Can asthma be prevented?

Kathy Lee-Sarwar

Can asthma be prevented (by modifying the microbiome)?

Kathy Lee-Sarwar

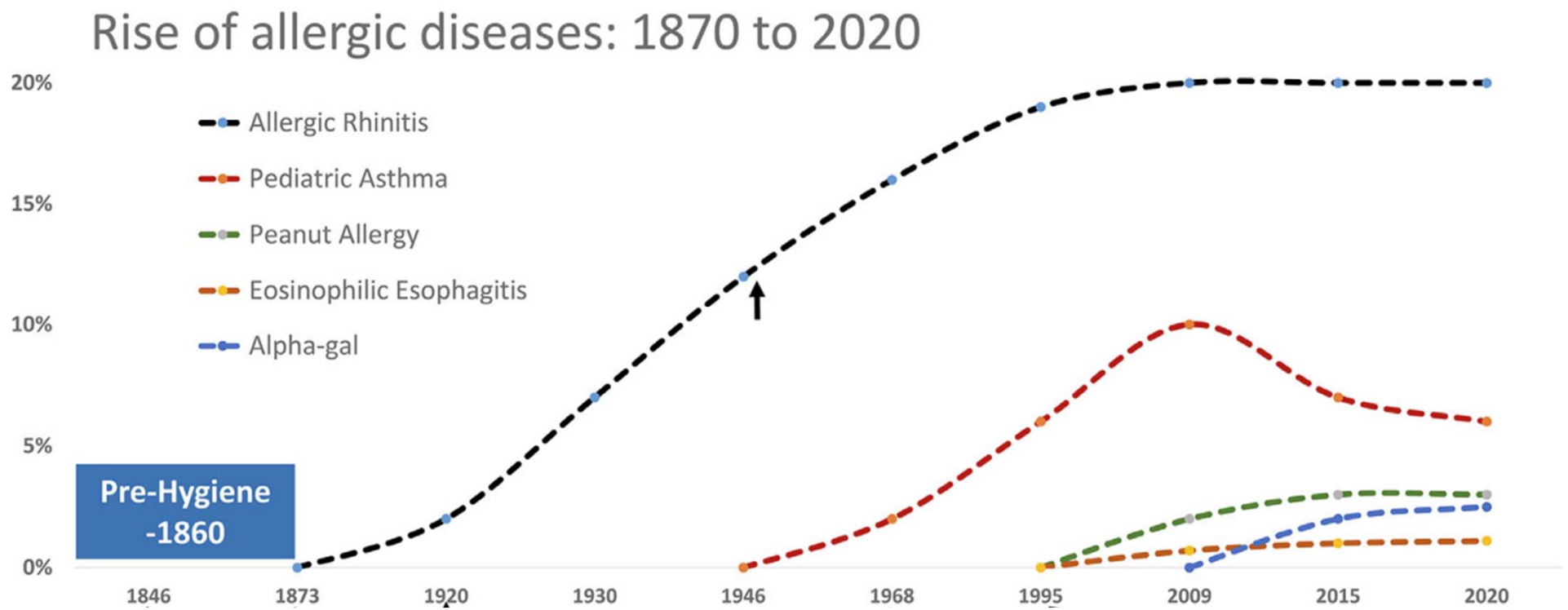


Figure from:
Platts-Mills TAE, et al. Can we alter the course of allergic disease? Ann Allergy Asthma Immunol. 2022 Sep;129(3):271-273.

Meta-Exposome Suspects in Asthma Pathobiology

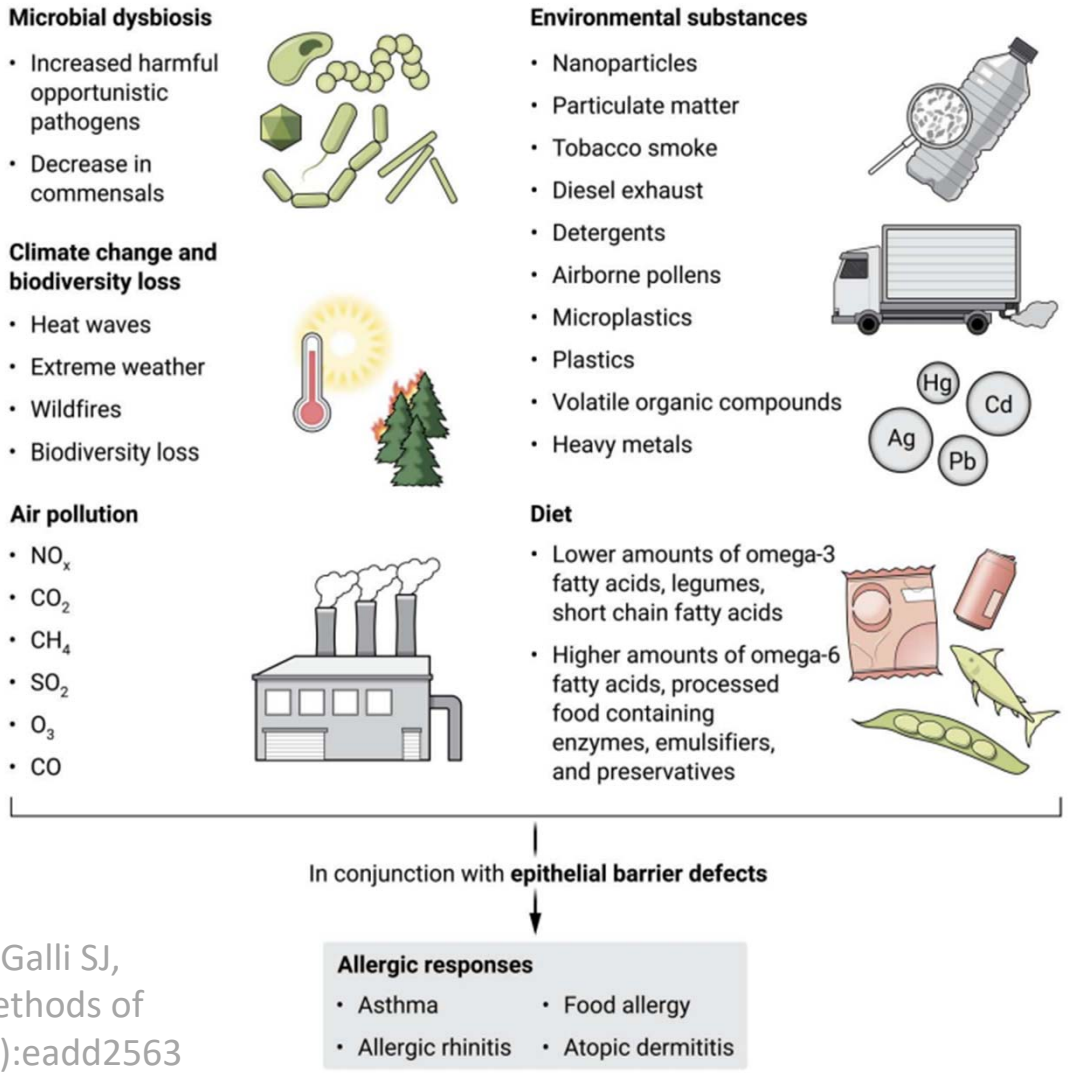


Figure from: Akdis CA, Akdis M, Boyd SD, Sampath V, Galli SJ, Nadeau KC. Allergy: Mechanistic insights into new methods of prevention and therapy. Sci Transl Med. 2023;15(679):eadd2563

Meta-Exposome Suspects in Asthma Pathobiology

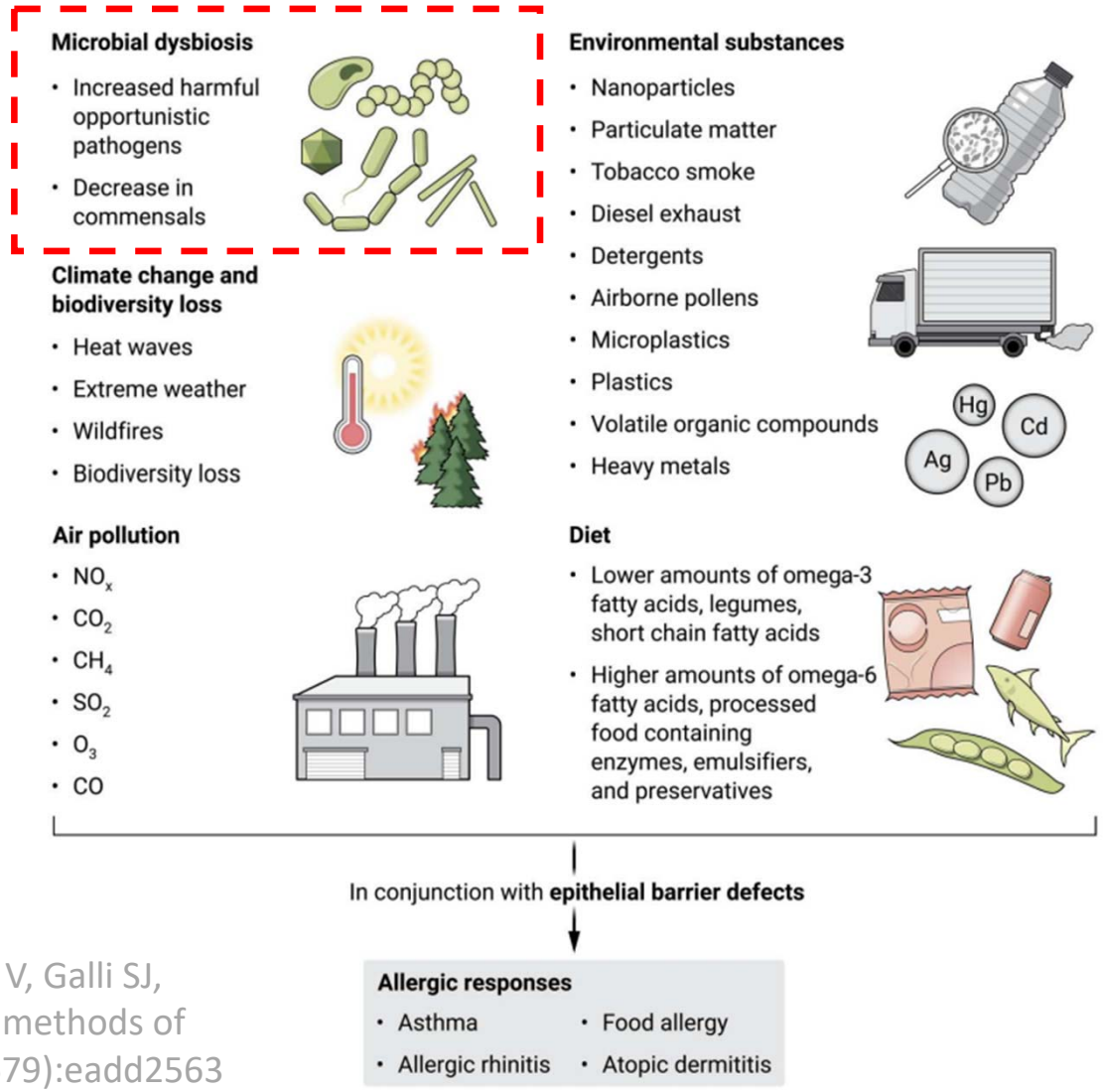
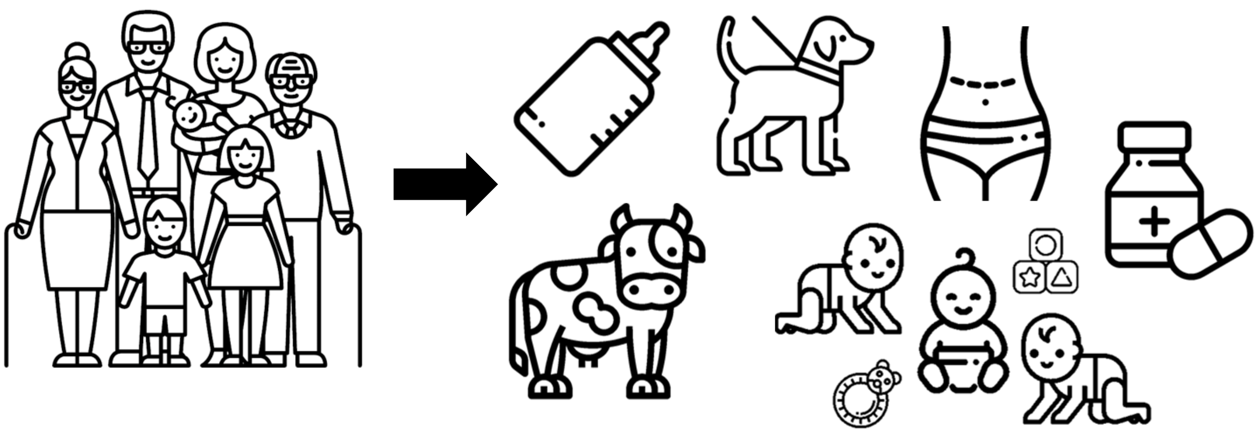


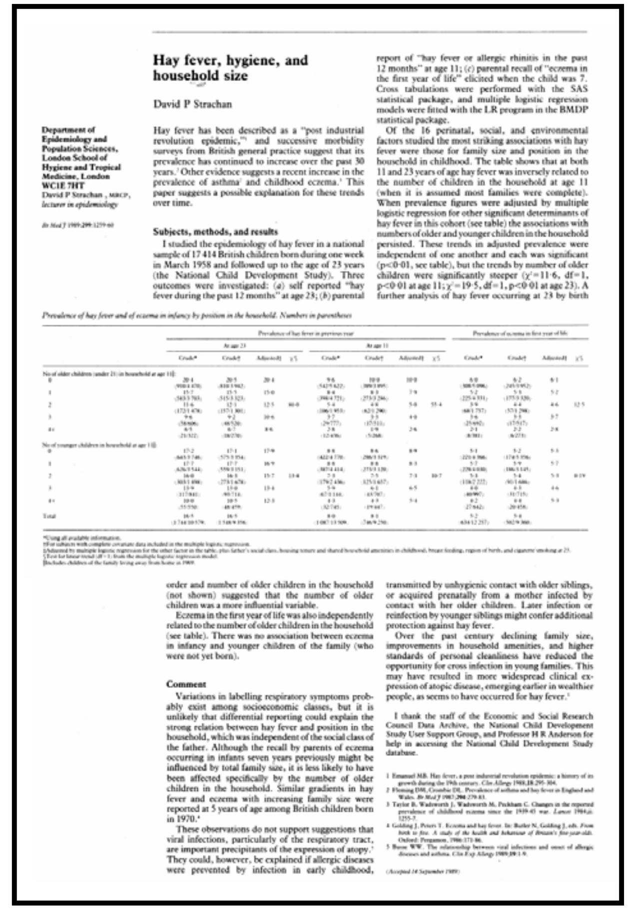
Figure from: Akdis CA, Akdis M, Boyd SD, Sampath V, Galli SJ, Nadeau KC. Allergy: Mechanistic insights into new methods of prevention and therapy. Sci Transl Med. 2023;15(679):eadd2563

Hygiene hypothesis:

Reduced microbial exposure caused increase of allergic disease



Several asthma and allergy risk factors impact microbial exposures.



Hay fever, hygiene, and household size

David P Strachan

Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London WC1E 7HT
David P Strachan, MRCP, lecturer in epidemiology

Br Med J 1989;299:1259-60

Hay fever has been described as a "post industrial revolution epidemic,"[1] and successive morbidity surveys from British general practice suggest that its prevalence has continued to increase over the past 30 years.[2] Other evidence suggests a recent increase in the prevalence of asthma[2] and childhood eczema.[3] This paper suggests a possible explanation for these trends over time.

Subjects, methods, and results

I studied the epidemiology of hay fever in a national sample of 17 414 British children born during one week in March 1958 and followed up to the age of 23 years (the National Child Development Study). Three outcomes were investigated: (a) self reported "hay fever during the past 12 months" at age 23; (b) parental report of "hay fever or allergic rhinitis in the past 12 months" at age 11; (c) parental recall of "eczema in the first year of life" elicited when the child was 7. Cross tabulations were performed with the SAS statistical package, and multiple logistic regression models were fitted with the LR program in the BMDP statistical package.

Of the 16 perinatal, social, and environmental factors studied the most striking associations with hay fever were those for family size and position in the household in childhood. The table shows that at both 11 and 23 years of age hay fever was inversely related to the number of children in the household at age 11 (when it is assumed most families were complete). When prevalence figures were adjusted by multiple logistic regression for other significant determinants of hay fever in this cohort (see table) the associations with numbers of older and younger children in the household persisted. These trends in adjusted prevalence were independent of one another and each was significant (p<0·01, see table), but the trends by number of older children were significantly steeper (χ^2=11·6, df=1, p<0·01 at age 11; χ^2=19·5, df=1, p<0·01 at age 23). A further analysis of hay fever occurring at 23 by birth order and number of older children in the household (not shown) suggested that the number of older children was a more influential variable.

Prevalence of hay fever and of eczema in infancy by position in the household. Numbers in parentheses

Eczema in the first year of life was also independently related to the number of older children in the household (see table). There was no association between eczema in infancy and younger children of the family (who were not yet born).

Comment

Variations in labelling respiratory symptoms probably exist among socioeconomic classes, but it is unlikely that differential reporting could explain the strong relation between hay fever and position in the household, which was independent of the social class of the father. Although the recall by parents of eczema occurring in infants seven years previously might be influenced by total family size, it is less likely to have been affected specifically by the number of older children in the household. Similar gradients in hay fever and eczema with increasing family size were reported at 5 years of age among British children born in 1970.[4]

These observations do not support suggestions that viral infections, particularly of the respiratory tract, are important precipitants of the expression of atopy.[5] They could, however, be explained if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally from a mother infected by contact with her older children. Later infection or reinfection by younger siblings might confer additional protection against hay fever.

Over the past century declining family size, improvements in household amenities, and higher standards of personal cleanliness have reduced the opportunity for cross infection in young families. This may have resulted in more widespread clinical expression of atopic disease, emerging earlier in wealthier people, as seems to have occurred for hay fever.[1]

I thank the staff of the Economic and Social Research Council Data Archive, the National Child Development Study User Support Group, and Professor H R Anderson for help in accessing the National Child Development Study database.

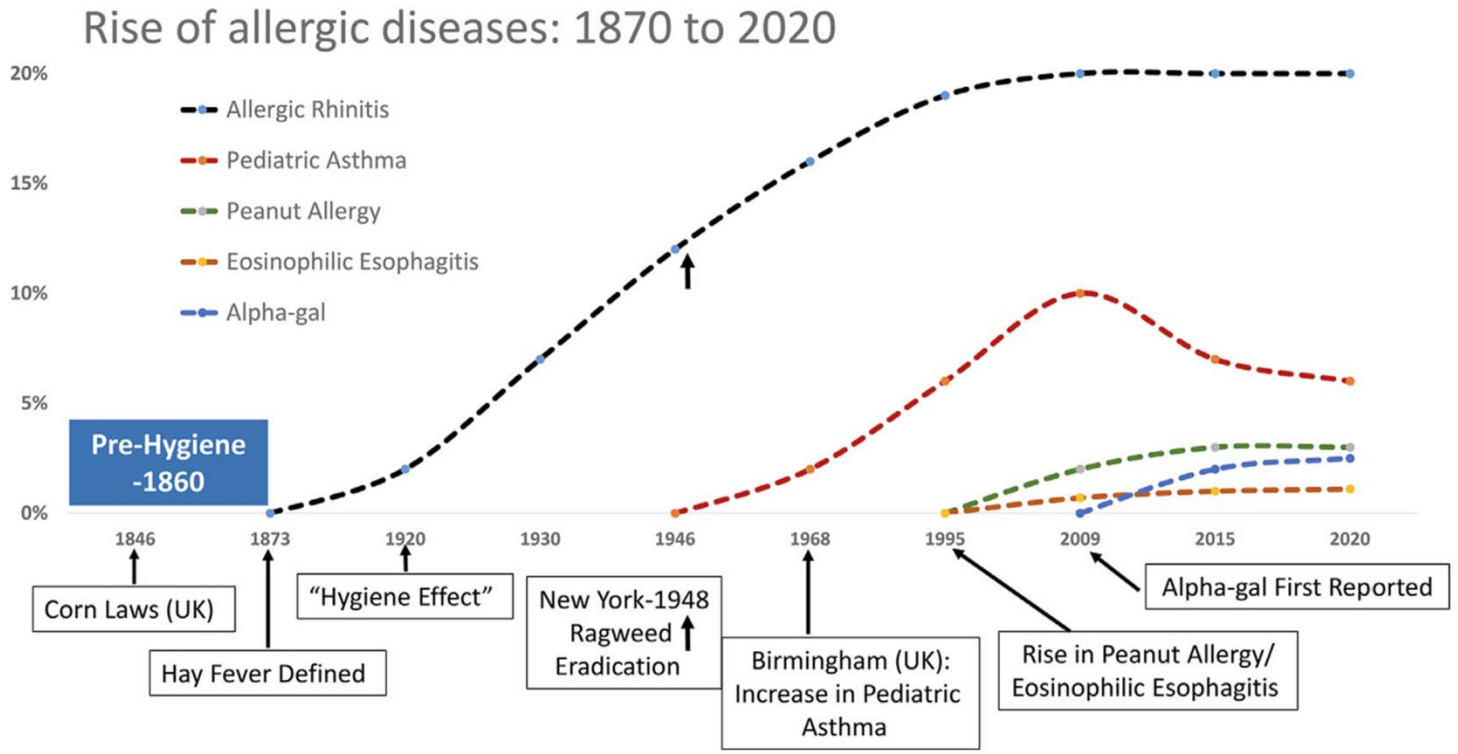
1 Emanuel MB. Hay fever, a post industrial revolution epidemic: a history of its growth during the 19th century. Clin Allergy 1988;18:295-304.
2 Fleming DM, Crombie DL. Prevalence of asthma and hay fever in England and Wales. Br Med J 1987;294:279-83.
3 Taylor B, Wadsworth J, Wadsworth M, Peckham C. Changes in the reported prevalence of childhood eczema since the 1939-45 war. Lancet 1984;ii:1255-7.
4 Golding J, Peters T. Eczema and hay fever. In: Butler N, Golding J, eds. From birth to five. A study of the health and behaviour of Britain's five-year-olds. Oxford: Pergamon, 1986:171-86.
5 Busse WW. The relationship between viral infections and onset of allergic diseases and asthma. Clin Exp Allergy 1989;19:1-9.

(Accepted 14 September 1989)

von Mutius E, J Allergy Clin Immunol 2016.
Lynch S, Curr Opin Allergy CI 2016.

Strachan DP. "Hay fever, hygiene, and household size." BMJ 1989

Problems with the Hygiene Hypothesis



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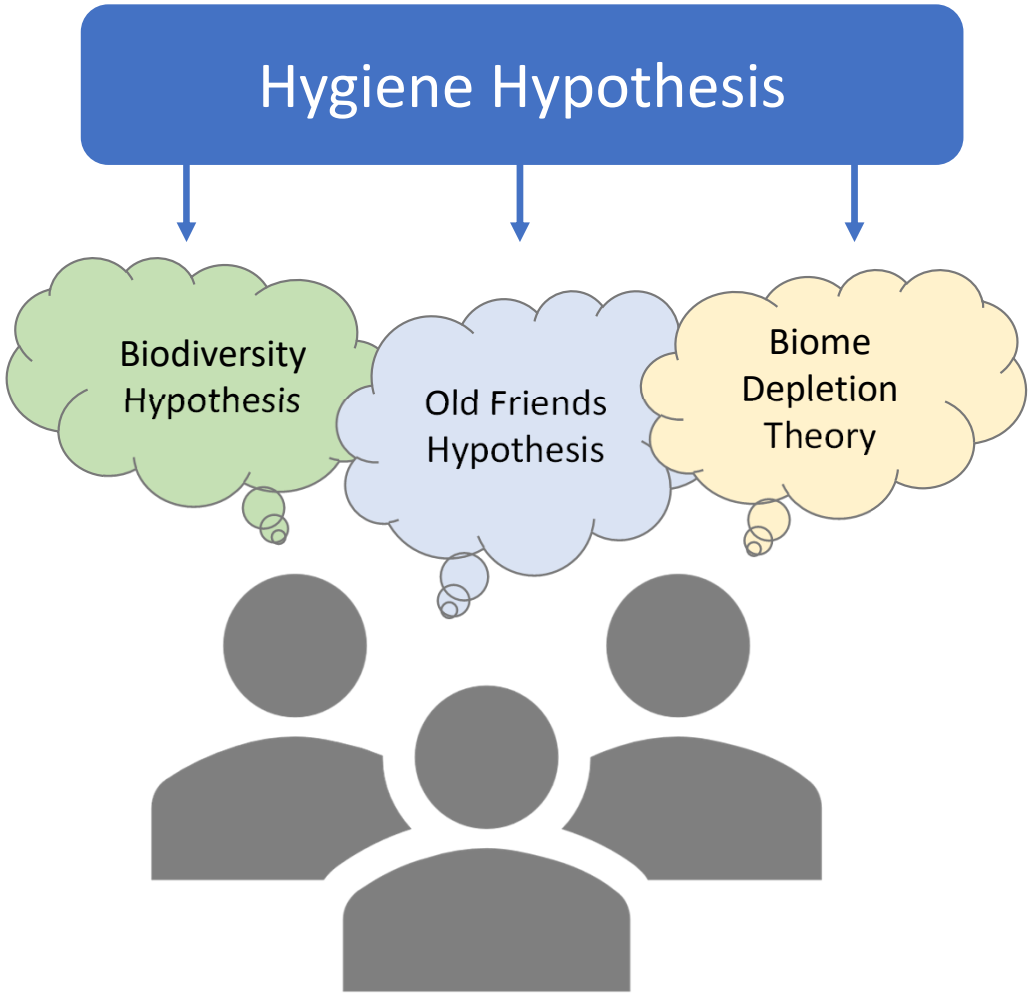
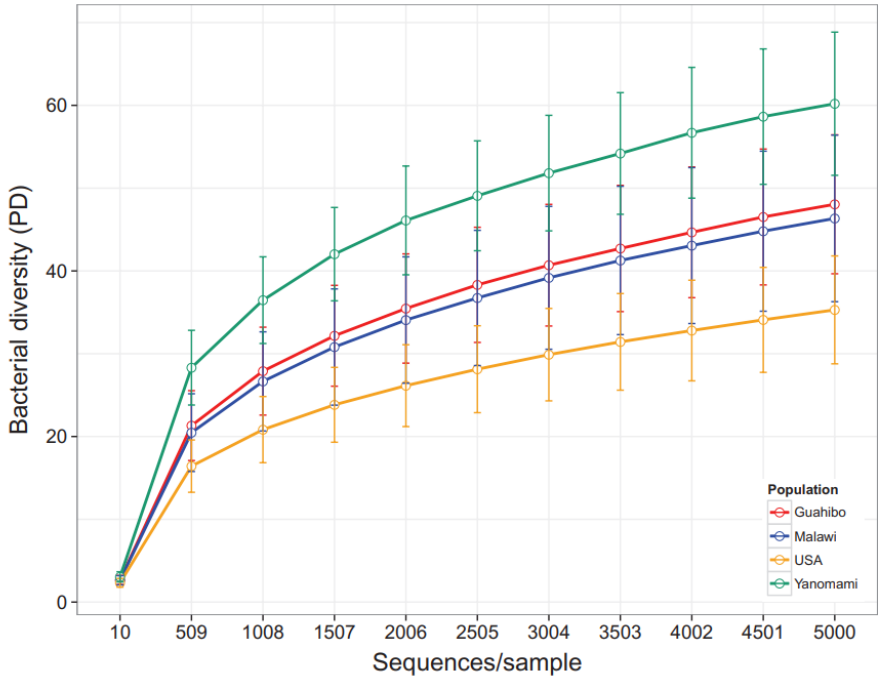
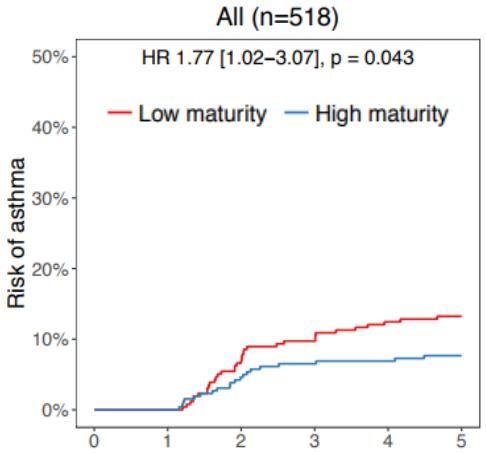




Clemente, Sci Adv 2015

Pfefferle, et al. The Hygiene Hypothesis – Learning From but Not Living in the Past. Front Immunol 2021.

Rationally targeting the microbiome: Epidemiologic Evidence

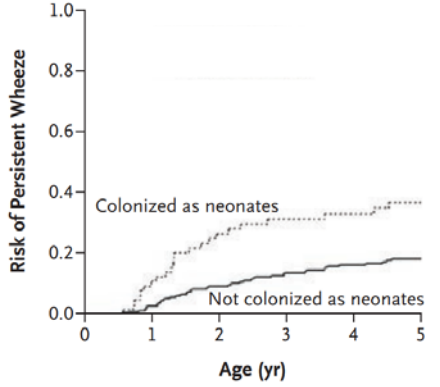


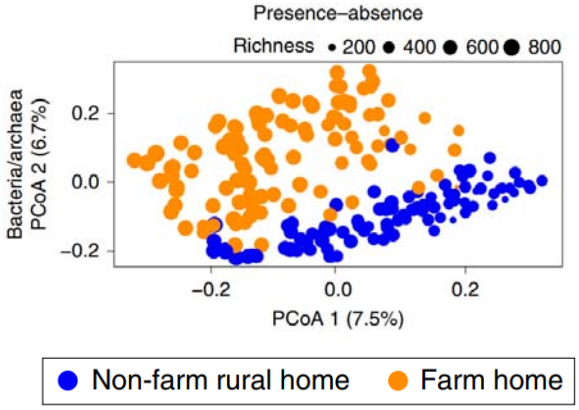
Perturbed ***maturation*** of the gut microbiome in infancy is associated with asthma at age 6 years.

Stokholm J, *et al.* Nat Comm 2018.

Colonization of the hypopharynx at age 1 month with ***S. pneumoniae, M. catarrhalis*** **or** ***H. influenzae*** associated with asthma at age 5 years.

Bisgaard H, *et al*. N Engl J Med 2007.





Residence in a ***farm or farm-like home*** is associated with reduced childhood asthma.

Kirjavainen PV, *et al*. Nat Med 2019.

Rationally targeting the microbiome: Experimental Evidence

19/26 DECEMBER 2013 | VOL 504 | NATURE | 451

Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation

Nicholas Arpaia[1,2], Clarissa Campbell[1,2], Xiying Fan[1,2], Stanislav Dikiy[1,2], Joris van der Veeken[1,2], Paul deRoos[1,2], Hui Liu[3], Justin R. Cross[3], Klaus Pfeffer[4], Paul J. Coffer[1,2,5] & Alexander Y. Rudensky[1,2]

SCIENCE VOL 341 2 AUGUST 2013

The Microbial Metabolites, Short-Chain Fatty Acids, Regulate Colonic T_{reg} Cell Homeostasis

Patrick M. Smith,[1] Michael R. Howitt,[1] Nicolai Panikov,[1] Monia Michaud,[1] Carey Ann Gallini,[1] Mohammad Bohlooly-Y,[5] Jonathan N. Glickman,[6,7] Wendy S. Garrett[1,2,3,4]*

00 MONTH 2013 | VOL 000 | NATURE | 1

Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells

Yukihiro Furusawa[1,2]*, Yuuki Obata[1,2,3]*, Shinji Fukuda[1-4]*, Takaho A. Endo[1], Gaku Nakato[1], Daisuke Takahashi[1], Yumiko Nakanishi[4], Chikako Uetake[1], Keiko Kato[1,5], Tamotsu Kato[1], Masumi Takahashi[1], Noriko N. Fukuda[4], Shinnosuke Murakami[4], Eiji Miyauchi[1], Shingo Hino[6], Koji Atarashi[1,7], Satoshi Onawa[1], Yumiko Fujimura[2], Trevor Lockett[8], Julie M. Clarke[8], David L. Topping[8], Masaru Tomita[4], Shohei Hori[1], Osamu Ohara[1], Tatsuya Morita[6], Haruhiko Koseki[1,3,5], Jun Kikuchi[5,9], Kenya Honda[1,10], Koji Hase[1,2,7]* & Hiroshi Ohno[1,3,5]

Cell Host & Microbe

A bacterial bile acid metabolite modulates T_{reg} activity through the nuclear hormone receptor NR4A1

Li et al., 2021, Cell Host & Microbe 29, 1366–1377

Bile acid metabolites control T_H17 and T_{reg} cell differentiation

Nature | Vol 576 | 5 December 2019

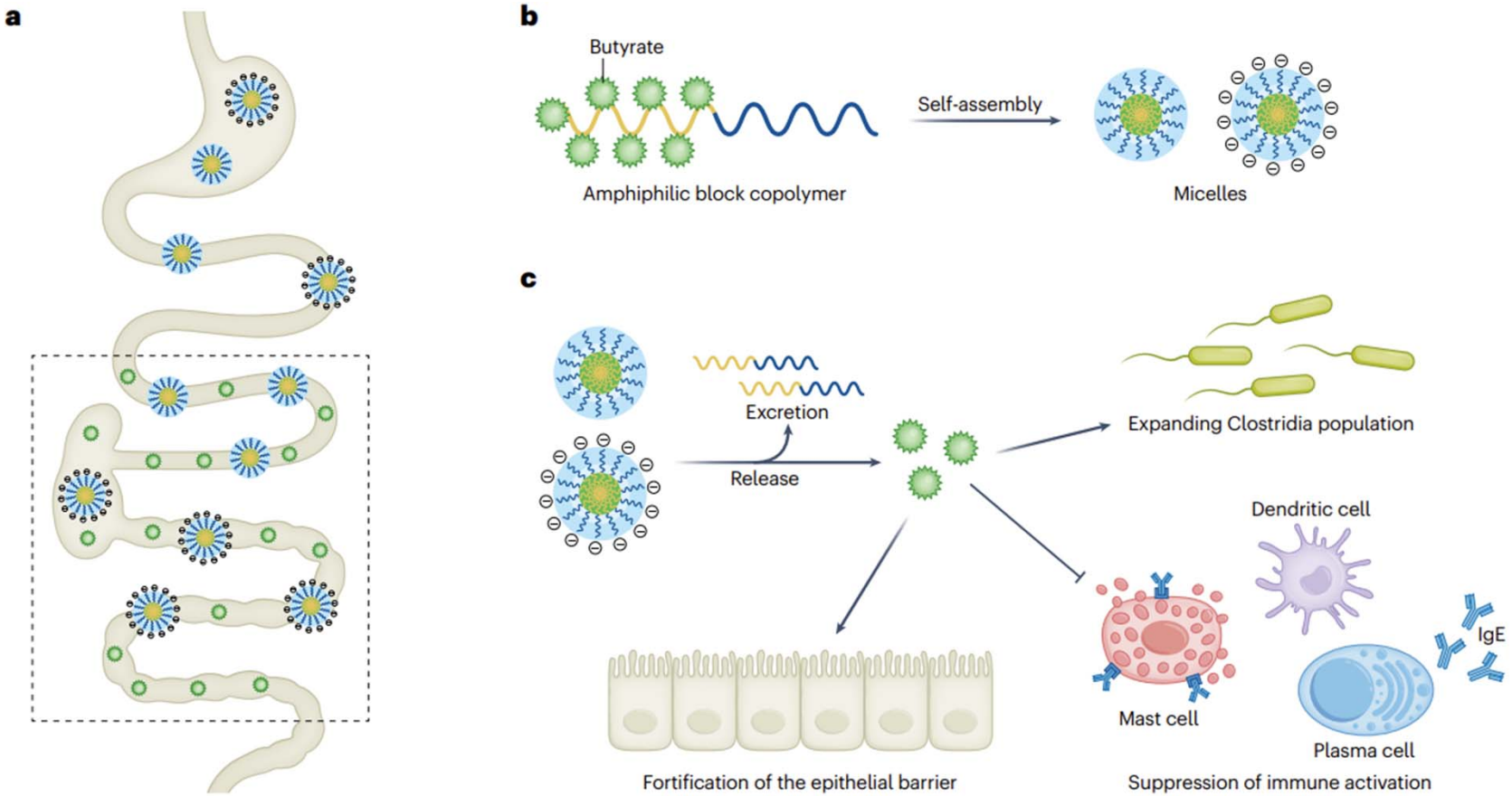
Saiyu Hang[1,12], Donggi Paik[1,12], Lina Yao[2], Eunha Kim[1], Jamma Trinath[3], Jingping Lu[4], Soyoung Ha[1], Brandon N. Nelson[5], Samantha P. Kelly[5], Lin Wu[6], Ye Zheng[7], Randy S. Longman[8], Fraydoon Rastinejad[4], A. Sloan Devlin[2], Michael R. Krout[5], Michael A. Fischbach[9]*, Dan R. Littman[6,10]* & Jun R. Huh[1,11]*

Bacterial metabolism of bile acids promotes generation of peripheral regulatory T cells

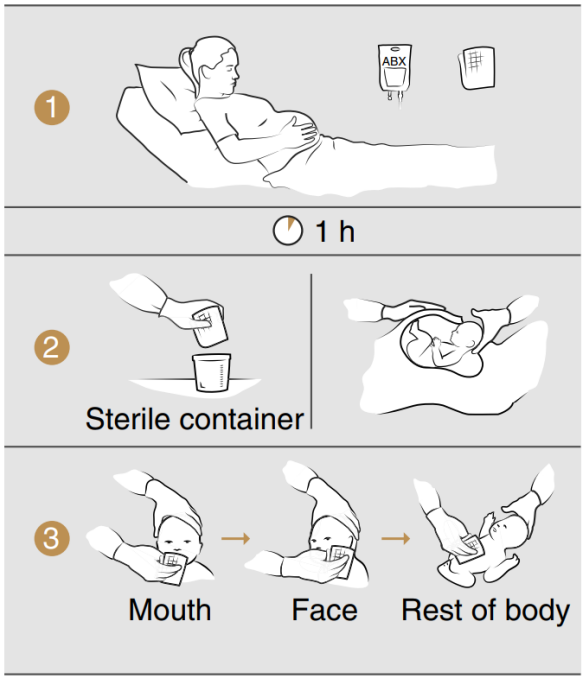
Clarissa Campbell[1,10]✉, Peter T. McKenney[1,2,10], Daniel Konstantinovsky[3], Olga I. Isaeva[4,5], Michail Schizas[1], Jacob Verter[1], Cheryl Mai[6], Wen-Bing Jin[7], Chun-Jun Guo[7], Sara Violante[8], Ruben J. Ramos[8], Justin R. Cross[8], Krishna Kadaveru[2], John Hambor[2] & Alexander Y. Rudensky[1,5,7,9]✉

Nature | Vol 581 | 28 May 2020

Local Butyrate Delivery



Wang, et al. Nature Biomed Eng 2022. Fig: Wang, Liu. Nat Biomed Eng 2023.



Vaginal Seeding after Cesarean Section

- 2016: Initial report of vaginal seeding to restore the newborn microbiome.
- Several clinical trials with asthma and allergy primary outcomes are ongoing.
- The practice remains controversial and is not recommended by ACOG.

"In one sense, the science isn't settled yet. In another sense, compared to other choices you might be making this is a very natural choice. Had you not delivered your baby by C-section there's no way you could escape coating your baby in these bacteria." – Rob Knight, UCSD

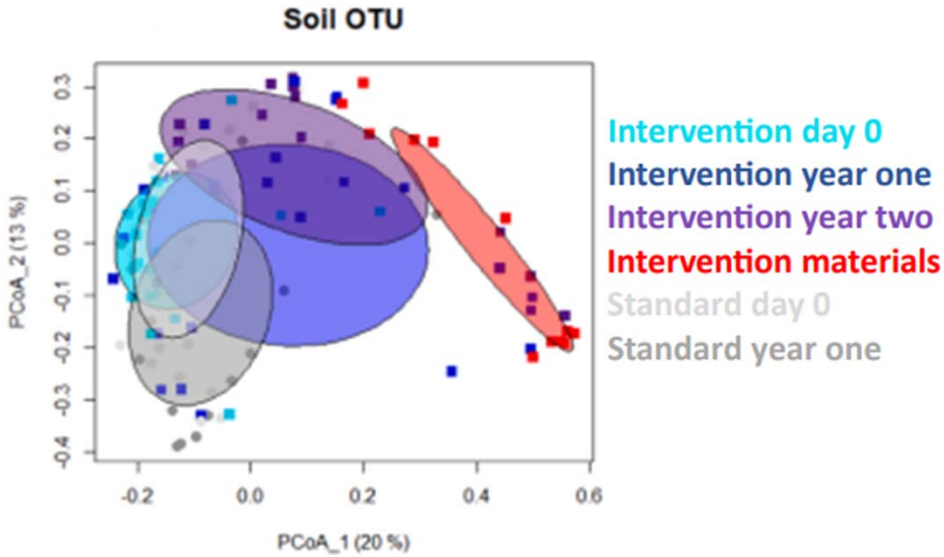
In the worst-case scenario, "you've taken a kid with low risk of infection and you've rubbed herpes all over their face." – Adam Ratner, NYU

Dominguez-Bello MG, et al. Nat Med 2016.

Engineering the Environmental Microbiome

Finnish study: Modifying outdoor play areas at urban daycares with forest floor vegetation and sod leads to changes in children's microbiomes.

ADELE research group, Environ Int 2021.



Other efforts include development of a door mat packed with microbe-rich soil to be used at the entries of urban homes

Martin Täubel, Finnish institute for health and welfare

Can asthma be prevented (by modifying the microbiome)?

Can asthma be prevented
(by modifying the microbiome)?

Maybe!

Can Asthma Be Prevented? Modification of allergic pathways in early childhood

Wanda Phipatanakul, MD, MS
Partners Asthma Grand Roundds
Professor of Pediatrics
Harvard Medical School
Director, Asthma Clinical Research Center
Boston Children's Hospital

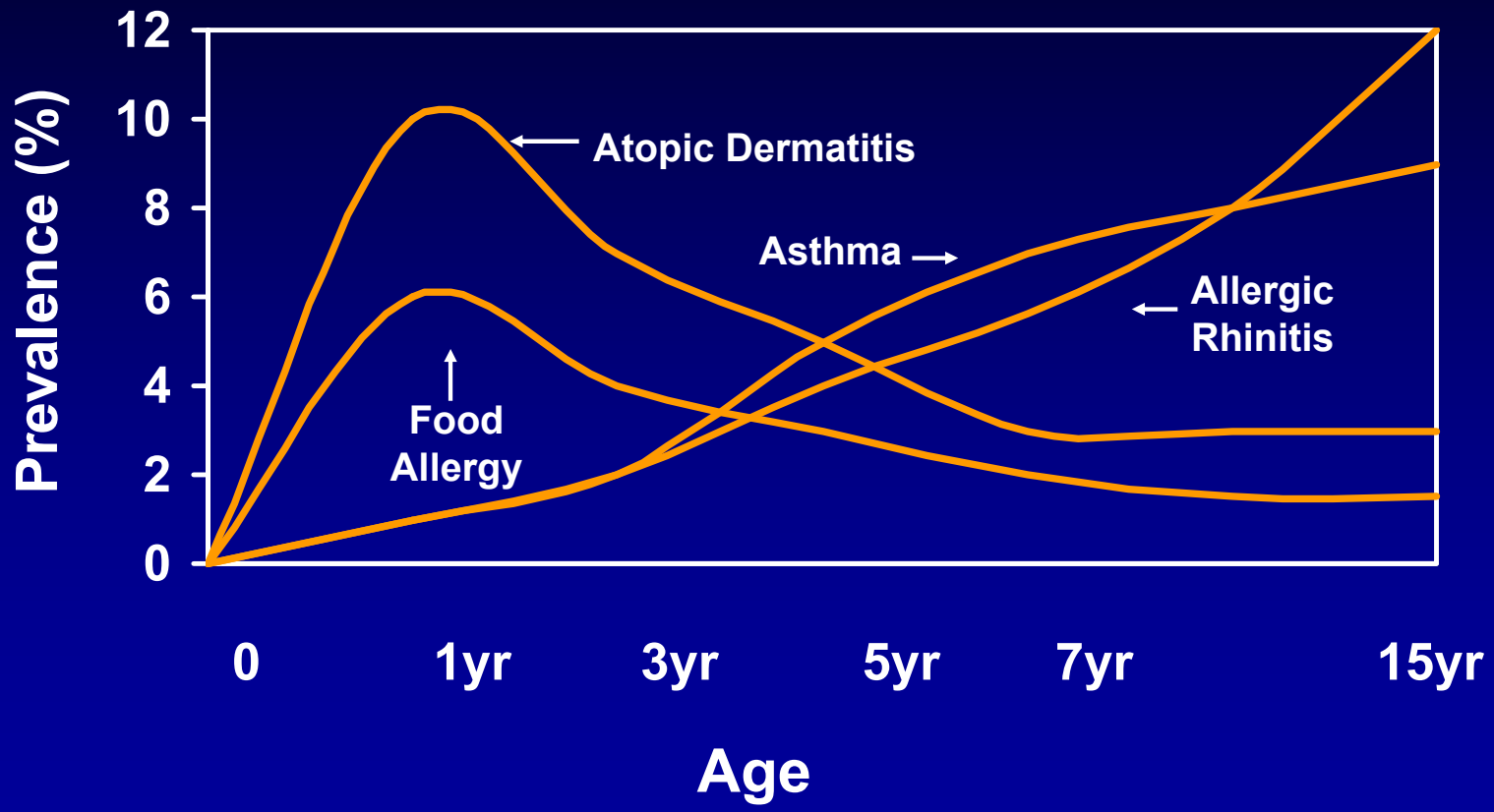
wanda.phipatanakul@childrens.harvard.edu

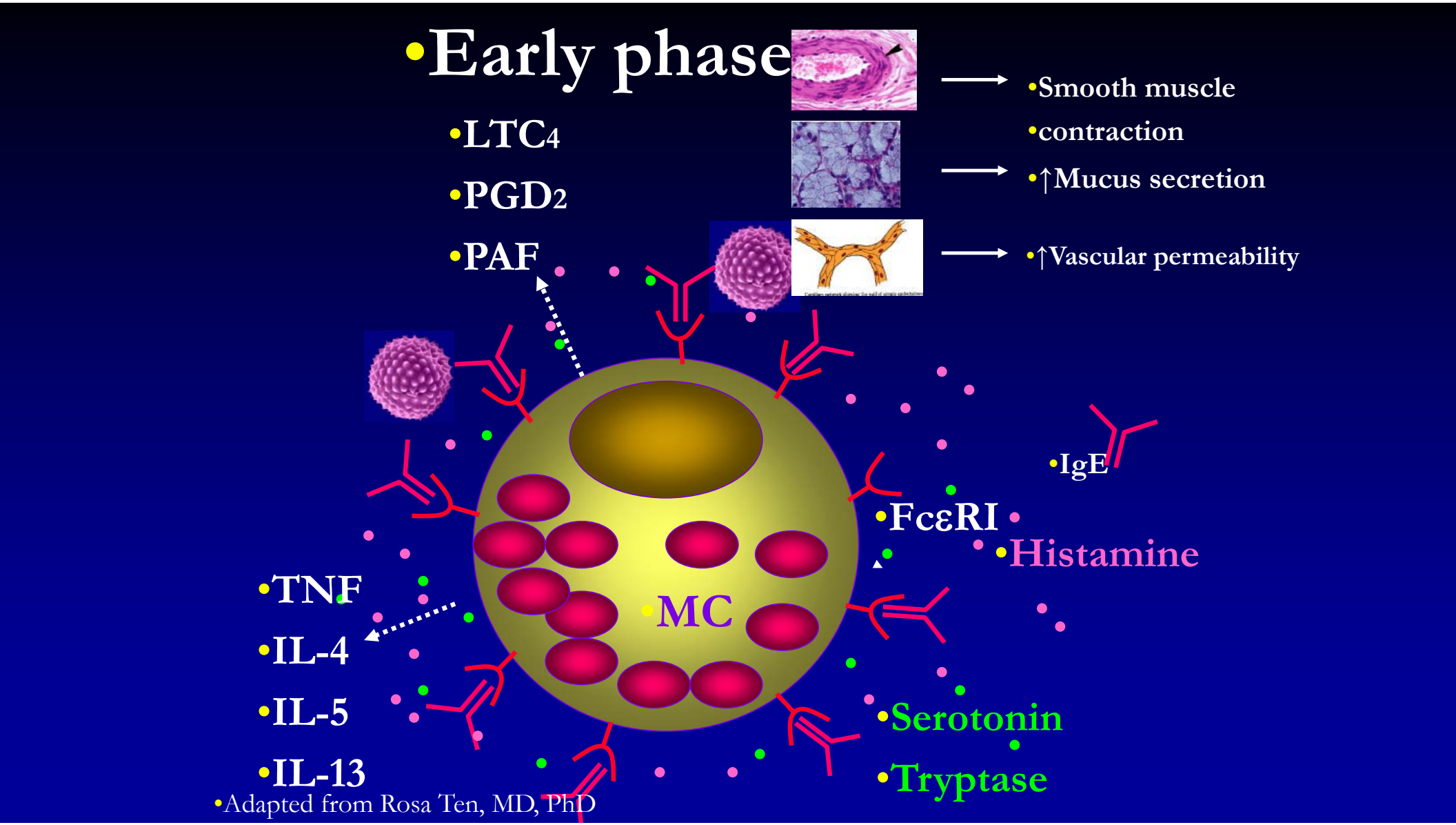
HARVARD
MEDICAL SCHOOL

Disclosures/Objectives

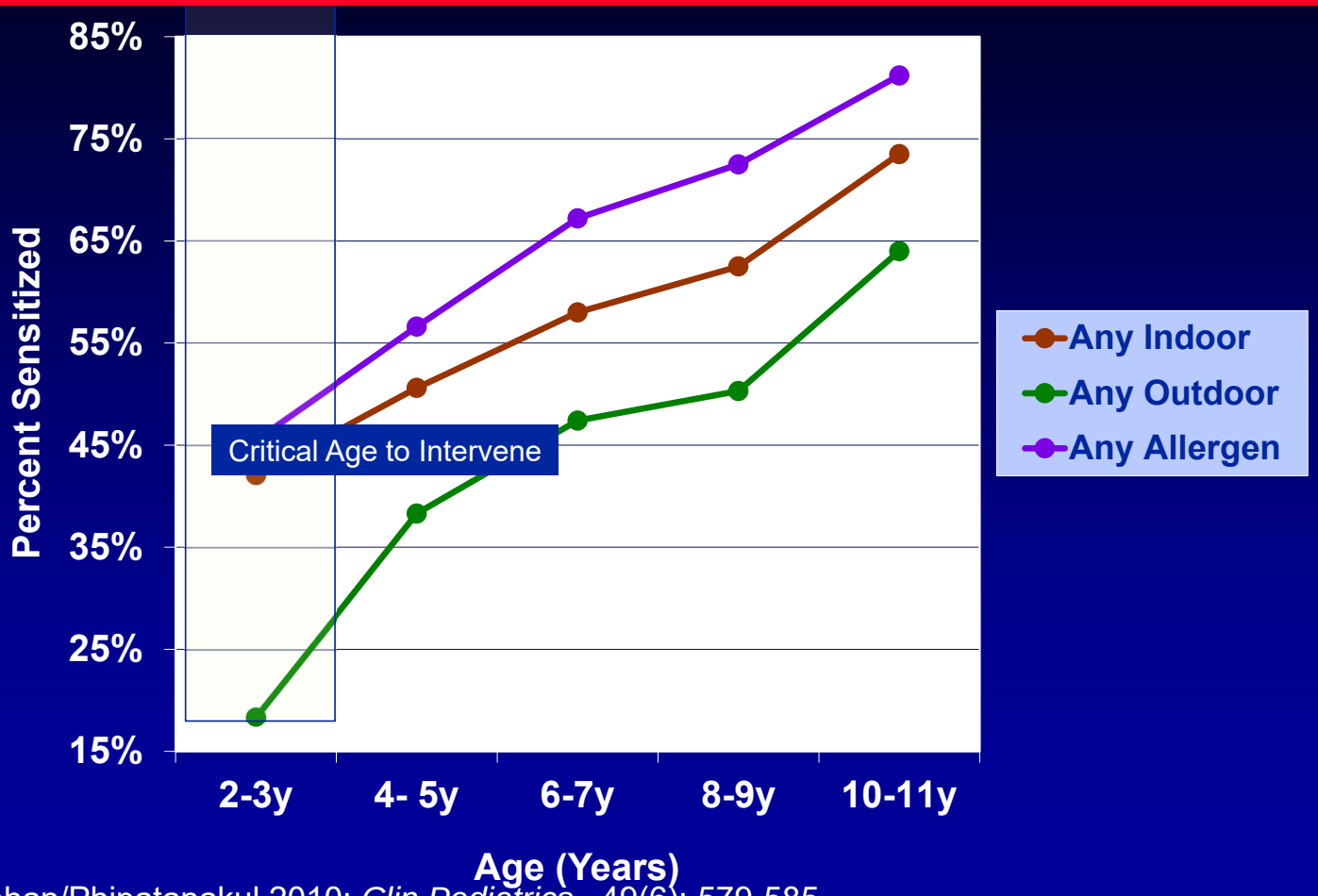
- Funding NIH, Genetech/Novartis, Regeneron
- Trial Support: Alk Abello, Monaghen, Lincoln Diagnostics, GSK
- Consultant Genentech, Novartis, Teva, Regeneron, GSK
- Goal: To Discuss Factors in the Progression of Asthma and Strategies for Prevention and Logical Next Steps

Relative Prevalence of Allergic Diseases



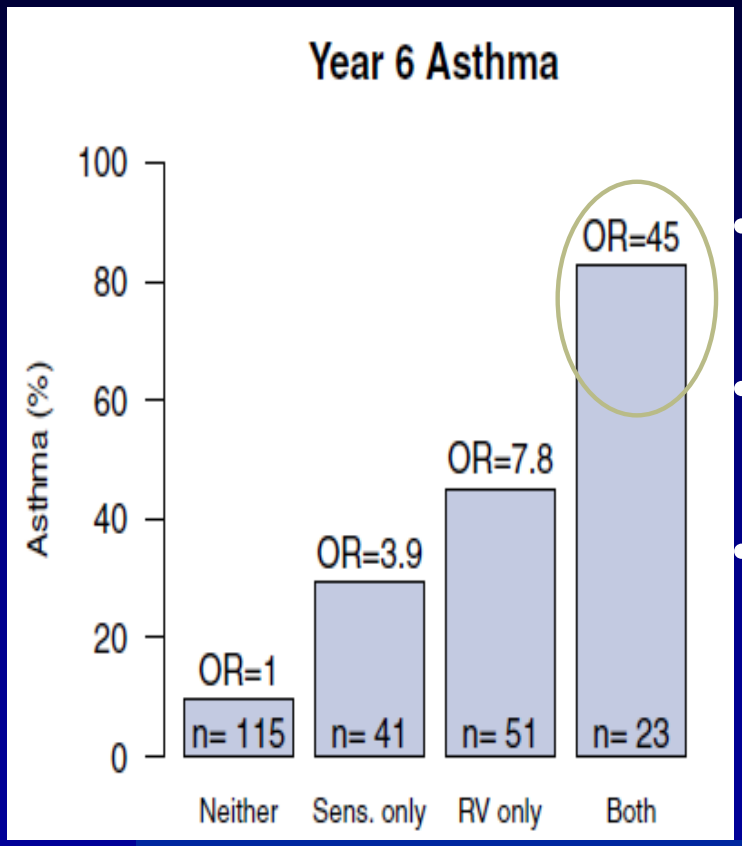

•Early phase
•LTC4
•PGD2
•PAF
•Smooth muscle
•contraction
•↑Mucus secretion
•↑Vascular permeability
•IgE
•FcεRI
•Histamine
•TNF
•IL-4
•IL-5
•IL-13
MC
•Serotonin
•Tryptase
•Adapted from Rosa Ten, MD, PhD

Allergen Sensitization (IgE) Begins in Early Childhood and then Takes Off "Atopic March"



Sheehan/Phipatanakul 2010; *Clin Pediatrics*. 49(6): 579-585

Childhood Origins of Asthma Cohort



- 217 children high risk children followed from birth
- Allergy prior to viral wheeze pivotal
- Timing and magnitude strong risk factor
- Atopy and Wheeze at age 3 markedly increases risk of lasting asthma

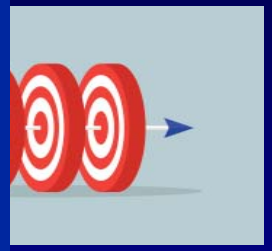
Relationship Persists into Adolescence

Rubner FJ, JACI 2017

Triple Threat: Important in the Development of Asthma

ATOPY

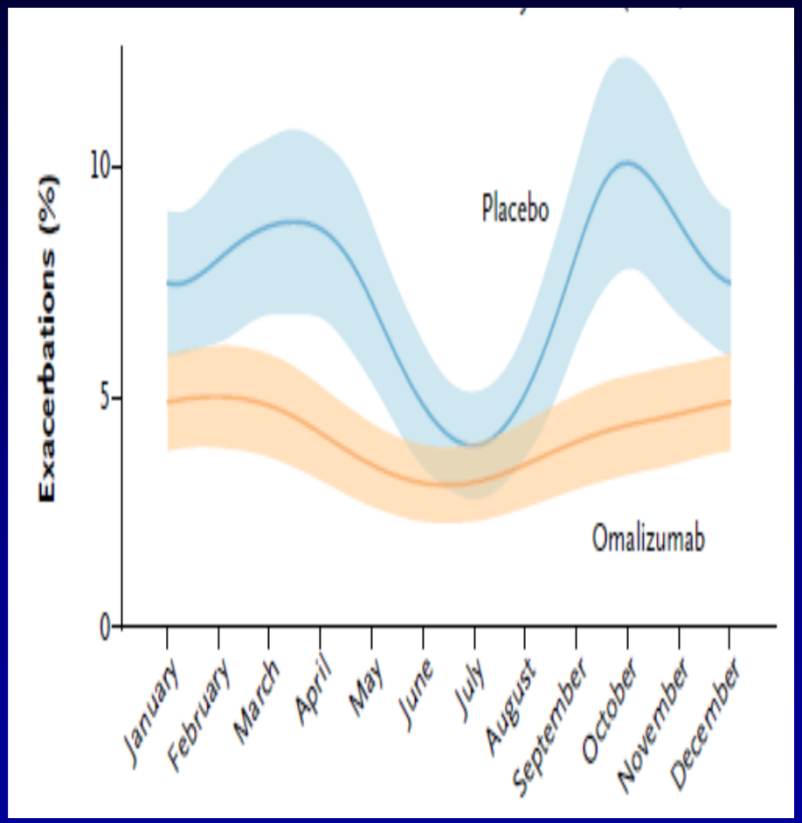
IS there anything available/feasible to use in young children that acts on the "triple threat" and could possibly PREVENT ASTHMA?

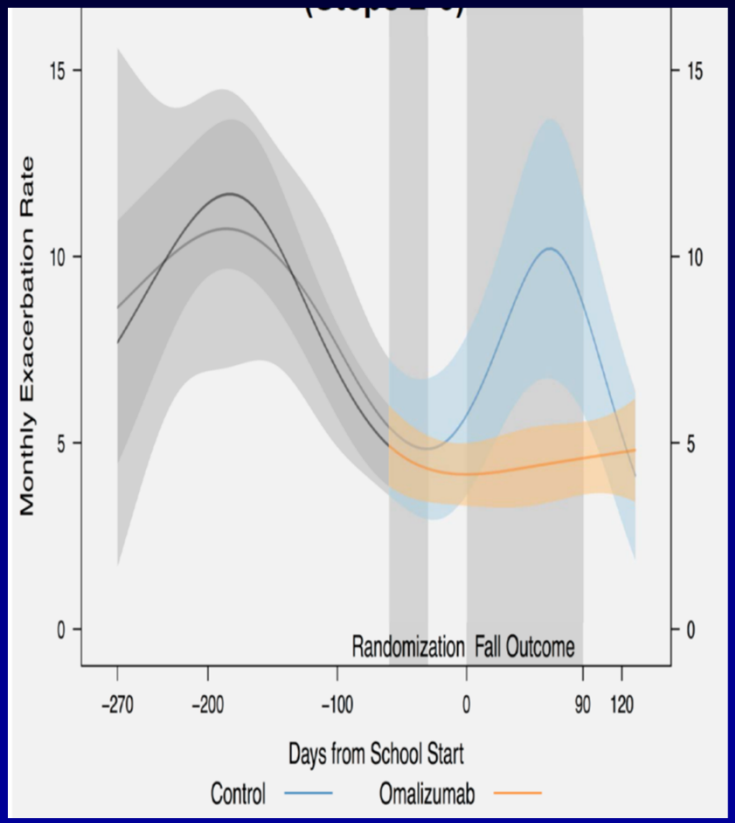


EXPOSURE

Anti-IgE works in asthma

AND it works on virally induced wheezing….



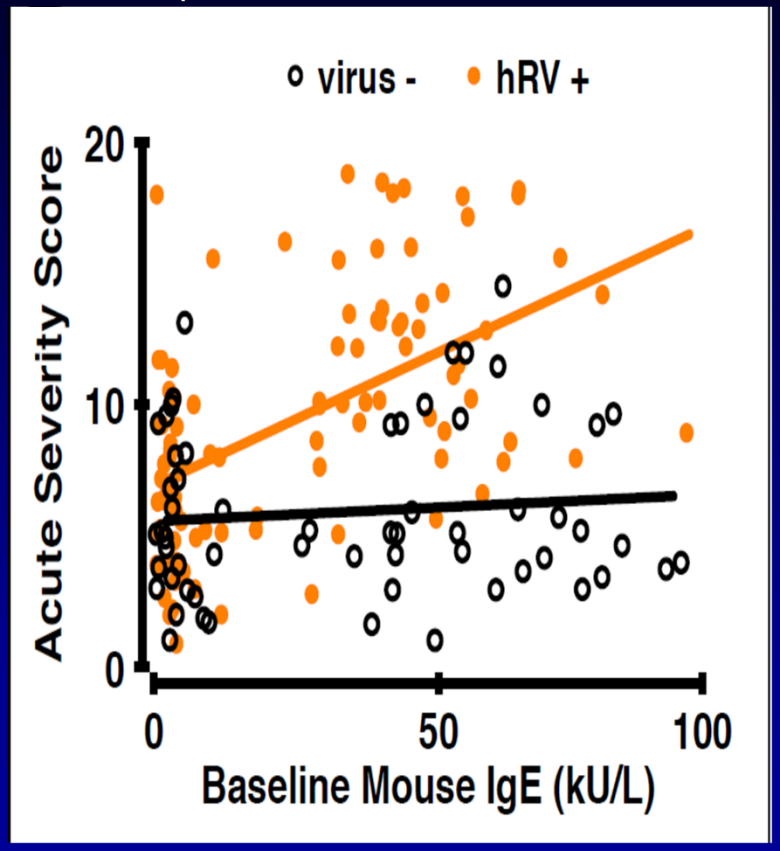


Busse WW, et al NEJM 2011,

Teach S, et al JACI 2015

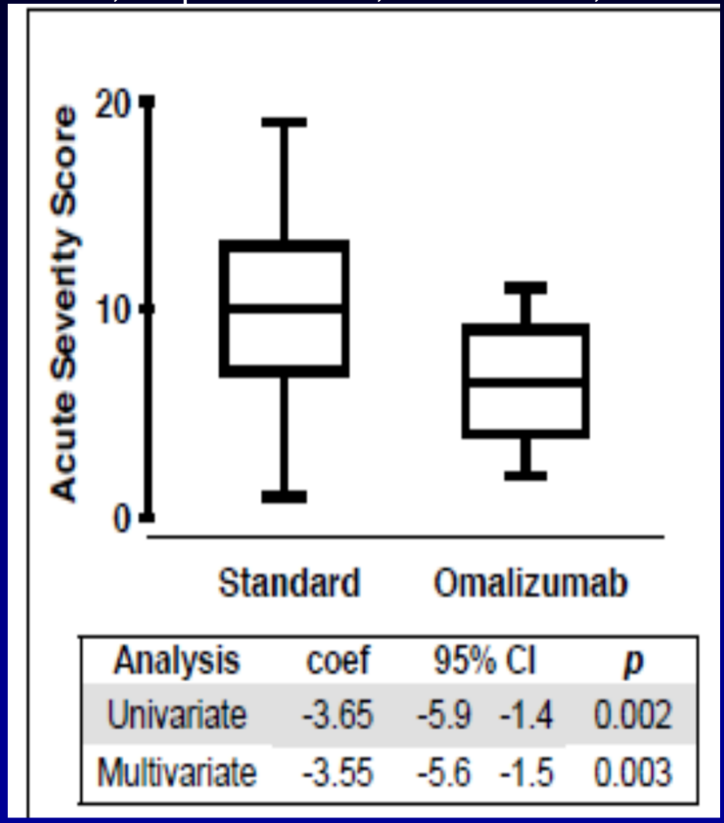
IgE and Rhinovirus Interact and Increases Asthma Severity

Kantor DB, Phipatanakul, Hirschhorn JACI 2016



anti-IgE Reduces this Severity in School Age Children

Kantor DB, Phipatanakul W, Hirschhorn J, Am J Resp CCM 2016



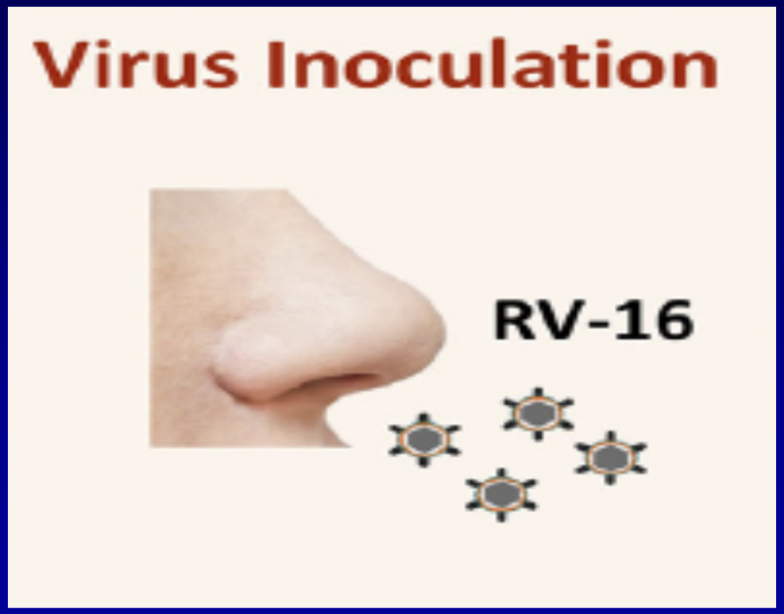
Analysis	coef	95% CI		p
Univariate	-3.65	-5.9	-1.4	0.002
Multivariate	-3.55	-5.6	-1.5	0.003

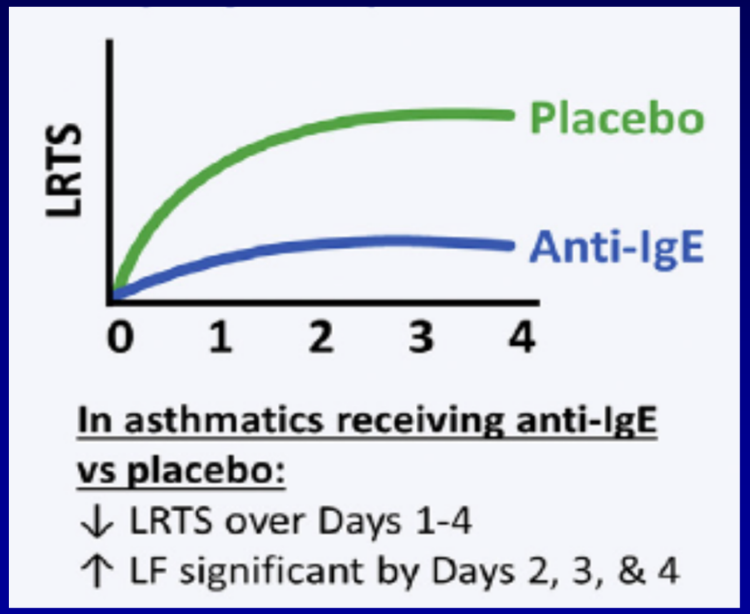
Understanding the asthmatic response to an experimental rhinovirus infection: Exploring the effects of blocking IgE

Check for updates

Peter W. Heymann, MD, MS, MPH,[a,b] Thomas A. E. Platts-Mills, MD, PhD, FRS,[a] Judith A. Woodfolk, MBChB, PhD,[a] Larry Borish, MD,[a] Deborah D. Murphy, RN,[a,b] Holliday T. Carper, BS,[a,b] Mark R. Conaway, PhD,[c] John W. Steinke, PhD,[a] Lyndsey Muehling, PhD,[a] W. Gerald Teague, MD,[b] Joshua L. Kennedy, MD,[d] Anne-Marie Irani, MD,[e] Matthew D. McGraw, MD,[f] Stephen V. Early, MD,[g] Lisa M. Wheatley, MD, MPH,[h] Amy P. Adams, PharmD,[i] and Ronald B. Turner, MD[j]

Charlottsville and Richmond Va, Little Rock, Ark, Rochester, NY, and Bethesda, Md



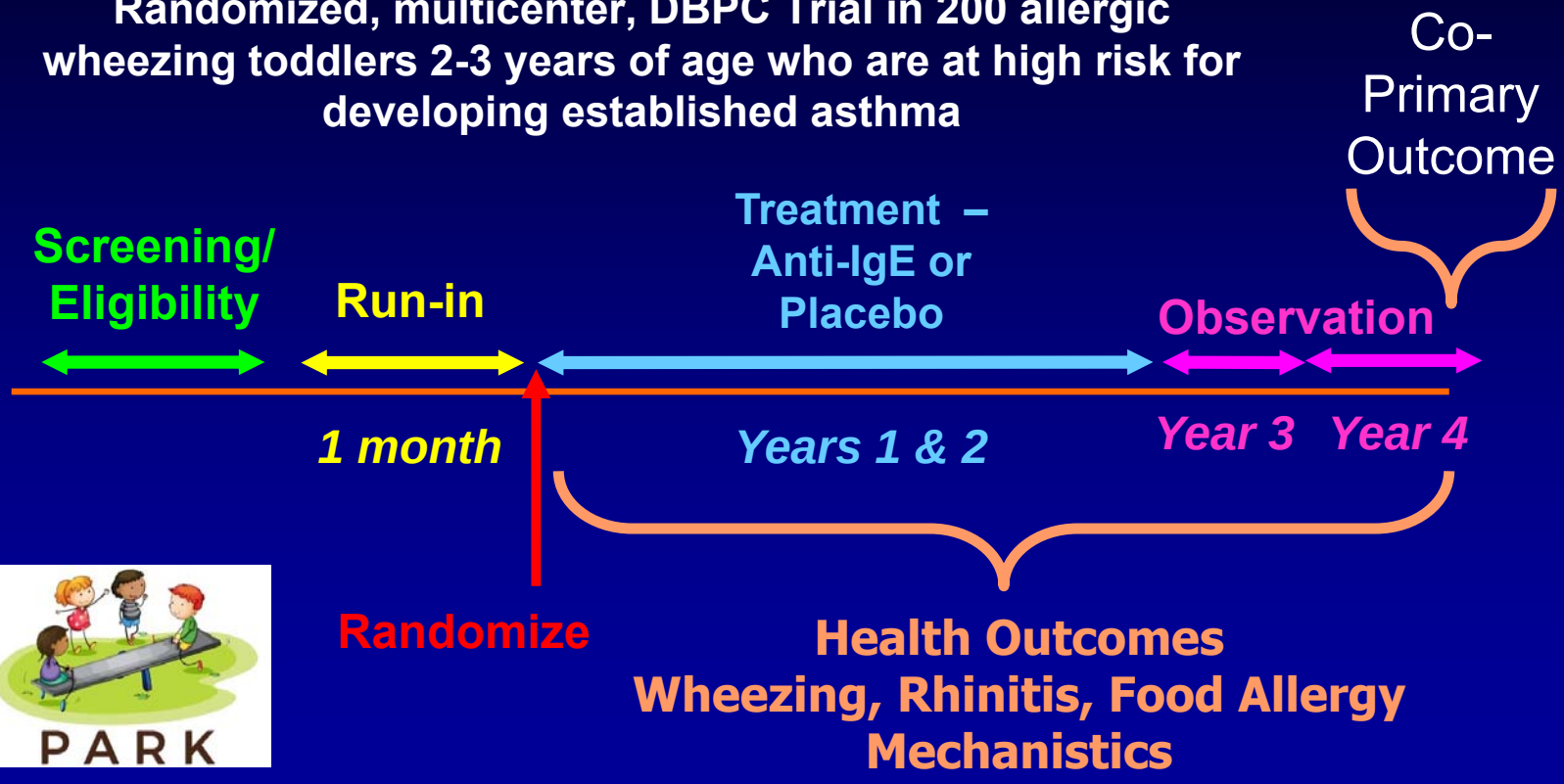


Heymann P, et al JACI 2020 ;146: 545-54

Preventing Asthma in High Risk Kids- PARK
https://parkstudy.org

U01AI126614- Principal Investigator Phipatanakul- NCT02570984

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



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

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/

Preventing Asthma in High Risk Kids (PARK)

PI: Phipatanakul U01AI126614 clinical trials.gov NCT02570984 parkstudy.org

- Elliot Israel, MD
- DCC-Penn State University- Dave Mauger, PhD
- Hans Oettgen, MD, PhD, Mechanistic Lead

Clinical Centers

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- Cincinnati- Theresa Guilbert, MD, MS
- Denver- Andy Liu, MD
- Hartford- Craig Lapin, MD
- Houston- Carla Walker, MD
- Indianapolis- Kirsten Kloepfer, MD
- Madison –Daniel Jackson, MD
- San Diego-Sydney Leibel, MD
- St. Louis – Jeffrey Stokes, MD
- Phoenix– Cindy Bauer, MD
- Washington, DC- Stephen Teach, MD

NIAID, Genentech/Novartis, Alk Abello, GSK, Lincoln Diagnostics Kaleo, Monaghan, Thermo Fisher

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Severe Asthma Course March 2023

Does Vitamin D Given to Pregnant Women Prevent Asthma in their offspring: Revisiting the Evidence

Scott T. Weiss, M.D., M.S.

Professor of Medicine, Harvard Medical School
Associate Director, Channing Division of Network Medicine
Brigham and Women's Hospital
Boston MA

BRIGHAM AND
WOMEN'S HOSPITAL

HARVARD MEDICAL
SCHOOL

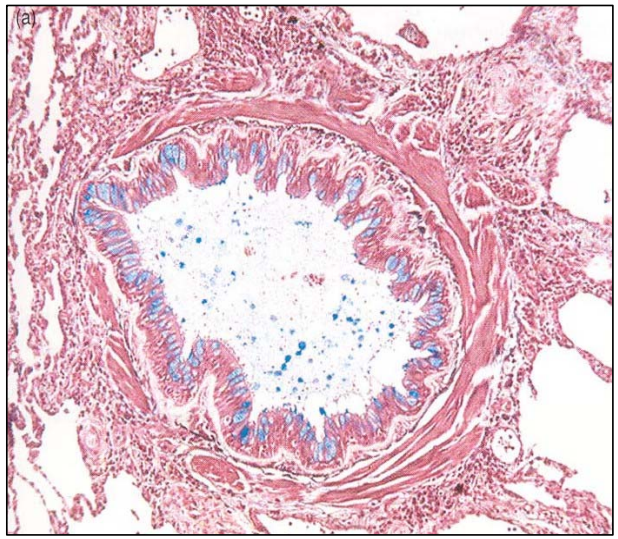
National Heart, Lung,
and Blood Institute

Disclosures

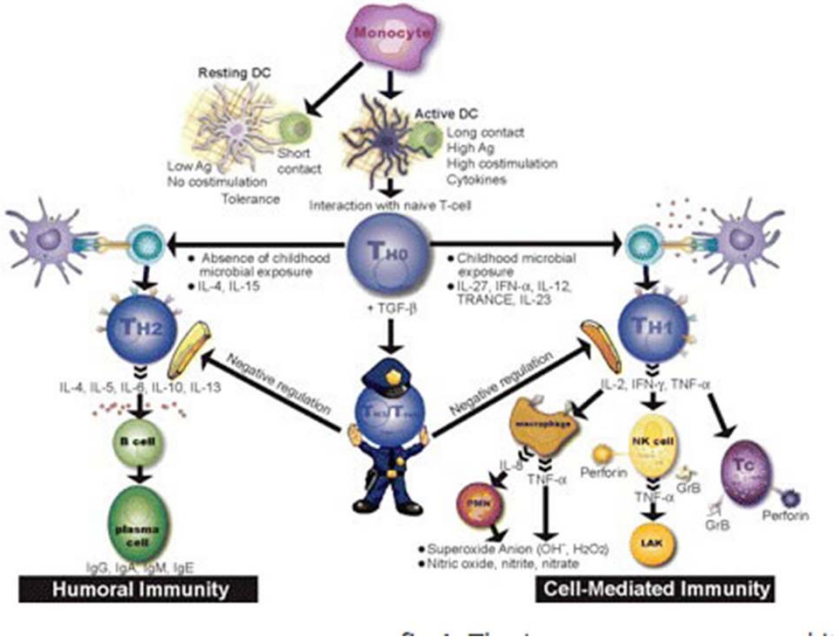
- Author for UpToDate
- On the board of Histolix a digital pathology company

Asthma: Pathophysiology

- Airway Inflammation
- Airway Remodeling
- **Airway Hyperresponsiveness**
- Reversible Airflow Obstruction
- Loss of Elastic Recoil
- Dysanaptic lung growth

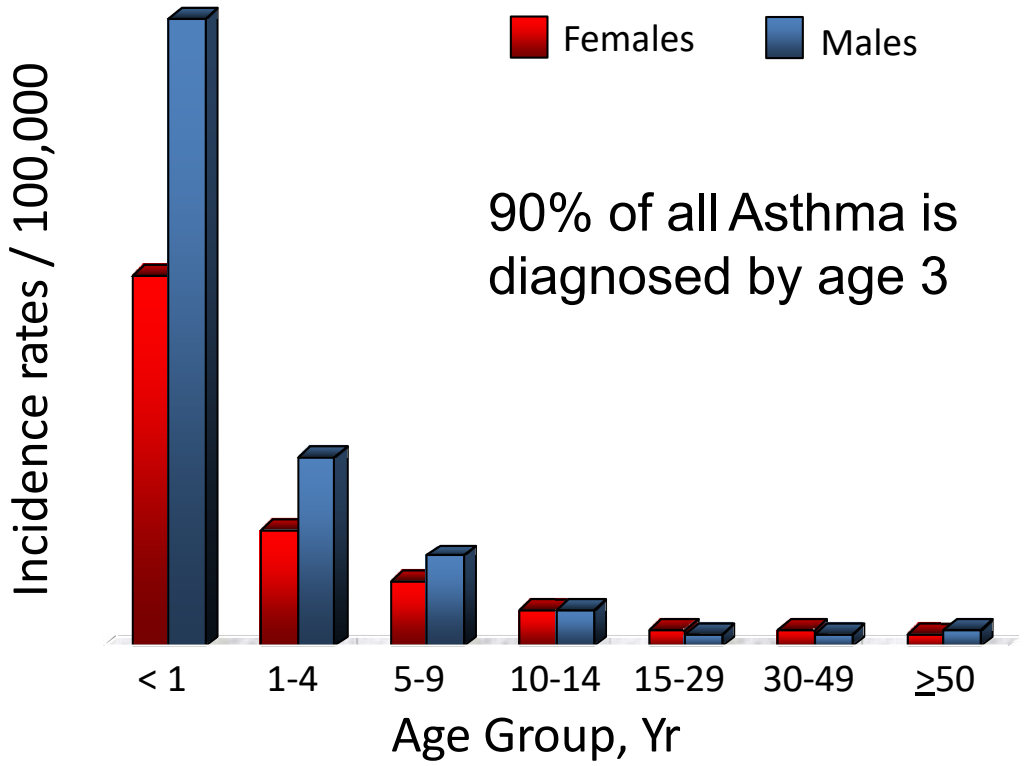


- Prevalence: 5-10%
- Prevalence increased markedly: 5% per year from 1979-2000 then leveled off
- Cost : In 2018, $80 billion per year



Annual Incidence Rates per 100,000 Person

Years by Sex & Age for Asthma Cases Among Rochester Minnesota Residents*(1964-1983)*

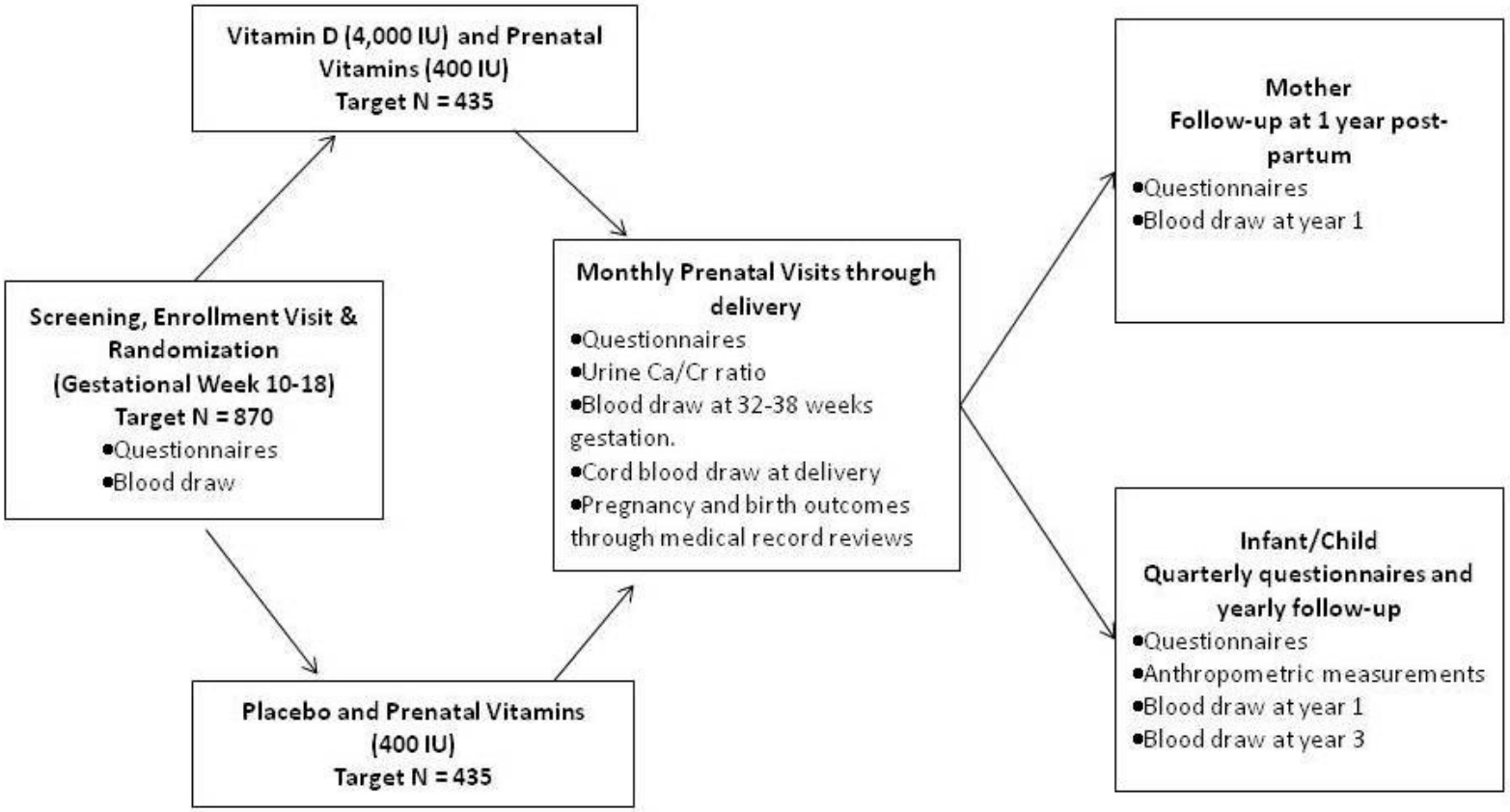


Yuninger JW. Am Rev Respir Dis 1992;146:888-894

Summary of Effect of Vitamin D on Asthma Pre VDAART

- VDR locus linked to asthma (Benj Raby Am J Respir Crit Care Med. 2004 Nov 15;170(10):1057-65.)
- Vitamin D intake (not levels) in mother linked to asthma wheeze outcomes in children (**50% reduction**) (Gus Litonjua Am J Clin Nutr. 2007 Mar;85(3):853-9, Carlos Camargo Am J Clin Nutr. 2007 Mar;85(3):788-95)
- Endocrine effects e.g. bone health linked to serum levels
- Immune effects linked to serum and tissue levels (ST Weiss unpublished)
- Vitamin D mediates all aspects of pregnancy and post natal immune function everything from implantation to gut microbiome, and innate and adaptive immune development in the first years of life

VDAART Study Design



VDAART

National Heart Lung and Blood Institute
National Institutes of Health

Litonjua et al. Contemp Clin Trials 2014
http://www.vdaart.com

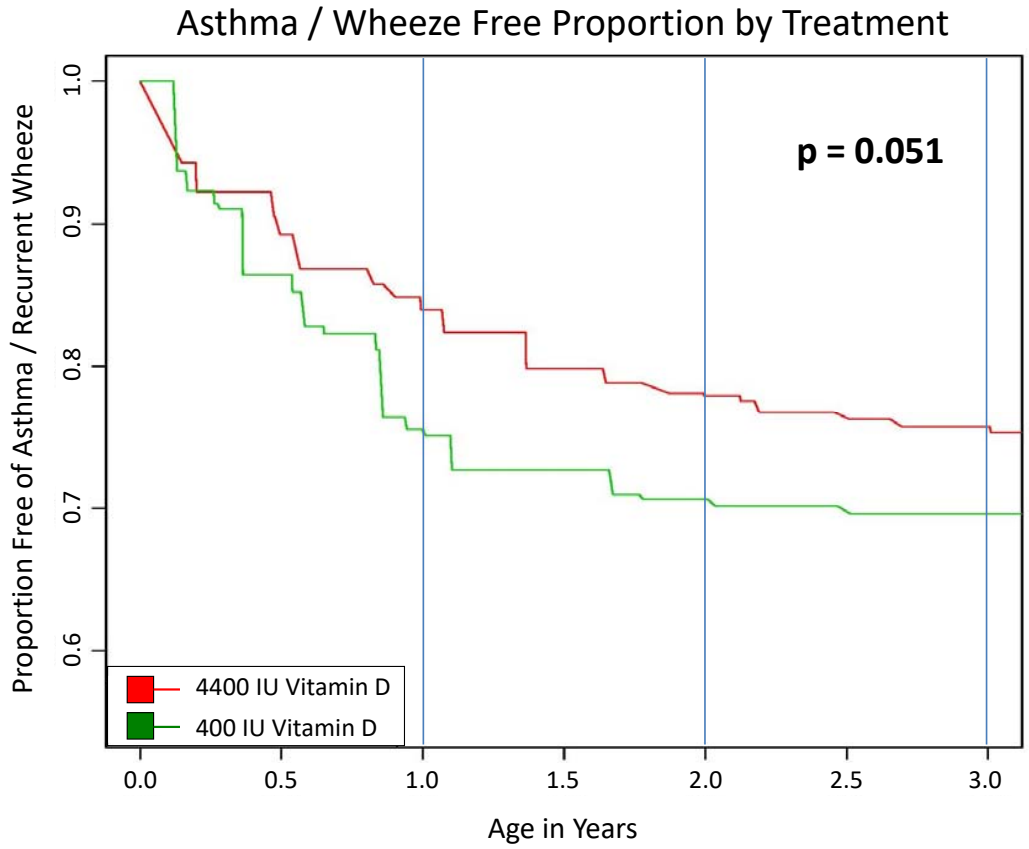
Proportion of mothers who achieved a 25OHD level of at least (20 and 30 ng/ml, respectively) at 3rd trimester

Target level	400 IU dose	4,400 IU dose	P-value
20 ng/ml	280/391 (71.6%)	342/386 (88.6%)	$< 5 \times 10^{-9}$
30 ng/ml	135/391 (34.5%)	290/386 (75.1%)	$< 2 \times 10^{-16}$

Conclusion: even at 4400 IU, 25% of mothers deficient

JAMA: 2016 Jan 26; 315(4):362-70

Effect of maternal vitamin D treatment on development of asthma/recurrent wheeze by age 3 years.



98 in 4,400 IU arm
120 in 400 IU arm

Rate difference of 6.1%

Reduction of 20%

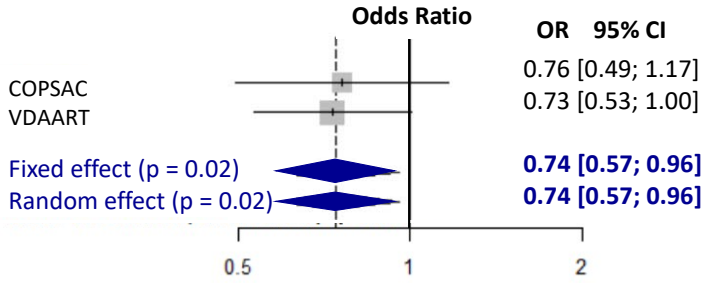
JAMA: 2016 Jan 26;315(4):362-70

Reasons why the year 3 intent to treat analyses were not statistically significant

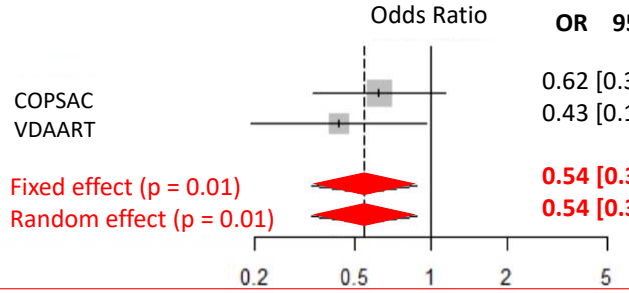
- **We didn't give enough vitamin D**
  - Only 75% of trial participants achieved a level of 30ng/ml
- **We didn't give vitamin D early enough in Pregnancy**
  - Vitamin D is important for successful conception, implantation and maintenance of a normal pregnancy in humans, mice, rats, monkeys and dogs **(Weiss 2011 in Litonjua ed Vitamin D and Lung Disease)**
  - **Immediately upon conception 1,25 OHD levels in the pregnant mother increase 10-fold over baseline (Hollis B Bone Research 2017:5: 1703)**
  - Vitamin D influences branching morphogenesis **(Kho, Tantisira BMC Medical Genomics 2013) 7-17 weeks gestation**
- **Nutrient trials are fundamentally different from drug trials. Vitamin D was present in subjects in both the treatment and the placebo arms of the trial and thus misclassification occurred reducing power to detect a difference in the two groups. (Robert P Heaney: Nutr Rev 2014;72:48-54)**

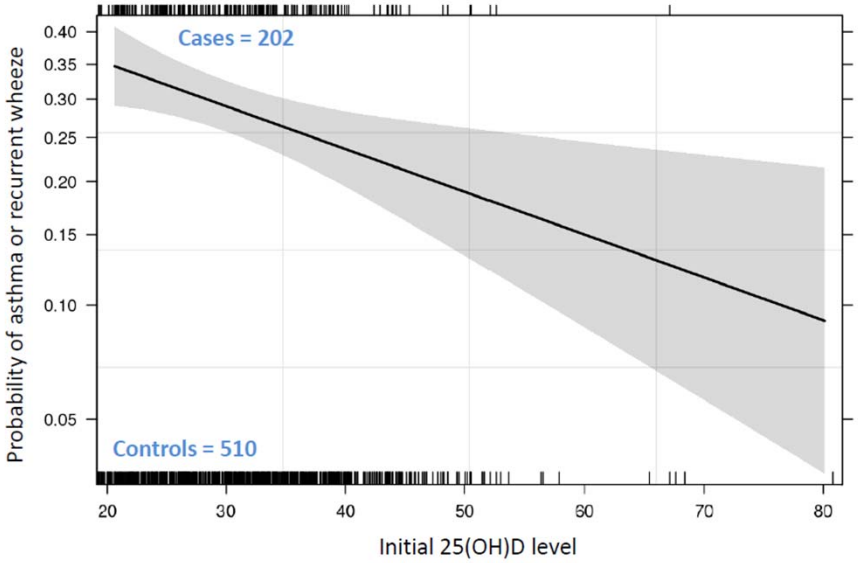
Meta-analysis of prenatal vitamin D trials

Overall Effect

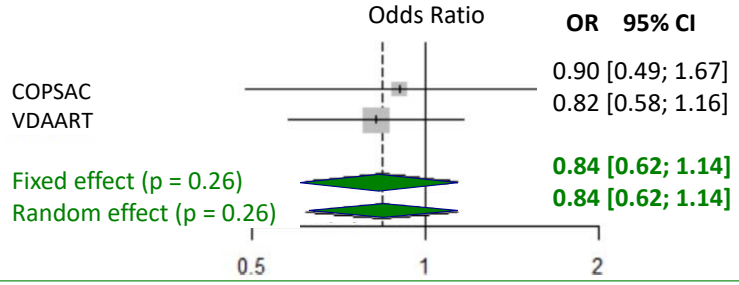


Initial 25OH Vit D ≥ 30 ng / ml





Initial 25OH Vit D < 30 ng / ml



Wolsk H et al PLOS ONE 2016:12: e0186657,
Wolsk H et al J Allergy Clin Immunol. 2017 Nov;140(5):1423-1429

The risk of asthma in the offspring at age 6 years was significantly reduced in those mothers in the treatment group with the lowest levels of vitamin D at entry to the trial

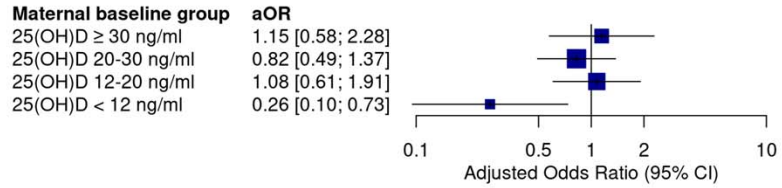


Figure 3. The effect of prenatal vitamin D supplementation (4400 vs 400 IU/daily) on asthma or recurrent wheeze by age of six years according to maternal baseline 25(OH)D status in VDAART. Adjusted odds of asthma or recurrent wheeze among offspring born to women with 25(OH)D levels of ≥ 30 ng/ml, 20-30 ng/ml, 12-20 ng/ml and < 12 ng/ml at 10-18 weeks of gestation (number of cases and controls in each group [subpopulation weight]: 72/104 [22%], 119/176 [37%], 109/114 [28%], and 57/50 [13%], respectively). Effect size estimates and 95% confidence intervals are provided for each group analysis. Adjusted for: intervention group, maternal age, maternal education, maternal asthma, paternal asthma, study site, preterm birth, maternal race, child gender, gestational age at the enrollment and season of blood drawn.

I Shadid et. al. Submitted

The earlier in pregnancy that vitamin D was started the greater the reduction in asthma risk at age 6

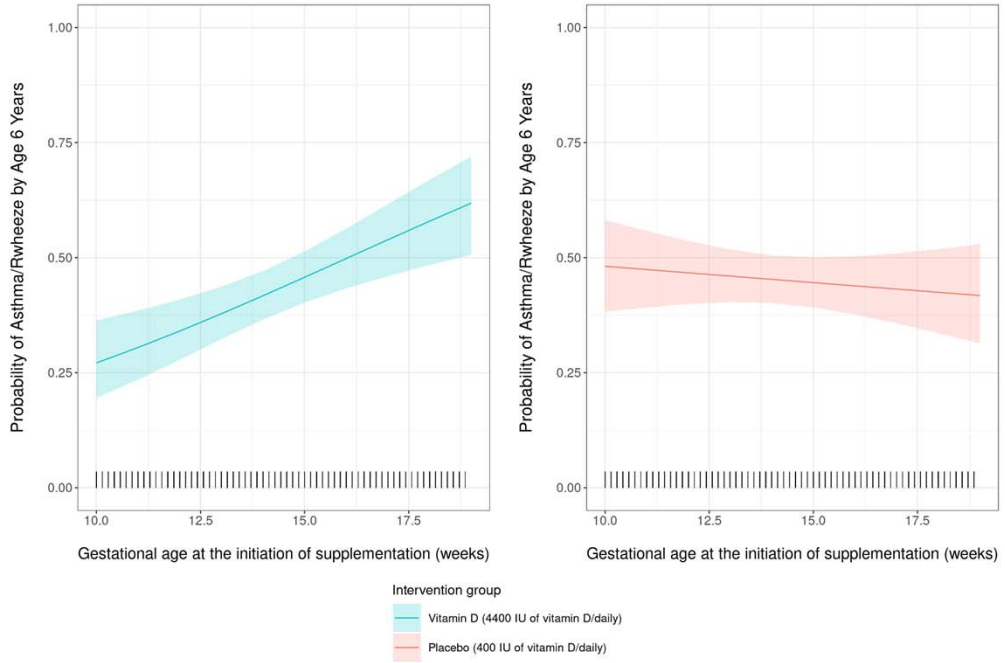


Figure 5. The effect of timing of supplementation initiation on the probability of offspring asthma or recurrent wheeze per intervention group. The association between offspring's gestational age at the initiation of supplementation at trial enrollment and asthma or recurrent wheeze by age 6 years is demonstrated for the treatment group (left) and placebo group (right). Population means and 95% confidence intervals are shown as respectively colored lines and shading. Inward ticks on the x-axis mark the data range and distribution. Adjusted for: maternal baseline 25(OH)D, maternal age, maternal education, maternal asthma, paternal asthma, study site, preterm birth, maternal race, child gender and season of blood drawn.

I Shadid et al submitted

Vitamin D improves Lung Function in the VDAART Trial

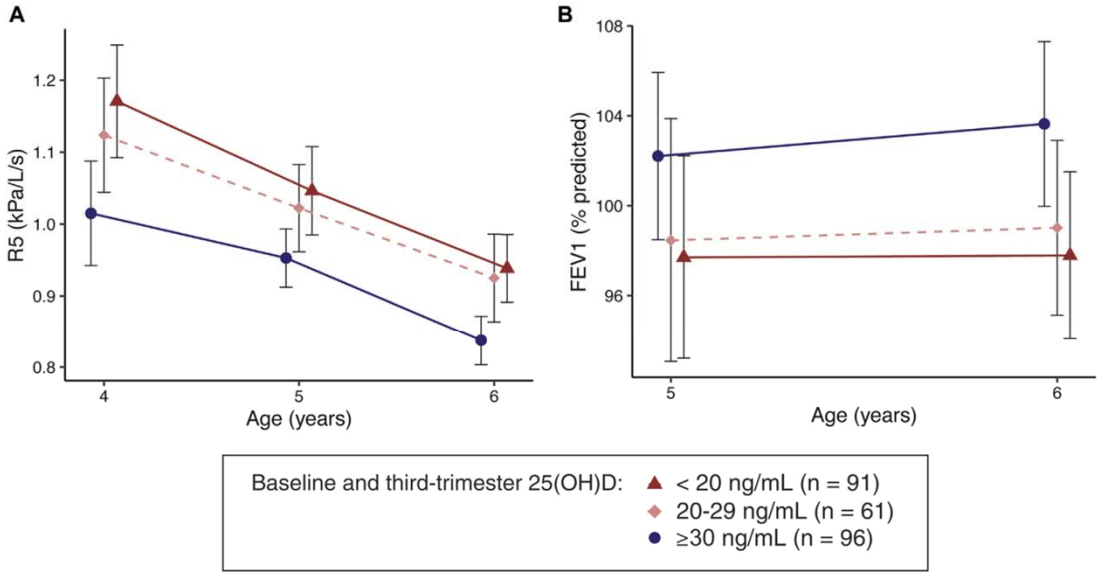


FIG 3. Mean values for child lung function at ages 4, 5, and 6 years among the subset of children whose mothers had either deficient (<20 ng/mL, n = 91), insufficient (20-29 ng/mL, n = 61), or sufficient (≥30 ng/mL, n = 96) 25(OH)D level at both baseline (10-18 gestational weeks) and third trimester (32-38 gestational weeks). **A,** R5. **B,** FEV_1.[22] Data points illustrate the mean values of the lung function indices for each group, and the whiskers illustrate the 95% CI.

Knihtila HA et al J Allergy Clin Immunol 2021: 148:110-9

Summary of Effect of Vitamin D on Pregnancy Post VDAART

- Pregnancy is a continum, vitamin D necessary at every stage of pregnancy and beyond
- vitamin D sufficiency early in pregnancy had a greater effect on asthma outcomes than later in pregnancy
- Nutrient trials are fundamentally different from drug trials because there is contamination of the control group
- Intent to treat analysis suggests congruence between observational and clinical trial results if initial level of vitamin D is accounted for
- **Effects of vitamin D are significant at 3 and 6 years for asthma and for lung function at age 6**

Recommendations for Vitamin D Levels and intake During Pregnancy

- **70% of pregnant women have vitamin D levels <30ng/ml**
- USDA recommends 600 IU of vitamin D during pregnancy
- IOM recommends a serum level of 20ng/ml during pregnancy
- **Endocrine Society recommends a serum level of 30 ng/ml and a dose of up to 4000 IU during pregnancy**
- Cochran Collaboration recommends further studies. Their meta-analyses do not account for baseline level
- Most academic OB programs (including BWH) do not recommend vitamin D supplementation during pregnancy

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