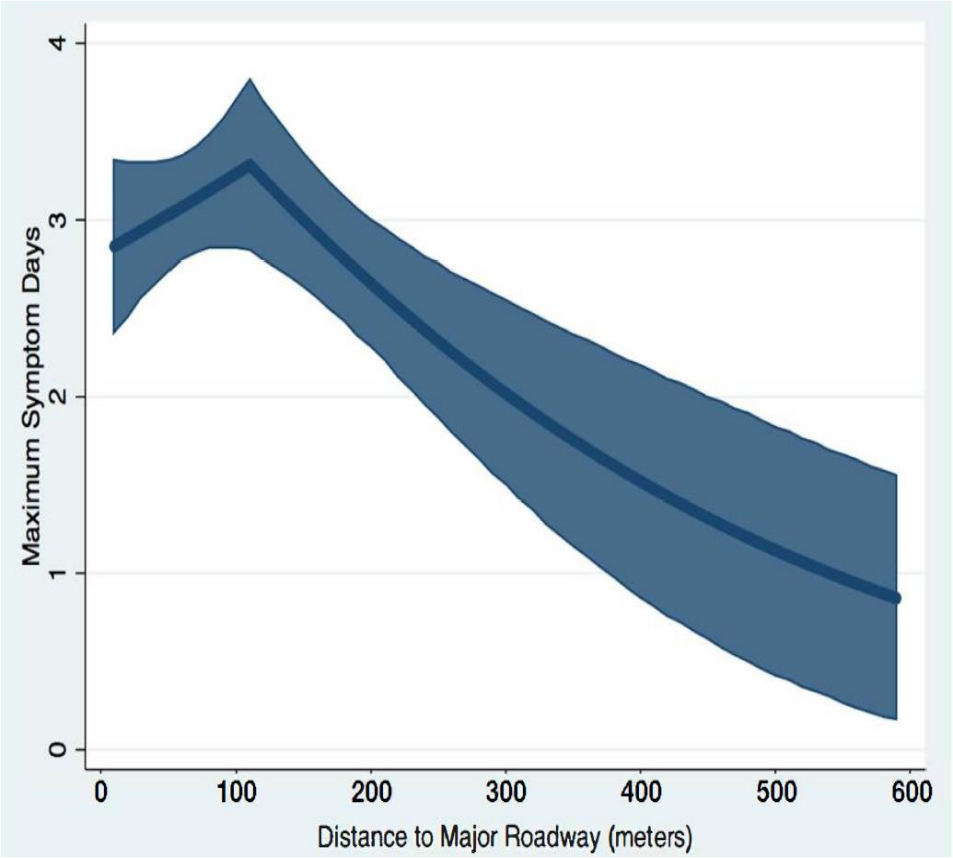
By **EMILY ATKIN** | August 23, 2017

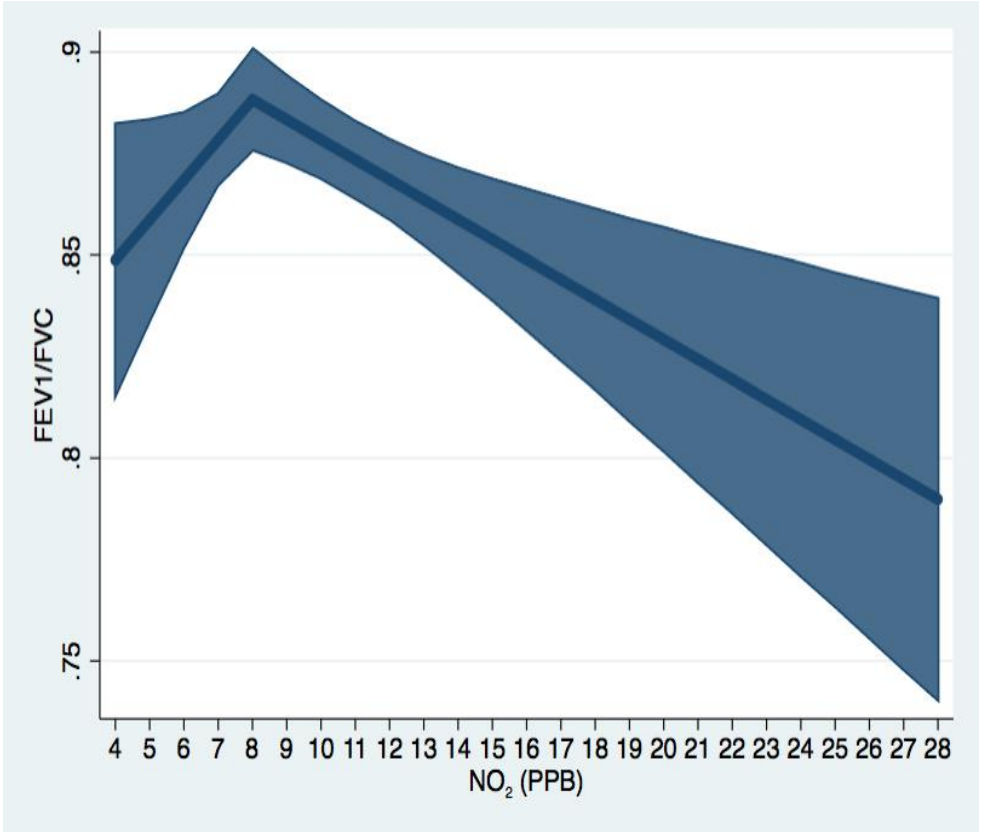
Bobby Corrigan is the rat master. Some call him the rat czar. To others, he is simply a rodentologist, or as NBC recently described him, "one of the nation's leading experts on rats." Call him what you want; he is mostly alarmed. "I travel all over the world with this animal, and the amount of complaints and feedback and questions I hear



Urban schools, traffic and distance to roadways, air pollution and asthma morbidity





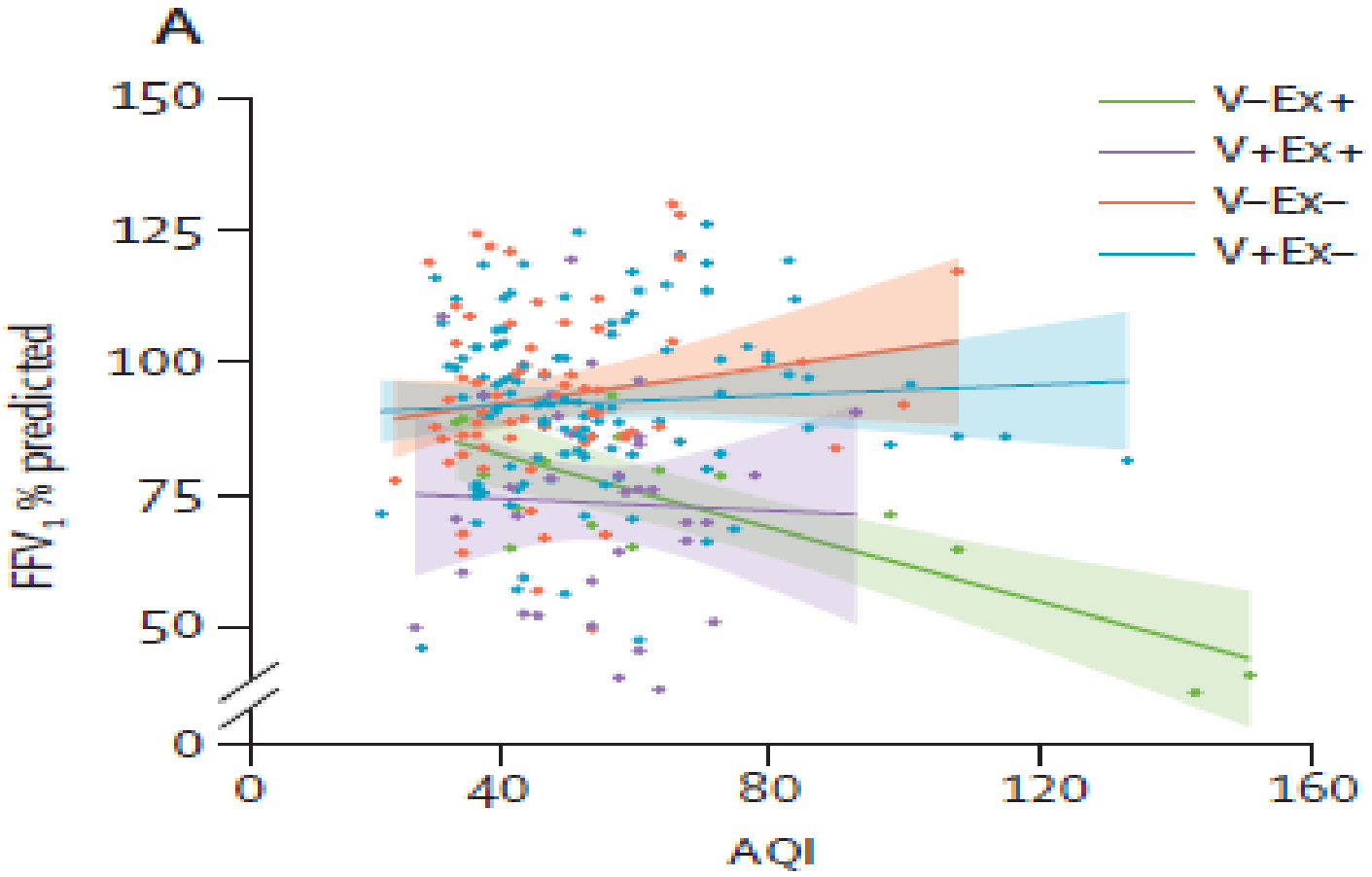


Gaffin, JM, et al JACI 2018 and Hauptman, et al JACI 2020

Air pollutants in low-income urban areas linked with youth asthma attacks:

Researchers were able to connect individual pollutants with certain changes in airway functions and T2 inflammatory gene expression during the attacks.

By Gianna Melillo | Jan. 05, 2023 Changing America

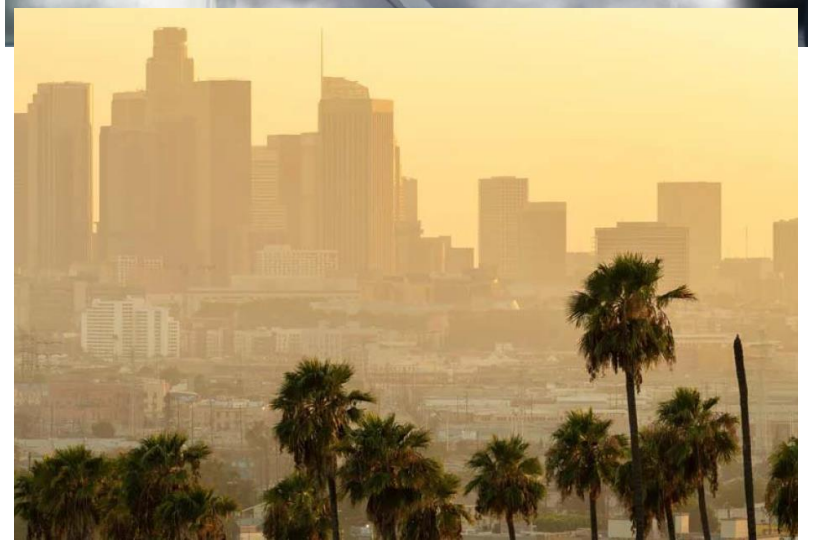


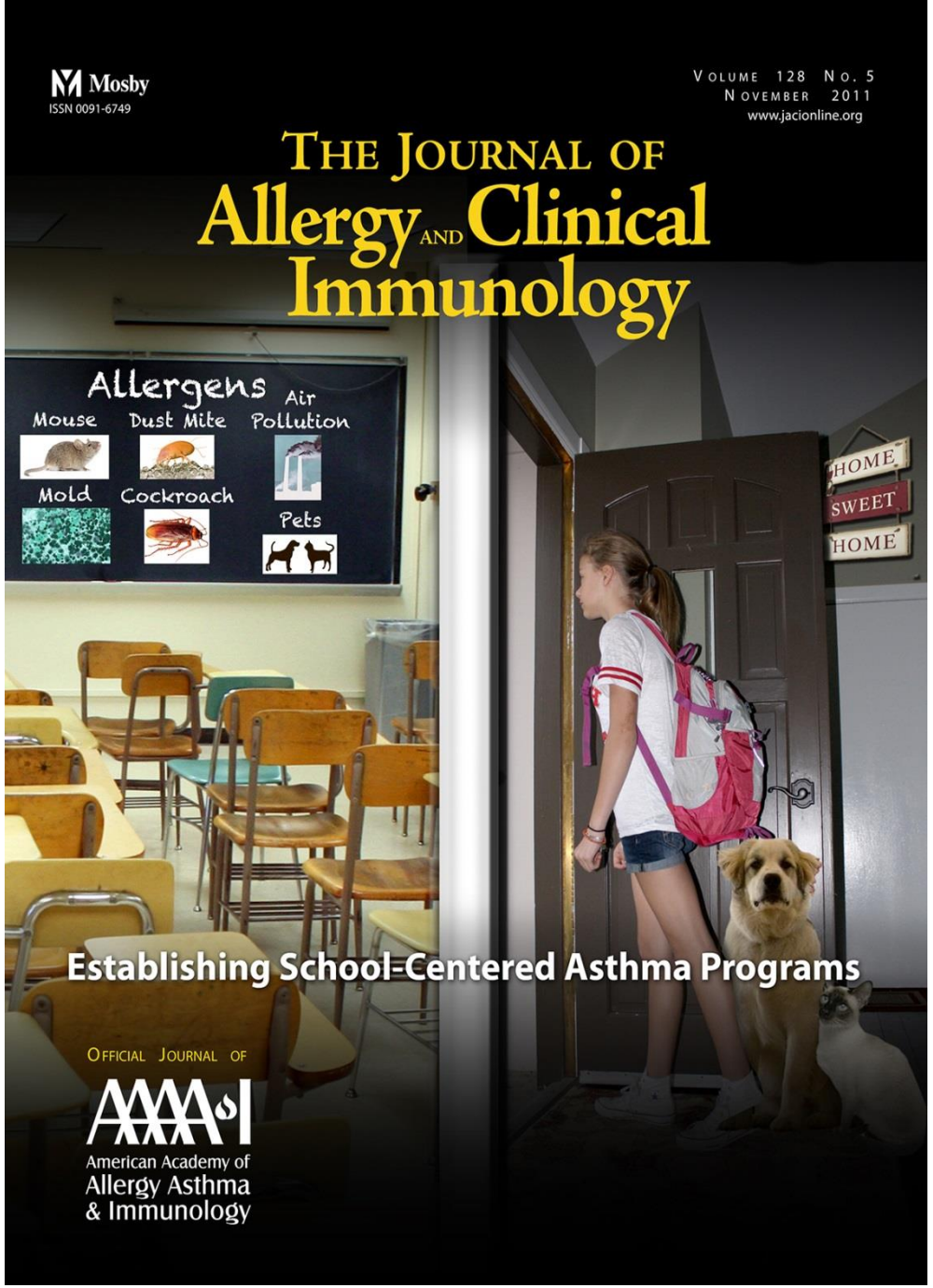
Altman M, et al Lancet Planet Health 2023

V= viral event
Ex= Exacerbation

Data from children living in low-
ncome urban areas across the country
show direct relationship

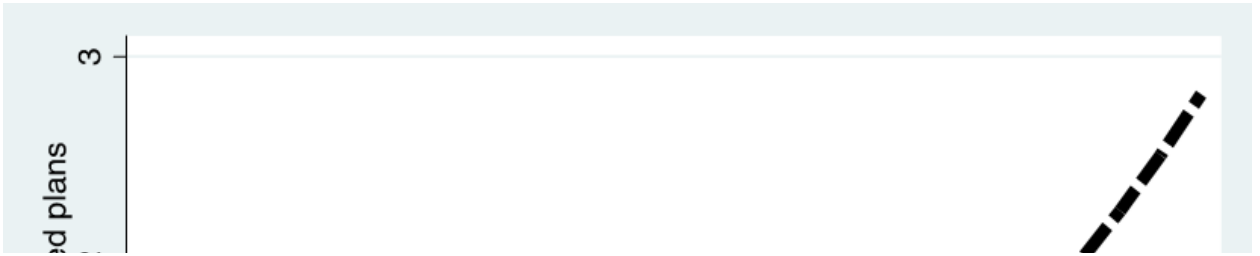
to ozone and fine particulate matter
exposure that are associated with
asthma attacks.



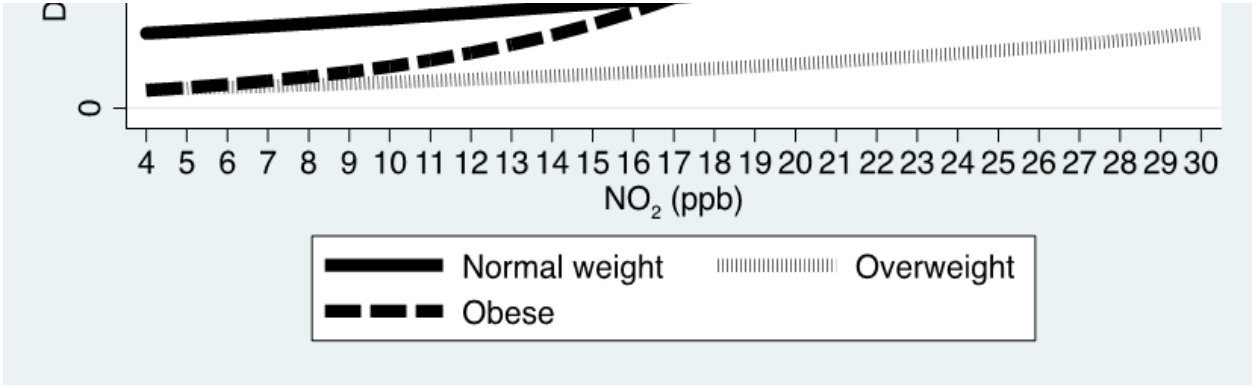


Designed Phipatanakul lab/AAAAI

How does BMI interact with school pollution exposure and asthma?



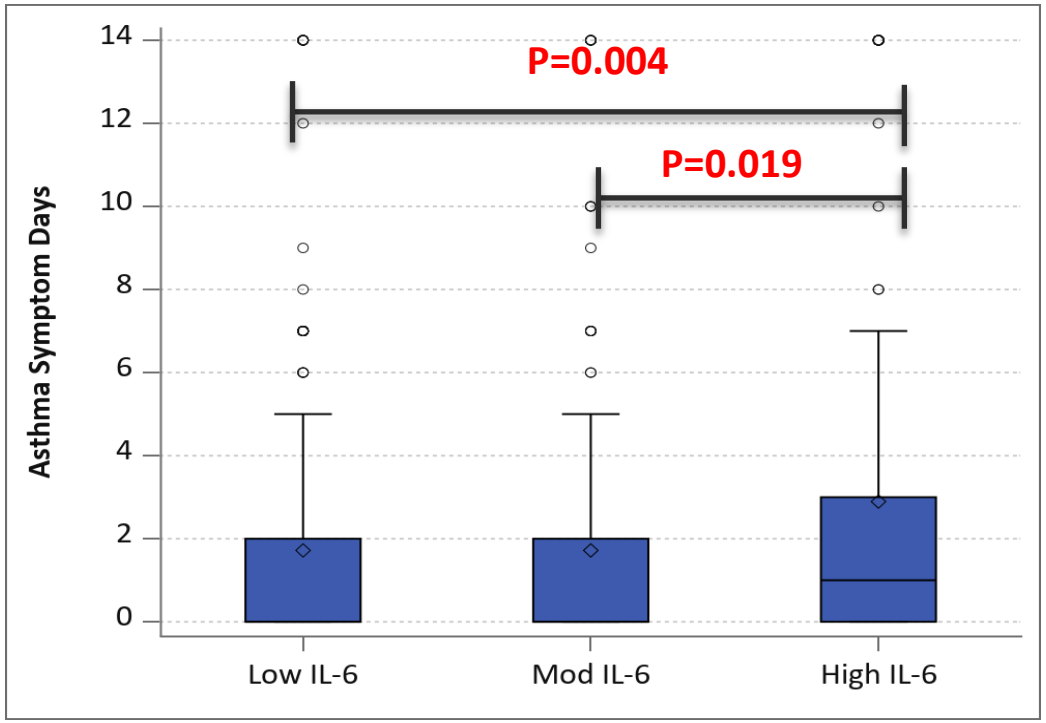
Strategies to normalize BMI (diet and exercise) and improve school environment is critical

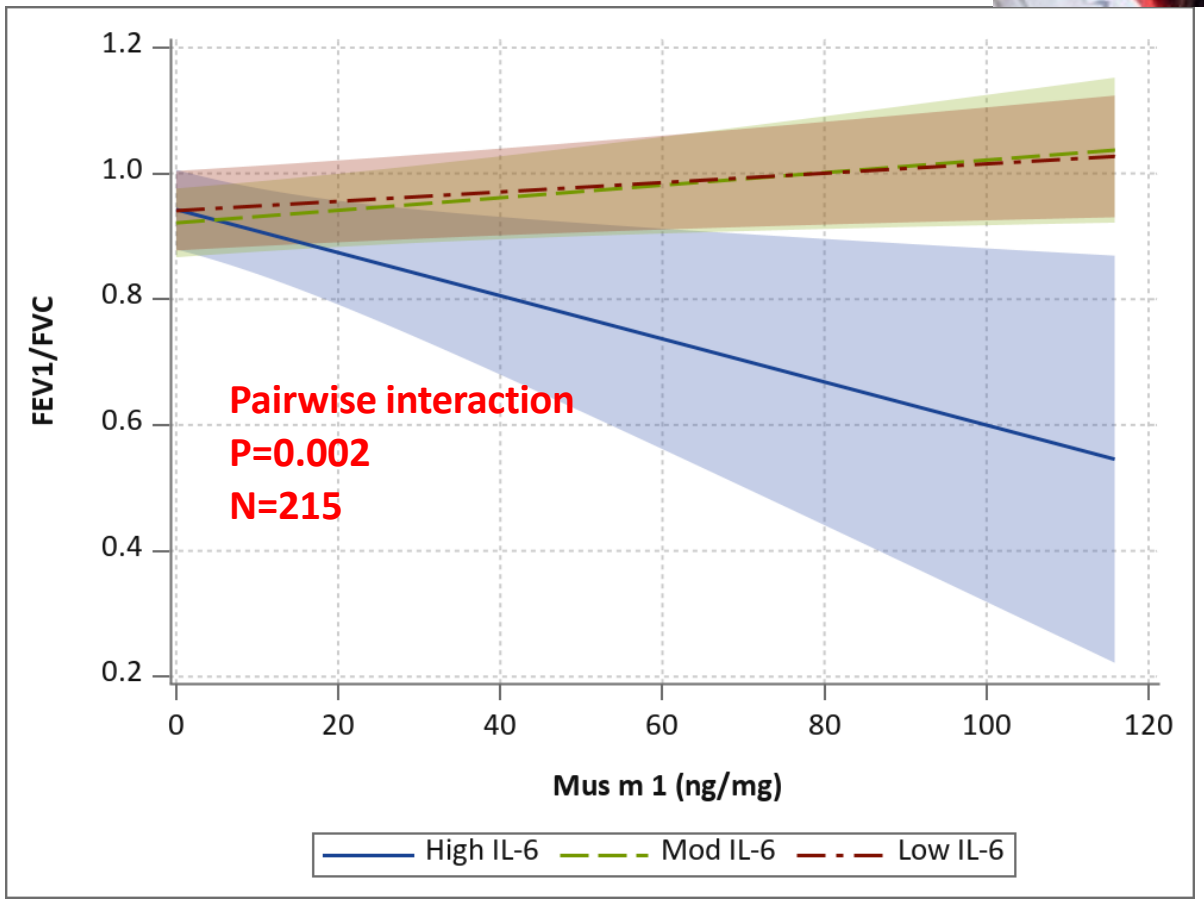


Permaul P, et al JACI Oct 2020

Relationships further modified by cytokines such as IL6
Permaul P, Peters MC, et al JACI In Practice 2021- Severe Asthma Research Program

High Plasma IL-6 Levels May Enhance the Adverse Effects of Mouse Allergen Exposure in Urban Schools on Asthma Morbidity in Children





Permaul P, et al JACI Dec 2023

September 07, 2023 3 min read

Inner-city kids with high IL-6 show more asthma symptoms, susceptibility to mouse aller

Key takeaways:

- Asthma and high IL-6 levels were linked with increased BMI and elevated C-reactive protein levels.
- High IL-6 levels increase susceptibility to the effects of classroom exposure to mouse allergens.

August 31, 2023 4 min read

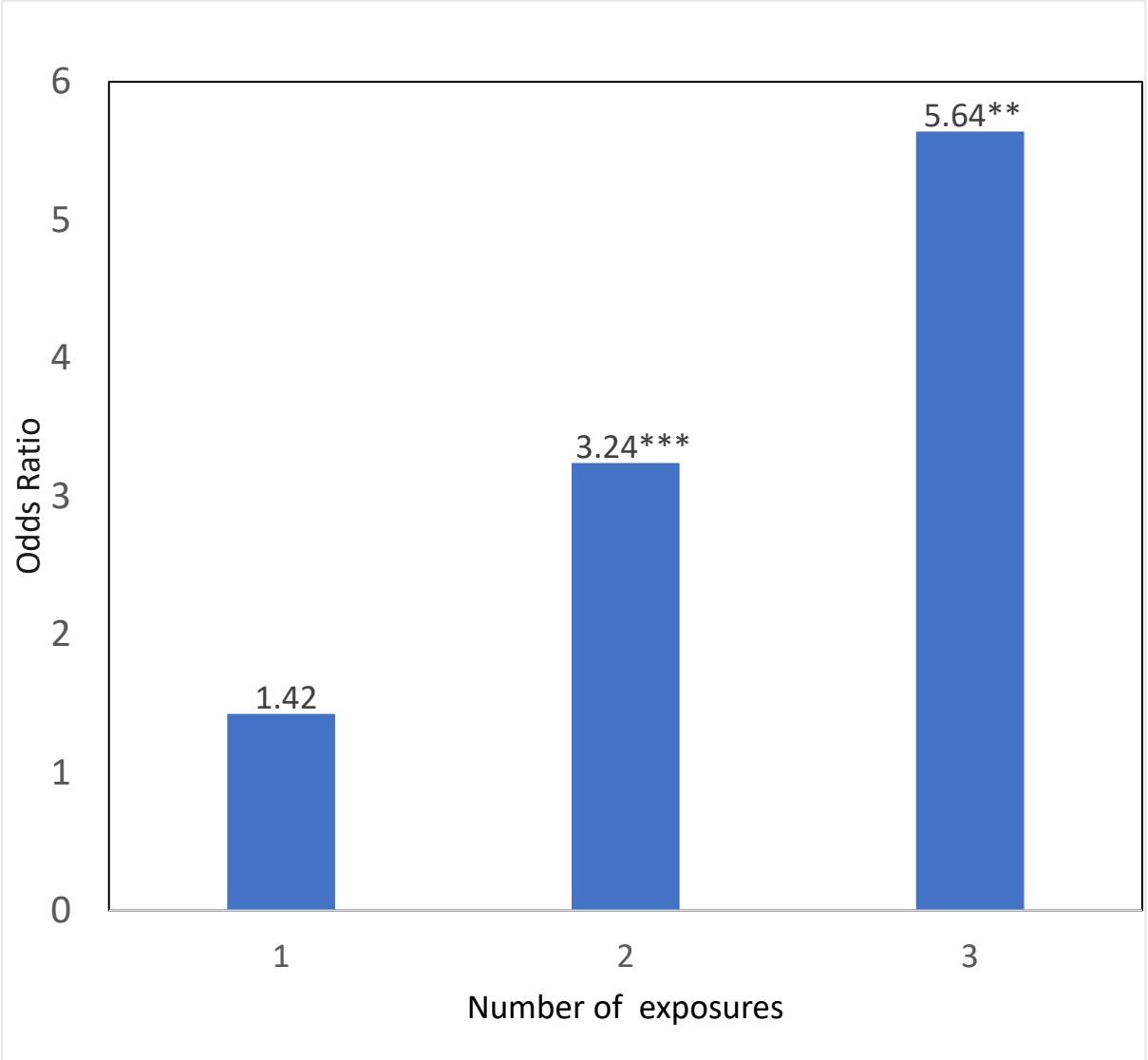
Neighborhoods with more opportunity associated with less pediatric asthma

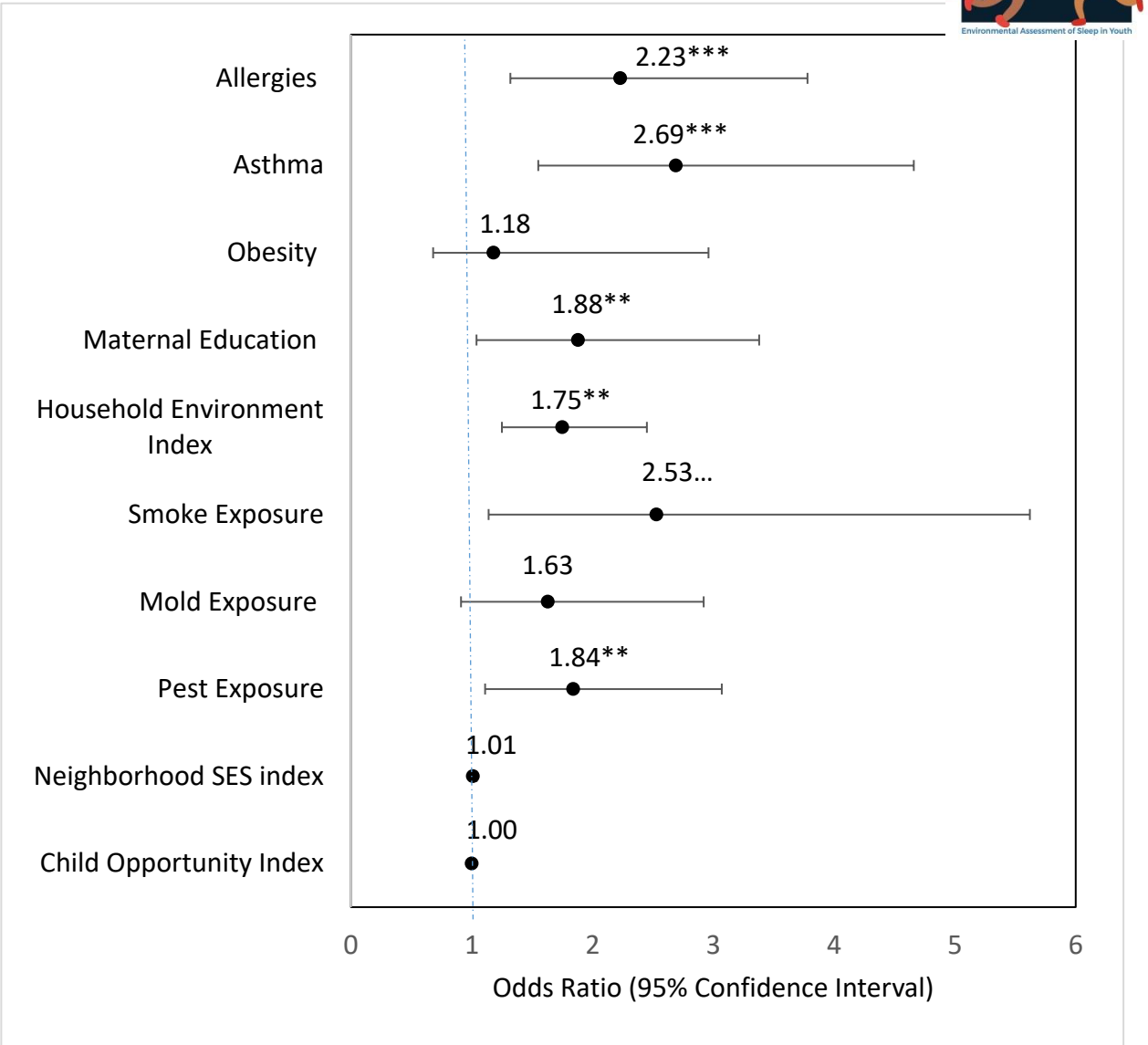
Key takeaways:

- 20.6% of children lived in areas with very high Child Opportunity Index (COI) and very low Social Vulnerability Ind scores.
- High and very high COI was associated with lower asthma incidence.

Obstructive Sleep Apnea-18 score in children

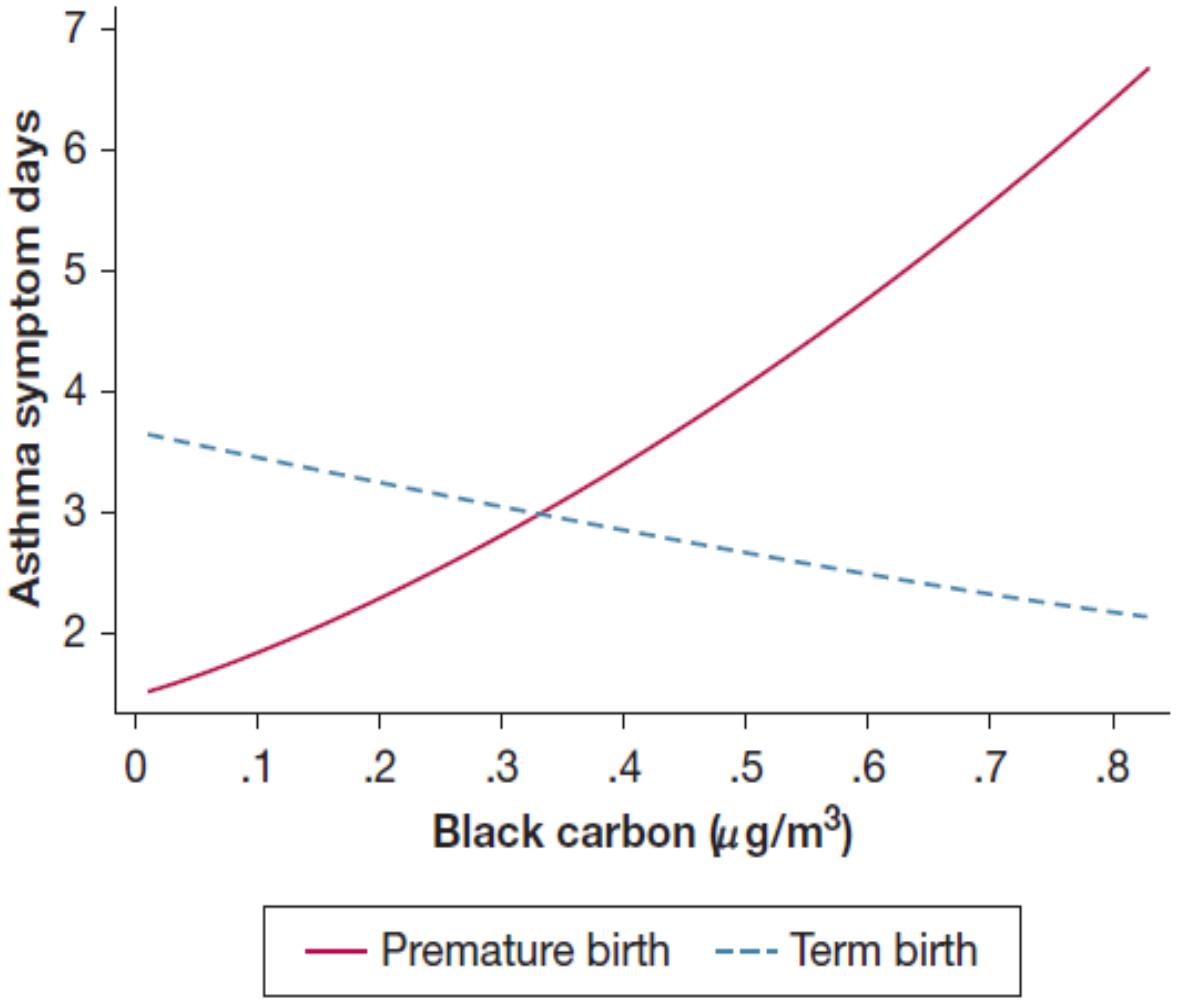
Strongest predictors are asthma/allergies and smoking exposure





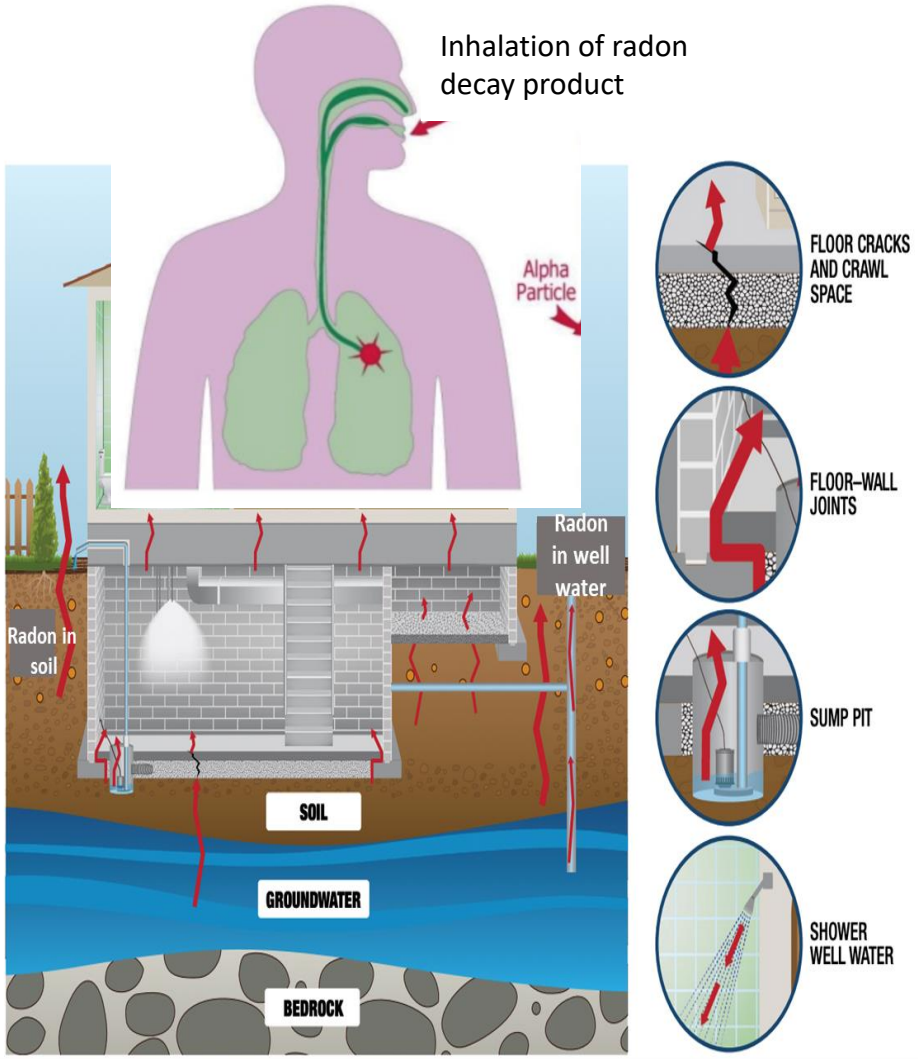
Gueye-Ndiaye S, et al CHEST Pulm 2023

Differential Effect of School-Based Pollution Exposure in Children With Asthma Born Prematurely



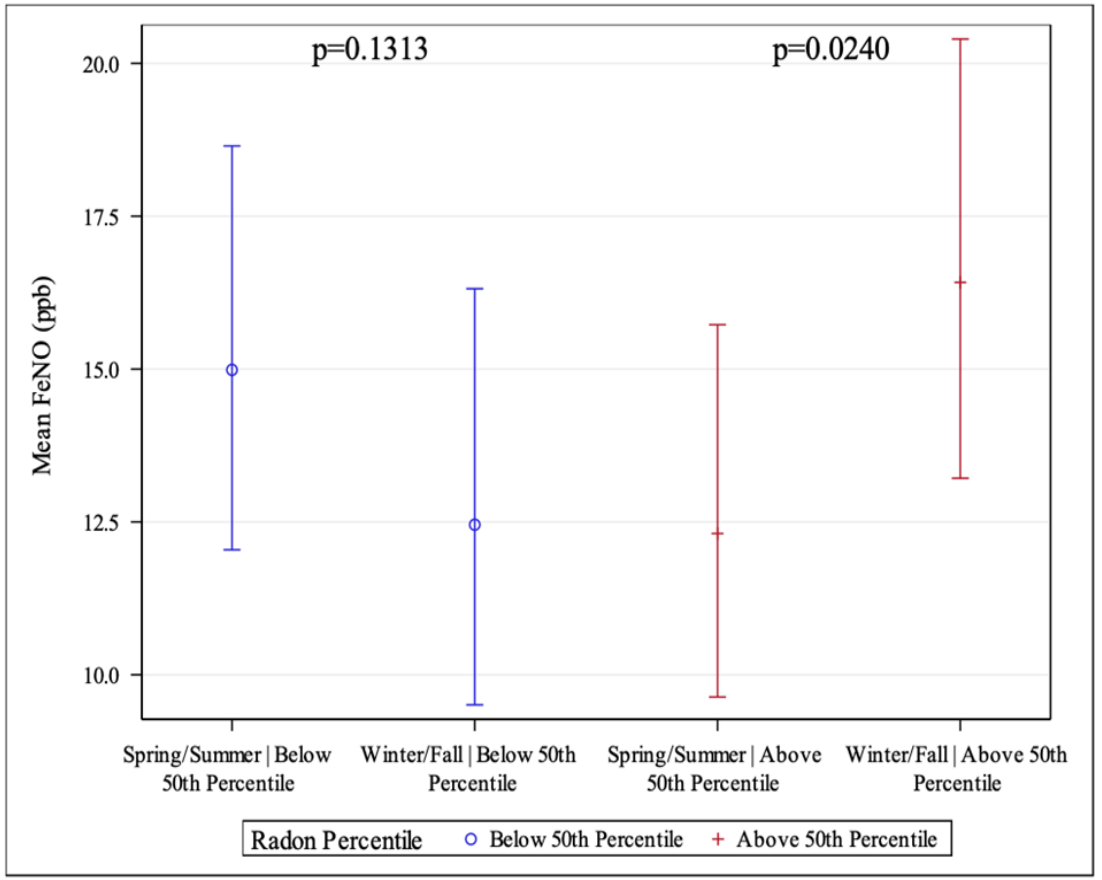
Gaffin JM, Phipatanakul, Chest 2020

Radon exposure, Asthma and Airway Inflammation



CRCPD Publication No. E-18-2

	Radon	
	IRR	p-value, 95% CI
Asthma Symptoms	1.014	p=0.0273, 1.002 to 1.027

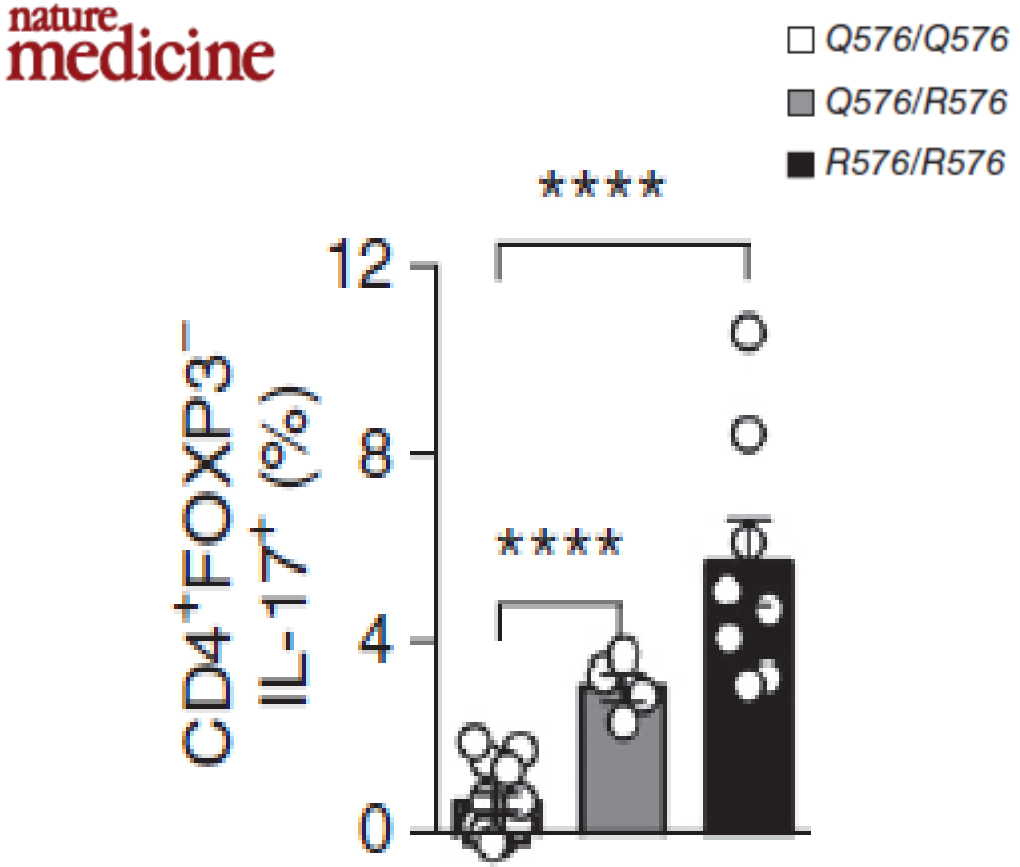


Banzon T, et al Peds Pulmonology 2023

Taking what we learned in schools to Precision Medicine

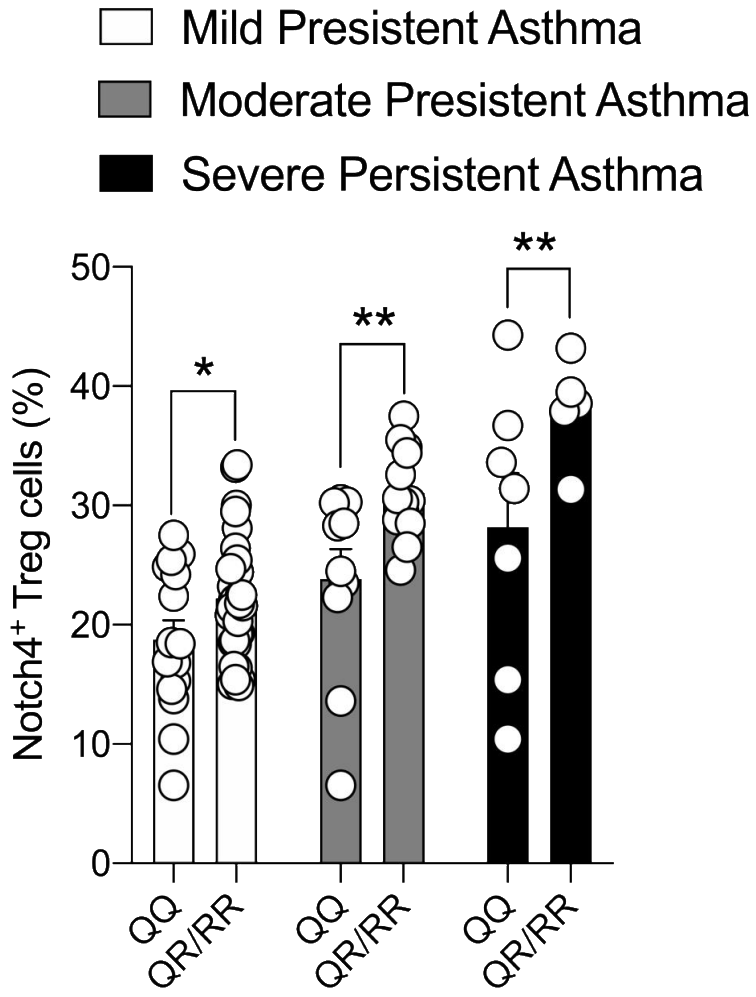
An asthma associated IL4R polymorphism Increases Airway Inflammation by Conversion of regulatory T cells to Th_{17}-like Cells

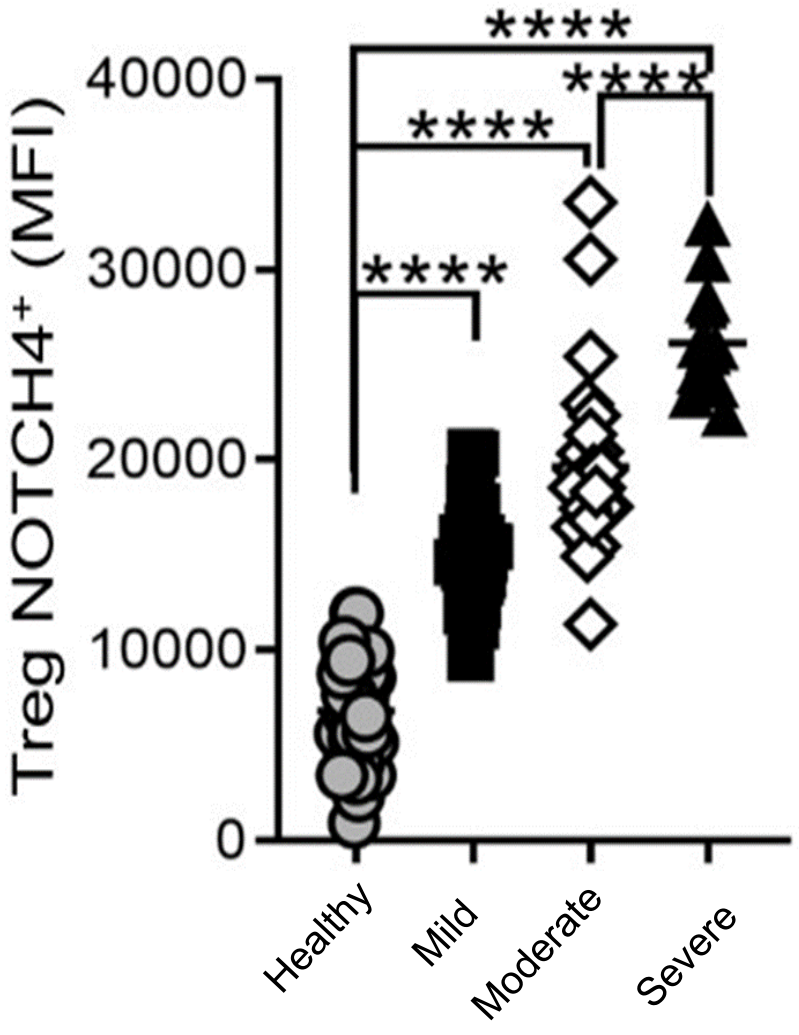
- IL-4Rα-Q576R polymorphism- (glutamine (Q) to arginine R substitution at position 576 of the IL-4Rα)
  - R allele frequency 68% (blacks/hispanics); 20% (whites)
  - R allele associated with severe asthma
  - Unique among *IL4R* polymorphisms, directly drives T_H2 to T_H17 inflammatory response in the airways
  - Dose response relation with severity
  - Endotoxin in schools is prevalent, associated with morbidity, and drives a Th2/Th17 skewing and appears to have negative, beneficial and equivocal effects in certain populations



Massoud et al, Nat Med 2016; 22(9):1013-22

IL-4RαR576 impacts % circulating NOTCH4⁺ Tregs and asthma severity

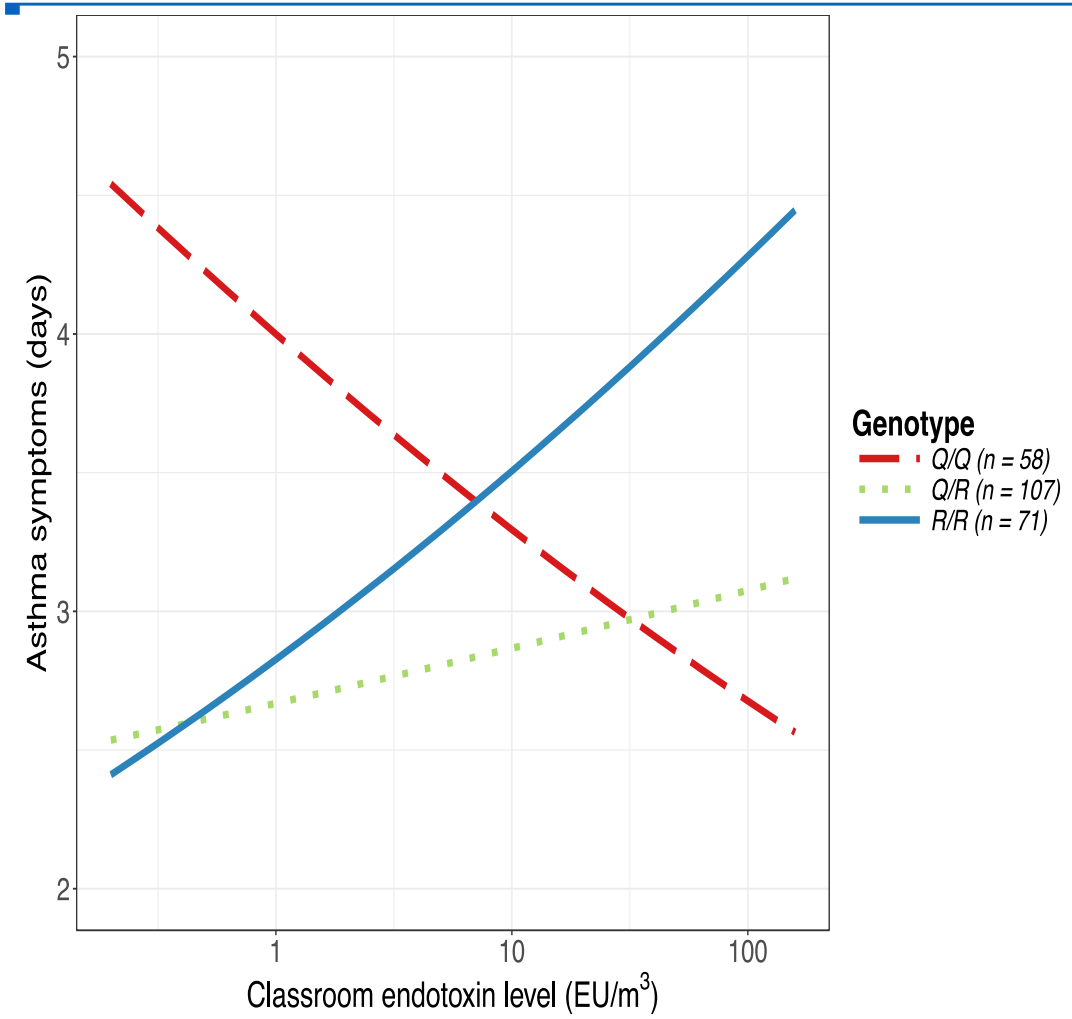




Hani H, et al … Phipatanakul W, and Chatila T, Nature Immunol November, 2020

Persistent Asthma

Asthma Symptoms Differ by Genotype and School Specific Exposure



***Q/Q wild type*: Protective**

***Q/R heterozygous mutant*: Equivocal**

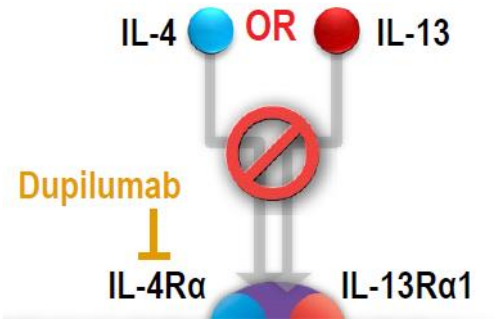
***R/R homozygous mutant*: Harmful**

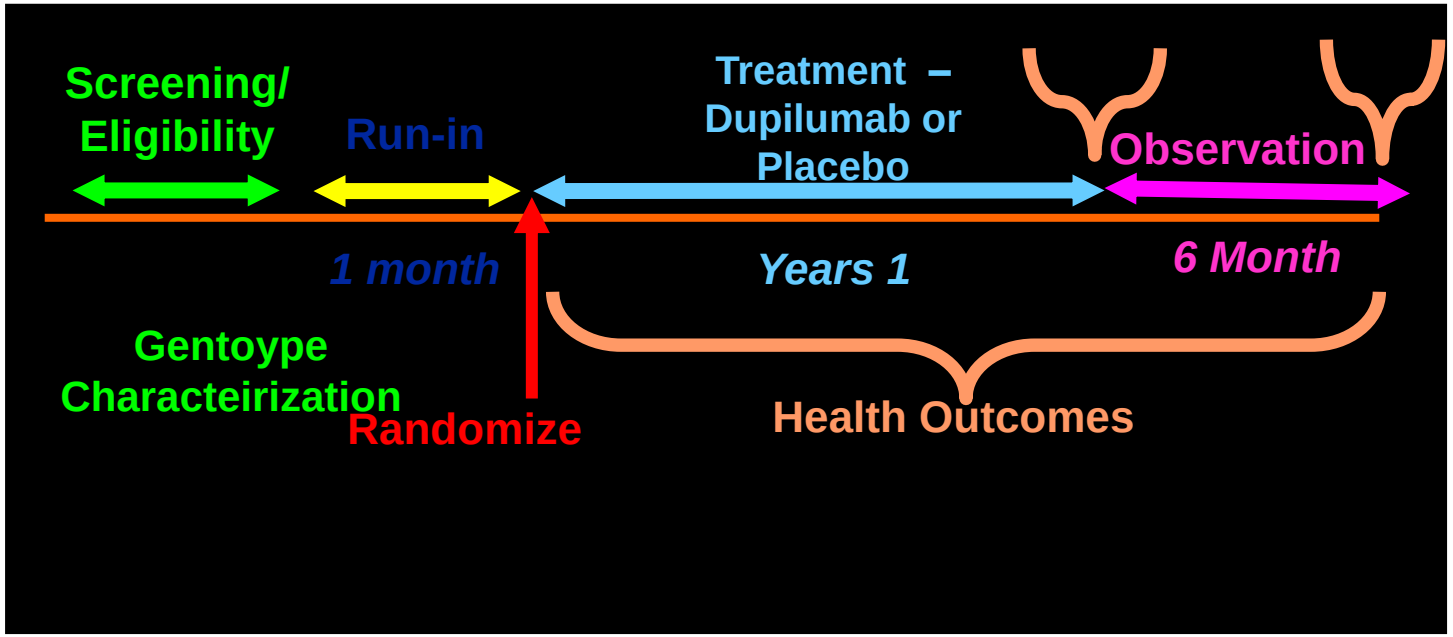
Lai PS, et al JACI 2018; 141 (2): 794-796

Investigating Dupilumab's Effect in Asthma by Genotype IDEA Trial
https://ideaasthma.org

Boston- Phipatanakul/Israel
New Jersey- Oppenheimer
Michigan- Kim/Zoratti
Cleveland-Kaleb
NY-Montefiore- Sjariwal
U Penn- Bamarjee

NIH U01 AI143514 – Phipatanakul/Chatila
3 Groups by Genotype 1: 1 Dupilumab vs. Placebo



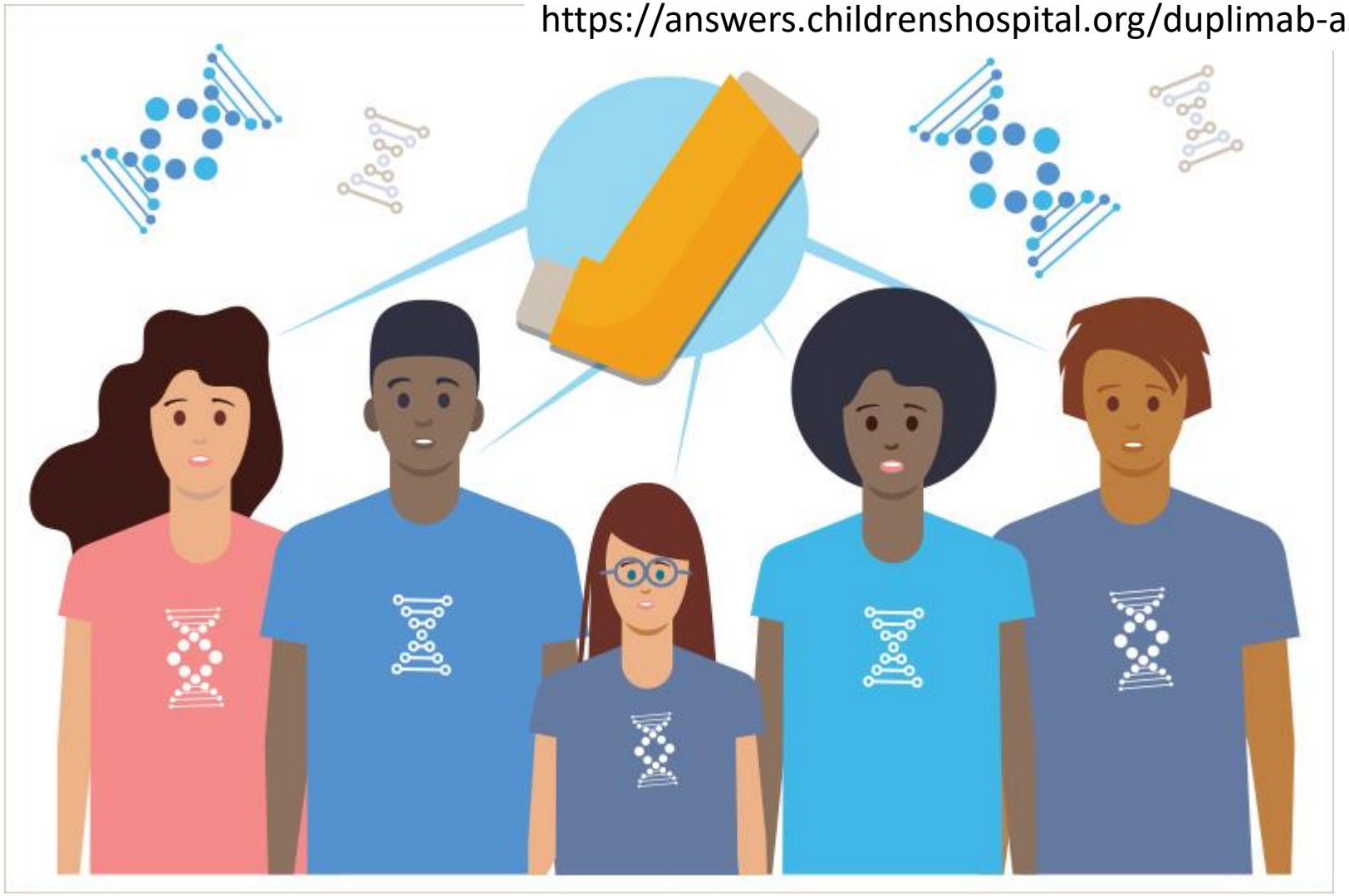


Will investigate genotype driven (personalized) response to therapy and study preliminary mechanisms in disease modification

Trial for severe asthma targets a mutation common in children of color

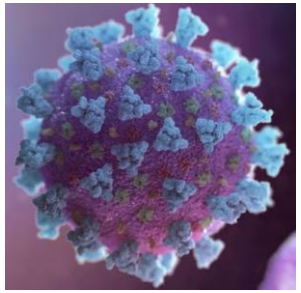
Posted on September 7, 2021 by Nancy Fliesler | Clinical, Research
Tags: asthma, clinical trials, genetics and genomics, precision medicine

https://answers.childrenshospital.org/duplimab-asthma/

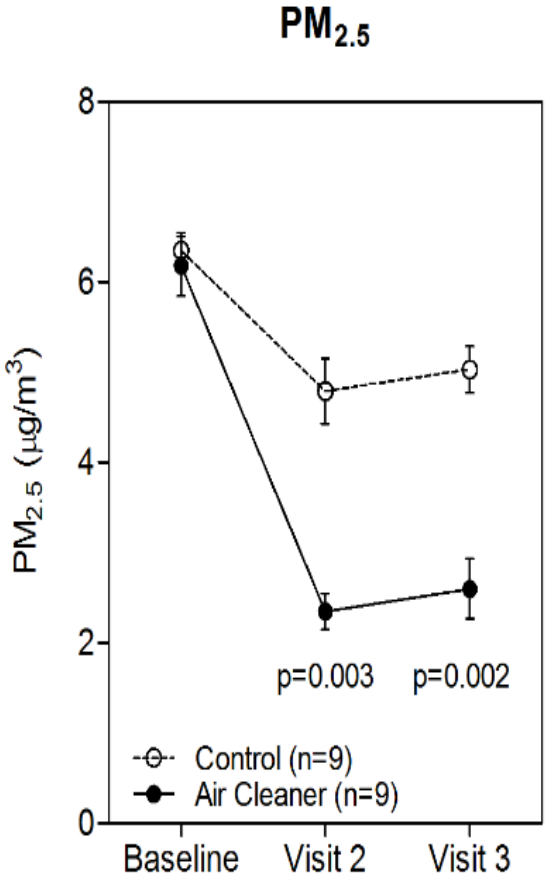


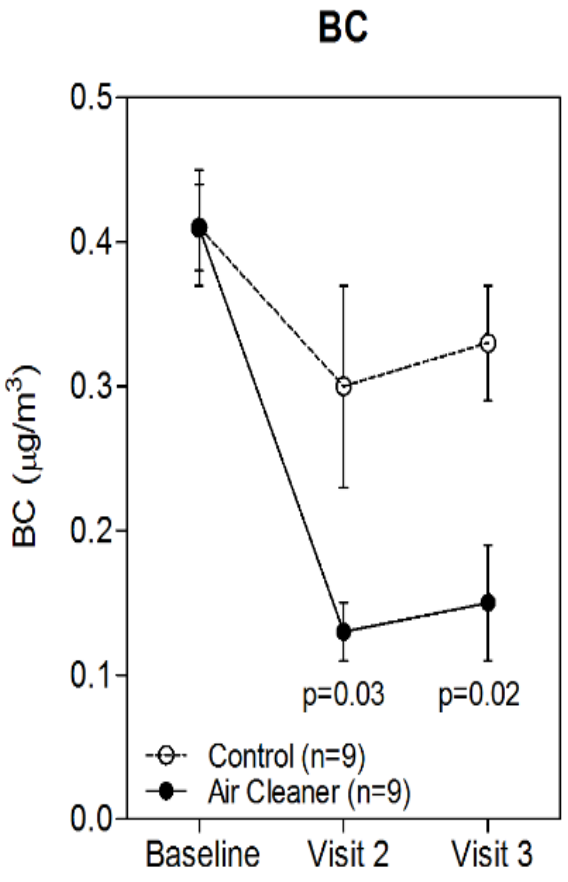
Future Directions

Classroom HEPA Filters Reduce Particulate Pollutants and Airborne Allergens Compared to Sham



BA.2.86





Novel NOTCH4 Pathway of Asthma Severity in Urban School Children (SICAS3) R01

Microbiome and asthma morbidity in school children R01

Molecular epidemiology of viruses in Schools R21

HEPA cleaners, and viruses in schools- R21 (SICAS 4)

Jhun, Phipatanakul, JACI in Practice 2017; 5(1):154-159

Phipatanakul, W, et al JMA Sept 2021

In Summary…

- Drivers of asthma in school children include multiple social determinants of health
- Home and School environments (i.e. allergenic, pollutant, and viral exposures) play important role in asthma morbidity- specifically in vulnerable populations
- Vulnerable populations have risk factors that can guide effective interventions
- Host factors such as obesity, metabolic syndrome, cytokine responses, sleep disordered breathing, prematurity affect interactions allergenic/microbial and other exposures on health outcomes
- Genetic and environment interactions in a home/school setting have effects on disease- and precision therapeutic approaches are key to the future
- Fully understanding the complexity of these factors allow us to incorporate future strategies to provide healthy environments for kids in school, considering social determinants of health, and other precision therapeutic approaches
- Policies for fair and equitable resource allocation in underserved populations are important considerations- during and post pandemic

Acknowledgements/Funding

COLLABORATORS

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- Hans Oettgen, MD, PhD- IgE mechanism

K-R from Lab

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- Peggy Lai, MD, MPH, R01AI144119, R21 AI 17965/ R21178155
- Melody Duvall, MD, PHD R01 NHLBI

K23 Trainees

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- David Kantor, MD, PhD, K-23 HL138162
- Lisa Bartnikas, MD, K23 AI125732 , LRP
- Elena Crestani, MD K23 AI146289
- Marike Rosenbaum, DVM, K23 ES 035460
- Tina Banzon, MD K23 ES 03545
- Medine Jackson-Browne, PhD- Diversity Supplement- K23

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U01 AI 08328 MAAIT (Matsui/Phipatankul)
R01HL137192 (Phipatanakul) EASY-SLEEP
U01AI126614(Phipatanakul) PARK
Mech-Oettgen- Genentech
K24 AI 106822 (Phipatanakul)
U10HL146002 (Levy/Israel SARP)
U19AR069526- PEPR (Lai/Paller)
IOF GIS/Activity FitBit IOF
U01 HL 1300045 (Martinez)- ORBEX
UG1 HL139124 (Israel- PreCISE)
R01AI065617/R21 AI 132843 (Chatila)
U01AI152033-Geha/Phipatanakul- ADRN
U01 AI 160087- Phipatanakul/Chatila-CAUSE SICAS 3

FELLOWS

- Carmela Socolovsky, MD Pulmonary
- Sigfus Gunlaugsson, MD Pulmonary
- Lana Mukharesh, MD Pumonary
- Julia Lee, MD, Pulmonary
- Ye Sun, Bob Sun, MD Pulmonary
- Ellen Conroy, MD, Allergy/Immunology
- Nicole Comfort F31 ES030973
- Seyni Gueye-Ndiaye, MD- Sleep Fellow/ Faculty