Addressing Inequities in the Pediatric Asthma Patient

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HARVARD
MEDICAL SCHOOL

Disclosures

Wanda Phipatanakul, M.D., MS

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- **Clinical Trial Support/Medications/Grant Support: Genentech, Novartis, Regeneron, GlaxoSmithKline, Thermo Fisher, Monaghen, Alk Abello, Lincoln Diagnositics, Kaleo**

- **Neither I nor my spouse/partner have any other relevant financial relationships with the manufacturer(s) or any commercial product(s) and/or provider of commercial products or services discussed in this CME activity.**
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Objectives

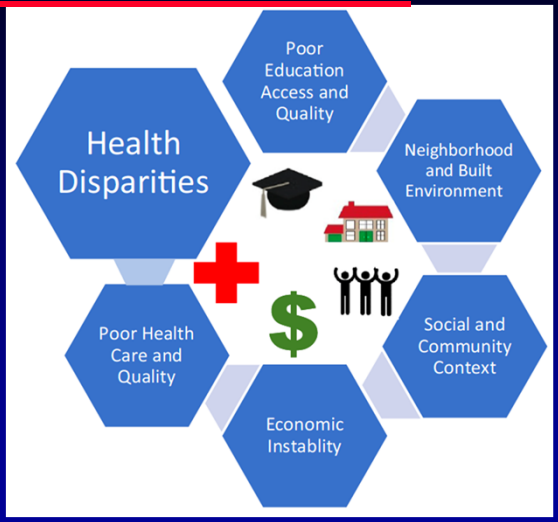
1. To further our understanding of community and environmental risk factors as social determinants of health
2. To identify interventions to reduce risk and even prevent disease outcomes
3. To identify predictors of response to these interventions

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 Social Determinants of Health 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

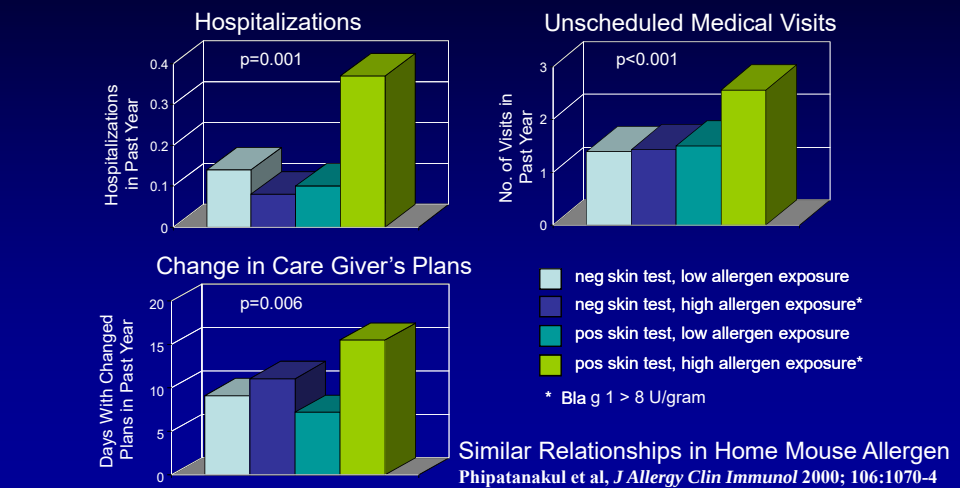
Addressing inequities in asthma by focusing on children's environments

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/

What do we know about HOME exposures and health disaprities?

Home Cockroach Allergen Exposure and Allergy Increases Asthma Morbidity in Urban Children



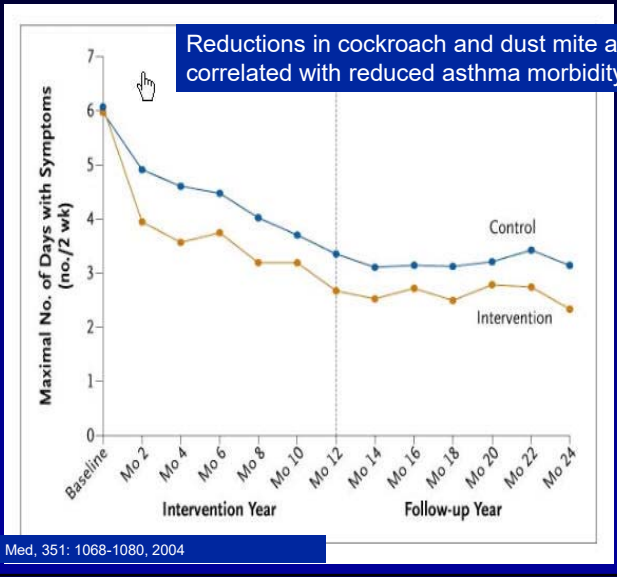
Rosenstreich et al., N Eng J Med, 336: 1356-1363, 1997

Similar Relationships in Home Mouse Allergen

Phipatanakul et al, *J Allergy Clin Immunol* 2000; 106:1070-4

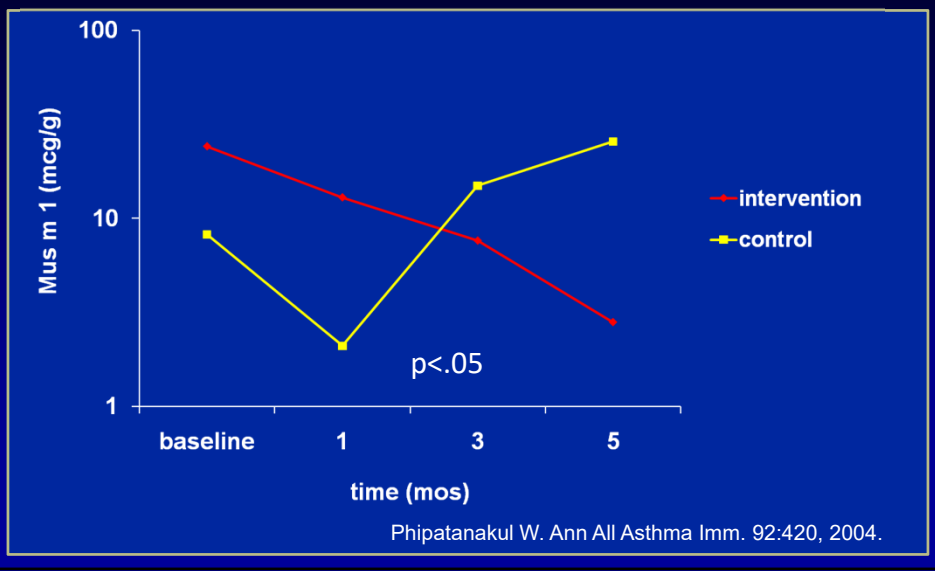
Phipatanakul et al, *J Allergy Clin Immunol* 2000; 106:1075-80

Multi-Faceted Home Intervention Works in Reducing Asthma Morbidity In Urban Kids



Morgan et al., N Eng J Med, 351: 1068-1080, 2004

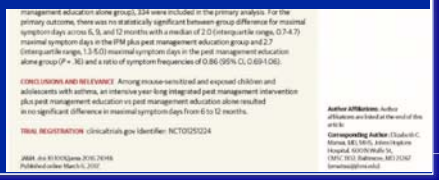
Focused Integrated Pest Management & Mouse Allergen



Phipatanakul W. Ann All Asthma Imm. 92:420, 2004.

Both IPM & Education Groups had ~70% reductions in home mouse allergen levels

Both arms had similar reductions in symptoms, morbidity



The JAMA Network

JAMA Journal of the American Medical Association

EC Matsui, M Perzanowski et al.. and W Phipatanakul

JAMA 2016

Effect of an Integrated Pest Management Intervention on Asthma Symptoms Among Mouse-Sensitized Children and Adolescents With Asthma: A Randomized Clinical Trial

EITHER arm that had 90% reduction in exposure, the benefit was similar or surpassed ICS without associated side effects

•Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com

jamanetwork.com

Decades of work in HOMES

What about schools?

School Inner-City Asthma Study Repeating Annual Schema

R01 AI073964 - Phipatanakul PI

350 children
38 schools

Class/Home Sampling Spirometry F_ENO

Class/Home Sampling Spirometry F_ENO

Spring **Summer** **Fall** **Winter** **Spring**

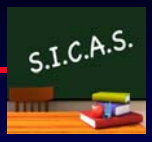
Screening & Recruitment 8-10 schools 75 Students/yr

Baseline Phenotype Survey Spirometry Skin testing Blood/Nasal

Asthma Symptoms

Quarterly Parental Surveys

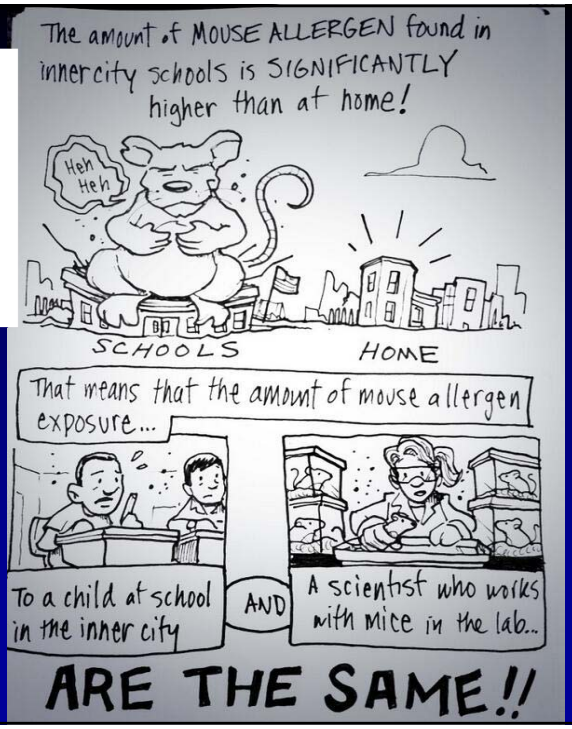
What's Involved in a Comprehensive School Study….



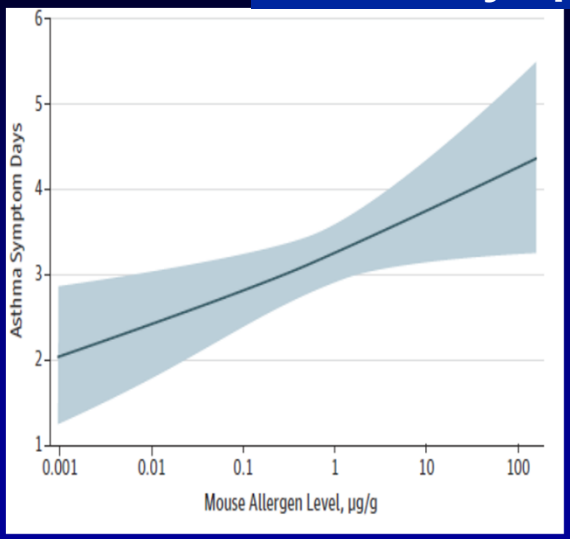
- 8 Air Samplers
- 2-3 Vacuums/ Dust Samplers
- 4 Burkard Mold Samplers
- 8 Pollution Samplers
- 8 NO_2 Samplers
- 3-4 Staff
- 1-2 Cars/Vans

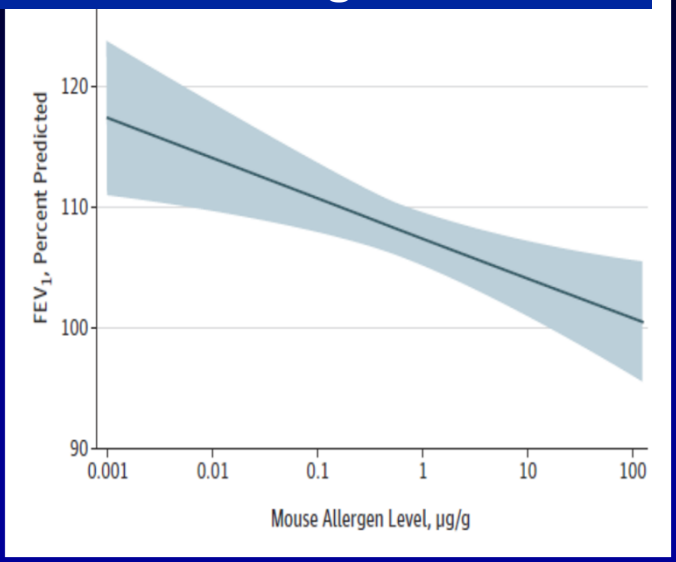
Twitter:
Booster Shot Comics
@BoosterShotCmx

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



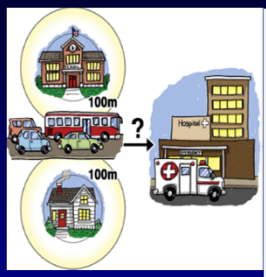
Classroom Mouse Allergen Exposure and Asthma Symptoms and Lung Function

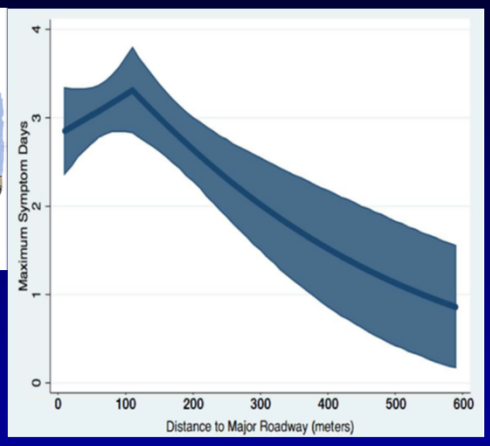


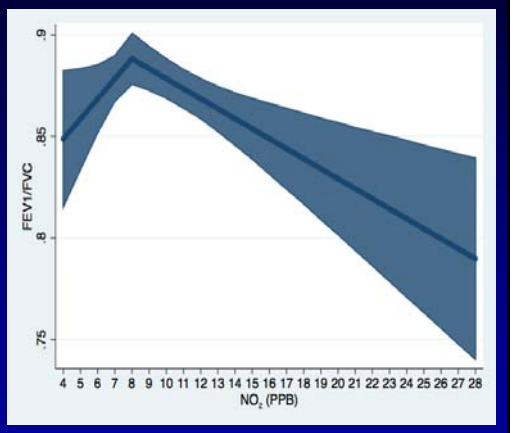


Sheehan WJ, et al JAMA Peds 2017

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



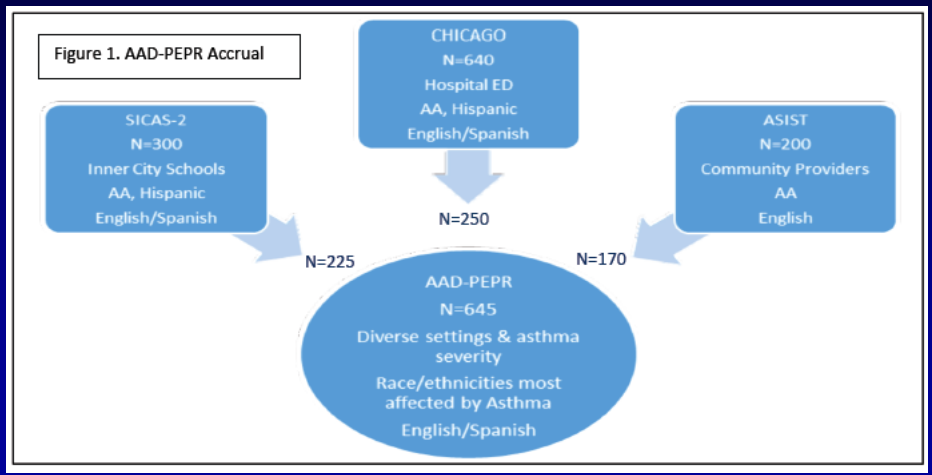




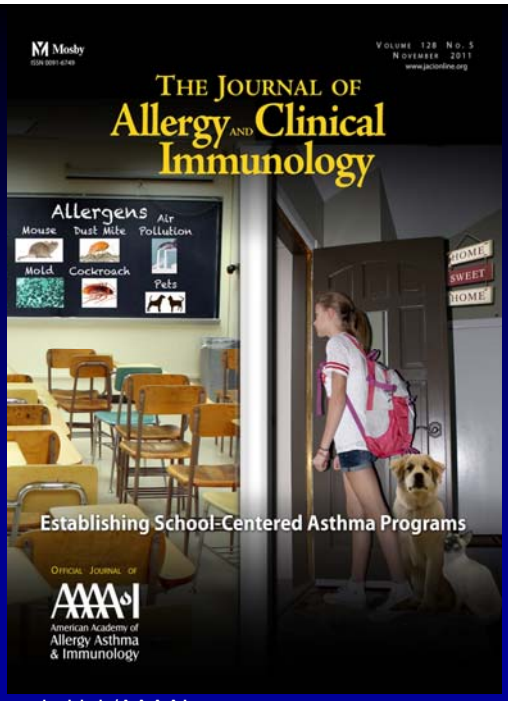
Gaffin, JM, et al JACI 2018 and Hauptman, et al JACI 2020

Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium

Type 1 Diabetes | Sickle Cell Disease | Rheumatic Disease (JIA, SLE) | IBD -Crohn's/UC | Chronic Kidney Disease | Cancer (Active) | Cancer (Survivorship)

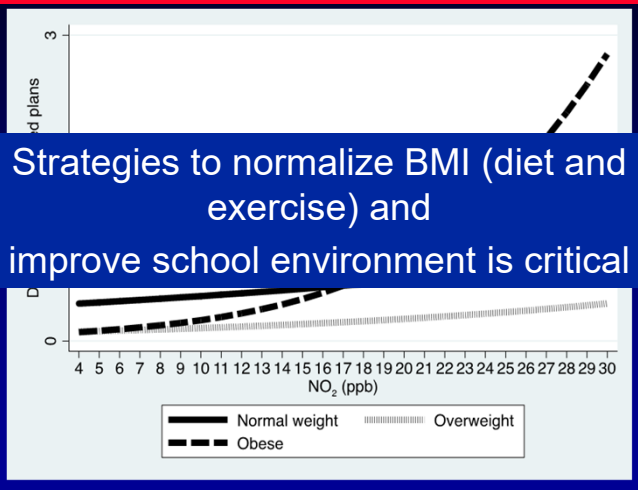


NIAMS U19AR069526-Phipatanakul/Hauptman Geocoding Core Lead



Designed Phipatanakul lab/AAAAI

How does BMI interact with school pollution exposure and asthma?

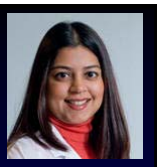


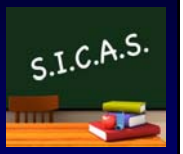
Strategies to normalize BMI (diet and exercise) and
improve school environment is critical

Permaul P, et al JACI Oct 2020

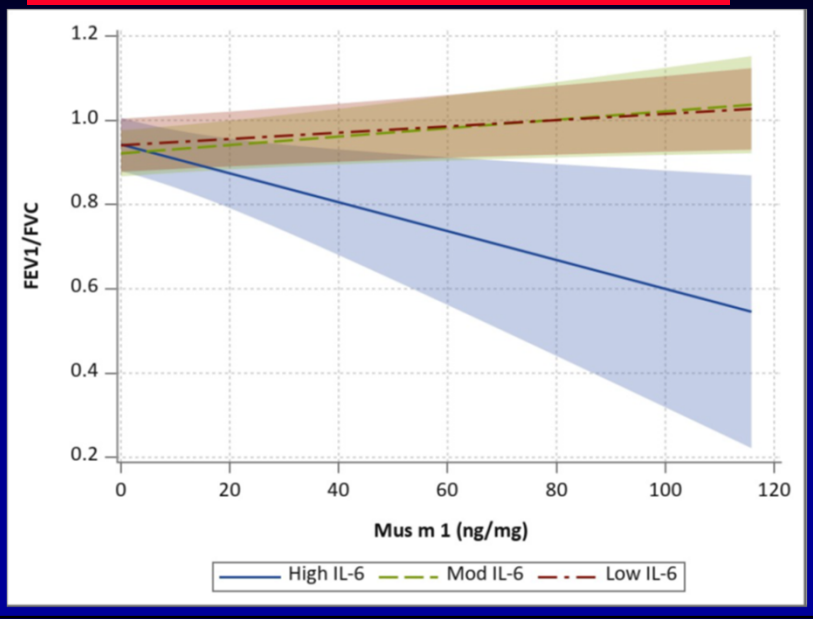
Relationships further modified by cytokines such as IL6
Permaul P, Peters MC, et al JACI In Practice 2021- Severe Asthma Research Program

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 2023

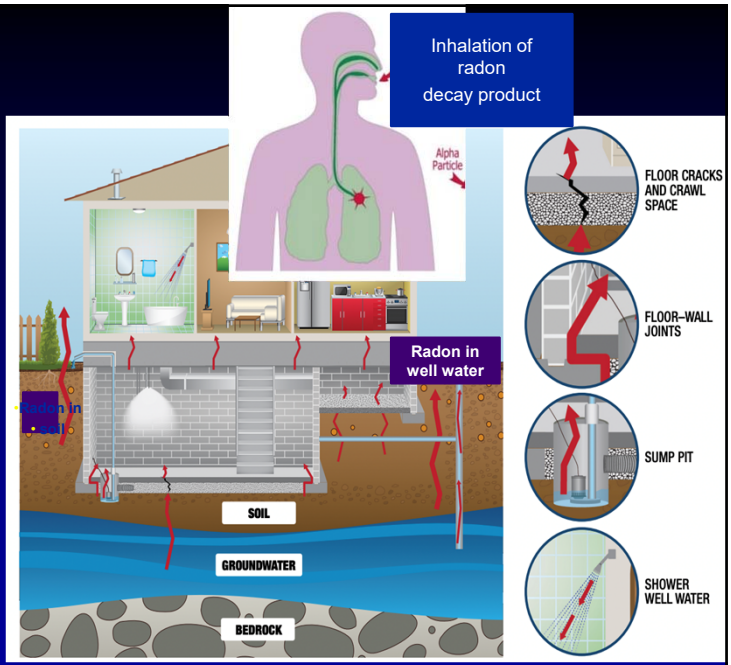


Radon is a naturally radioactive gas

- formed by the decay of uranium radionuclides naturally present in rocks in the earth's crust
- well-known for carcinogenic effects (lung cancer)
- oxidative stress in cell culture
- associated with COPD mortality

Asthma is well known to be triggered by environmental inhalants

No studies to date on radon and asthma morbidity



CRCPD Publication No. E-18-2

Long-term exposure to Radon is associated with asthma diagnosis in urban youth

Radon exposure (moving avg)	Asthma diagnosis	
	Home	School
1 month	1.2 (0.7-1.92)	**1.18 (1.62-6.5)[b]**
5 month	1.07 (0.67-1.69)	**1.48 (2.15-9.06)[b]**
7 month	1.26 (0.77-2.04)	**5.19 (2.33-11.5)[b]**
12 month	1.41 (0.84-2.34)	
24 month	1.61 (0.93-2.79)	
36 month	**2.01 (1.09-3.69)[a]**	
48 month	**2.15 (1.10-4.17)[a]**	
60 month	**2.25 (1.11-4.54)[a]**	

Greater effect size with longer exposure window

Short-term exposure to Radon is associated with respiratory symptoms in urban youth

Radon exposure (moving avg)	Wheezing		Nighttime difficulty breathing		Nocturnal cough		Missed school days	
	Home	School	Home	School	Home	School	Home	School
1 month	1.05 (0.65-1.67)	1.76 (0.89-3.48)	0.79 (0.39-1.62)	2.18 (0.88-5.42)	1.21 (0.77-1.89)	1.55 (0.82-2.95)	1.18 (0.64-2.19)	**5.27 (2.09-13.2)[b]**
5 month	1.03 (0.65-1.62)	**2.68 (1.34-5.38)[b]**	0.80 (0.40-1.61)	**3.53 (1.38-9.04)[b]**	1.20 (0.78-1.85)	**2.36 (1.23-4.53)[b]**	1.12 (0.61-2.04)	**7.63 (2.91-20)[b]**
7 month	1.16 (0.71-1.89)	**2.91 (1.34-6.33)[b]**	0.98 (0.48-1.99)	**4.46 (1.58-12.54)[b]**	1.37 (0.86-2.19)	**2.5 (1.21-5.18)[a]**	1.24 (0.66-2.33)	**8.98 (3.12-25)[b]**

Long-term exposure to Radon is associated with respiratory symptoms in urban youth

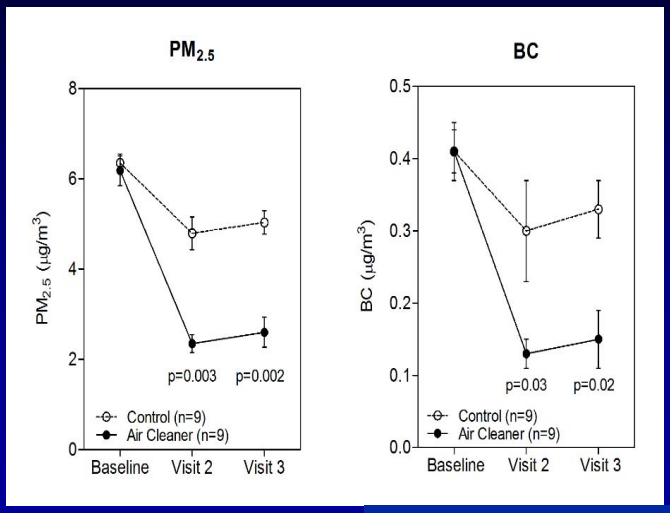
12 month	**1.2 (0.71-2.01)**		**1.08 (0.52-2.23)**		**1.50 (0.91-2.46)**		**1.36 (0.71-2.61)**	
24 month	1.34 (0.77-2.33)		1.15 (0.52-2.52)		**1.76 (1.03-3)[a]**		1.48 (0.74-2.98)	
36 month	1.55 (0.84-2.84)		1.27 (0.54-2.96)		**2 (1.11-3.62)[a]**			
48 month	1.67 (0.86-3.22)		1.31 (0.52-3.31)		**2.24 (1.17-4.25)[a]**		1.83 (0.79-4.22)	
60 month	1.75 (0.87-3.51)		1.31 (0.49-3.48)		**2.43 (1.23-4.78)[b]**		1.98 (0.81-4.8)	

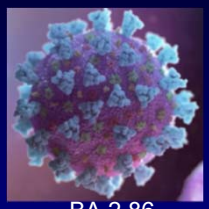
Mukharesh L., Phipatanakul W. and Gaffin JM. Peds Pulmonology 2022

Some lessons learned for far..

- The home is important in asthma morbidity and racial disparities
- Multi-faceted home interventions help and could potentially modify the disease
- Reducing mouse allergen in homes can work as well as ICS and benefits can last longer
- School environment is important in asthma disparities even after adjusting for home (particularly, mouse/mold allergen, pollutants, (radioactive particles?)) and other risk factors (obesity, sleep issues, inflammatory markers) augment this risk
- Can we do anything about this? Can we intervene in the schools and make an impact?

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





BA.2.86

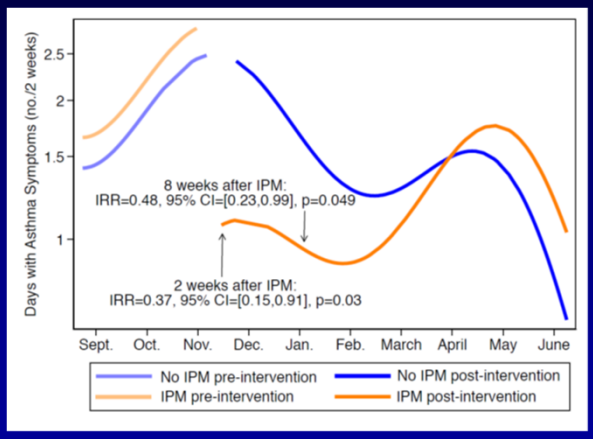
Lai PS R21 NIAID Molecular epidemiology of viruses in Schools

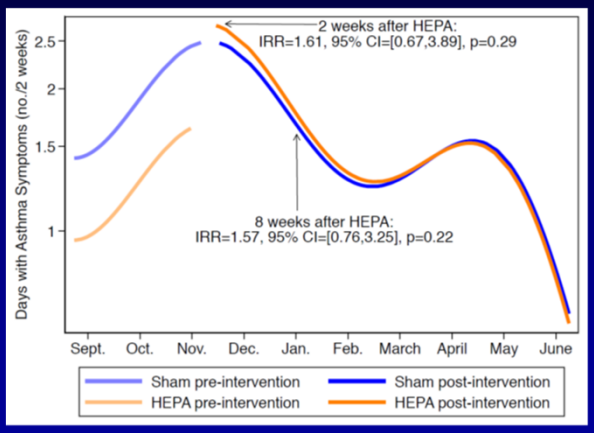
NIEHS R21-HEPA cleaners, and viruses in schools- SICAS 4

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

Phipatanakul, W, et al JMA Sept 2021

Time Effect of the School IPM and Classroom HEPA on Health Effects





Phipatanakul, W, et al JAMA Sept 2021

Classroom HEPA filtration in Students Exposed to Higher Indoor Classroom Mold than at Home

	HEPA (N=43)	Sham (N=38)	P
Group 1 (indoor mold)	-5.44	-3.30	0.025
Group 2 (outdoor mold)	-4.15	-3.93	0.330
Environmental Relative Mold Index (ERMI)	-1.29	+0.63	0.026
FEV1% increase	4.69	0.47	0.034

EPA Vesper, S, et al 2022 J Asthma

EDITORIAL

JAMA

School Classrooms as Targets to Reduce Allergens and Improve Asthma

William W. Busse, MD; Daniel J. Jackson, MD

…" implementing allergen avoidance with <u>targeted environments and in selected patients</u> may improve the likelihood of success…."

"Childhood asthma often is a lifelong disease"

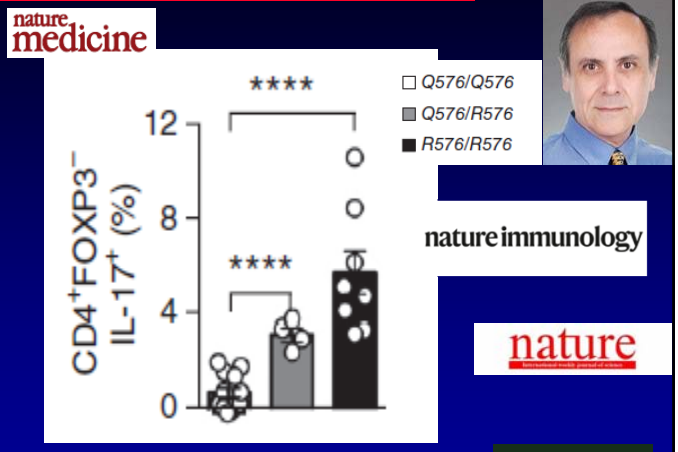
"Early life efforts to improve asthma control that are safe and effective may diminish consequences and need for systemic corticosteroids…"

"Allergen avoidance for asthma is <u>safe, rational, and remains worthy of continued consideration and study</u>"

Taking What We Learned in Schools to Precision Medicine

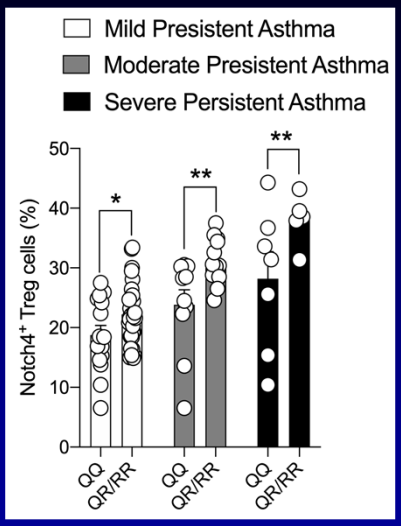
An asthma associated IL4R polymorphism Increases Airway Inflammation by Conversion of regulatory T cells to Th_{17}-like Cells

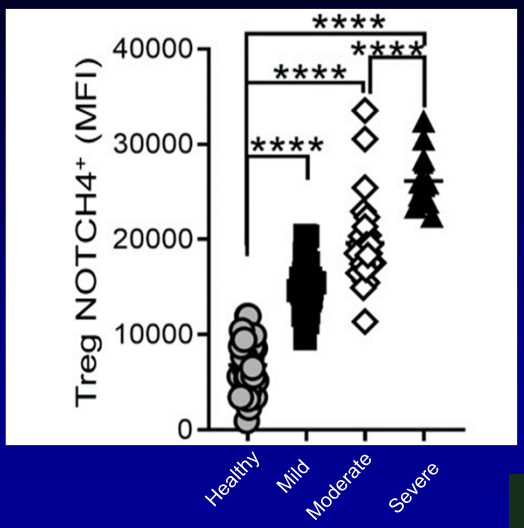
- IL-4Rα-Q576R polymorphism- (glutamine (Q) to arginine R substitution at position 576 of the IL-4Rα)
  - R allele frequency 68% (blacks/hispanics); 20% (whites)
  - R allele associated with severe asthma
  - Unique among *IL4R* polymorphisms, directly drives T_H2 to T_H17 inflammatory response in the airways
  - Dose response relation with severity
  - Augmented by obesity



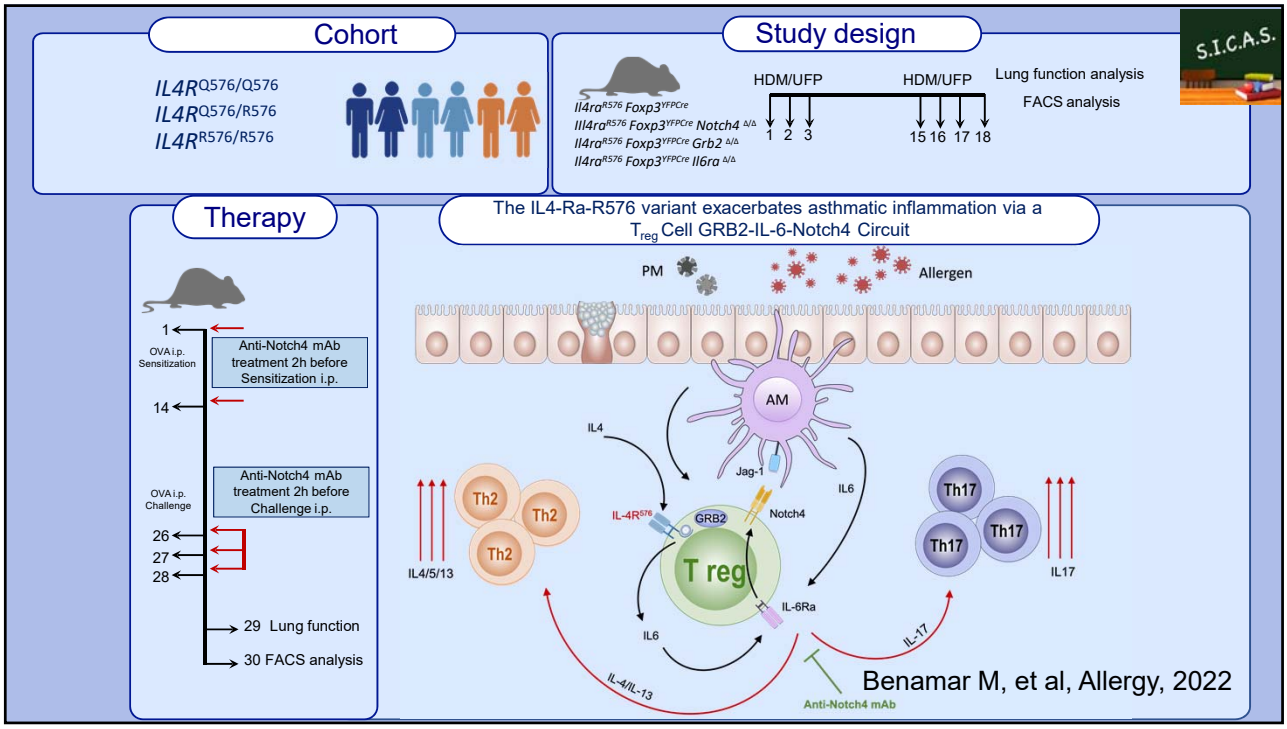
Massoud et al, Nat Med 2016; 22(9):1013-22
Hani H, et al Nature Immunol November, 2020
Babat, S, et al Nature March 2021

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





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

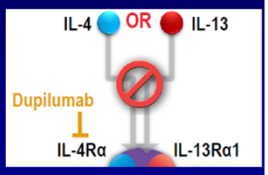


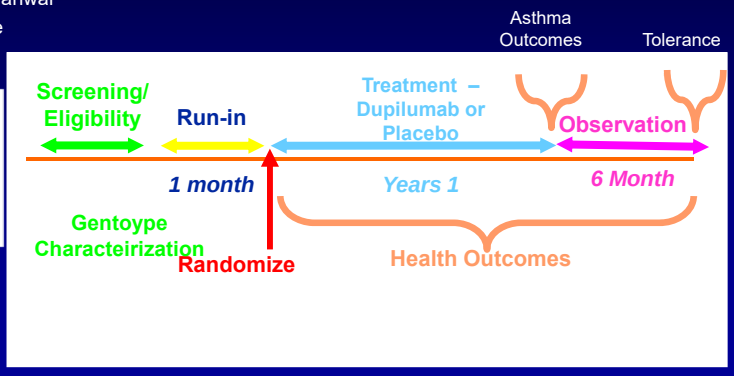
Benamar M, et al, Allergy, 2022

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





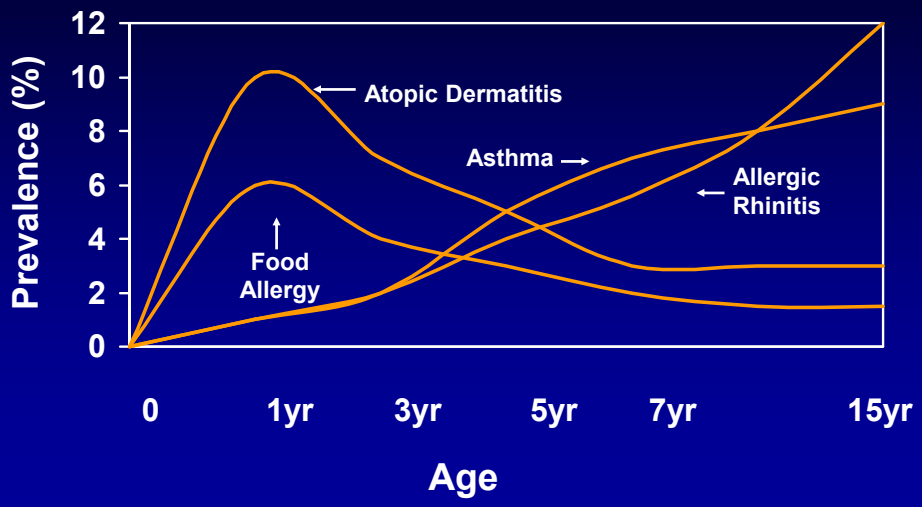
Will investigate genotype driven (personalized) response to therapy and study preliminary mechanisms in disease modification

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

https://ideaasthma.org

Biologics in Disease Modification and Prevention

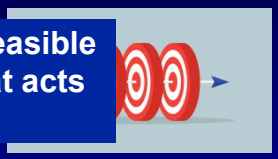
IgE Mediated "Allergic/Atopic March"



Triple Threat: Important in the Development of Asthma

ATOPY

IS there anything available/feasible to use in young children that acts on the "triple threat"?



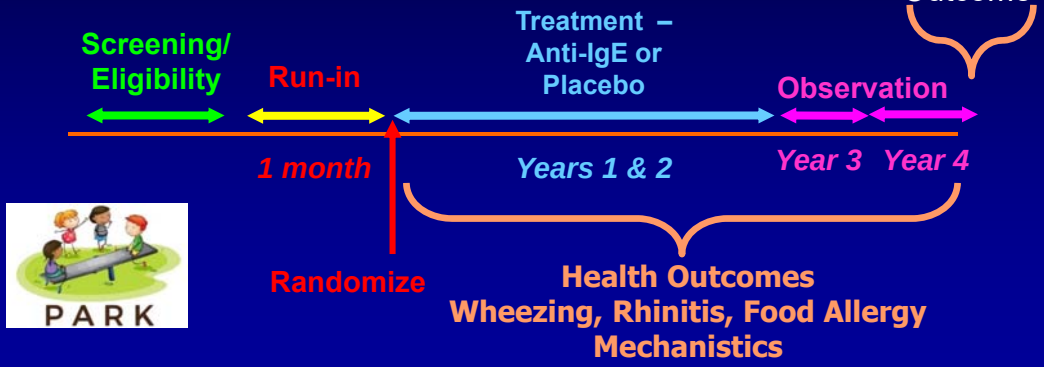
EXPOSURE

Preventing Asthma in High Risk Kids- PARK

https://answers.childrenshospital.org/asthma-prevention-xolair/

U01AI126614- Principal Investigator Phipatanakul- NCT02570984

Randomized, multicenter, DBPC Trial in 200 allergic wheezing toddlers age 2-3 who are at high risk for developing established asthma



Can asthma be nipped in the bud?

Posted on August 2, 2016 by Nancy Fliesler Posted in Pediatrics, Therapeutics

More On: asthma, clinical trials, Division of Allergy and Immunology, Wanda Phipatanakul

A multicenter randomized trial is testing omalizumab (Xolair) in wheezy toddlers. (FDA/Wikimedia Commons)

The randomized, double-blind **Preventing Asthma in High Risk Kids (PARK)** trial is supported by a seven-year, $20 million Asthma Prevention Grant from the NIH's National Institute of Allergy and Infectious Diseases (NIAID). By its end, it will enroll 250 wheezy 2- and 3-year-olds with a positive allergy test. The children will receive either Xolair or placebo and will be followed for four years — two years on the treatment, then two years off — to see what proportion of each group develops active asthma as defined by NIAID.

https://answers.childrenshospital.org/asthma-prevention-xolair/

In Summary…

- **School environment is important in asthma morbidity, where nearly every child spends their day**
- **We can intervene on relevant school specific exposures- but more sustained measures are needed to have lasting benefit on health**
- **Decade of community relationships allow us to expand our work into understanding of risk factors and intervention (i.e. obesity, metabolic syndrome, cytokines), microbial and other exposures, and gene x environment interactions in a home/school setting and its effects on disease – Timeliness of results can help inform future strategies to provide healthy environments for kids in school- which is critical in the wake of the pandemic**

Future Directions

- Biologics have changed the landscape on immune based therapies in the treatment of asthma necessitating Precision-Biomarker Driven Approaches
- NIH has several ongoing major efforts in Precision Medicine 1)genotype stratified precision therapy (IDEA), 2) novel therapies in an adaptive trial design (PreCISE)
- Understanding the role of IgE targeted biologics in allergic and rhinovirus induced disease have paved the way to consider immune based strategies to prevention (PARK)
- In the next decade we will have major advancements in understanding what may work in prevention and modifying disease progression -stay tuned

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