The Microbiome and Asthma

Kathleen Lee-Sarwar, MD, MS

Update on Severe Asthma 2024

Image Credit: Shutterstock

Conflicts of Interest

I am employed by and own stock in Vertex Pharmaceuticals.

1. Microbiome & how it could influence asthma

2. Associations between the microbiome & asthma
   - Airway microbiome
   - Environmental microbiome
   - Gut microbiome

3. Potential microbiome-based interventions

1. **Microbiome & how it could influence asthma**

2. Associations between the microbiome & asthma
   - Airway microbiome
   - Environmental microbiome
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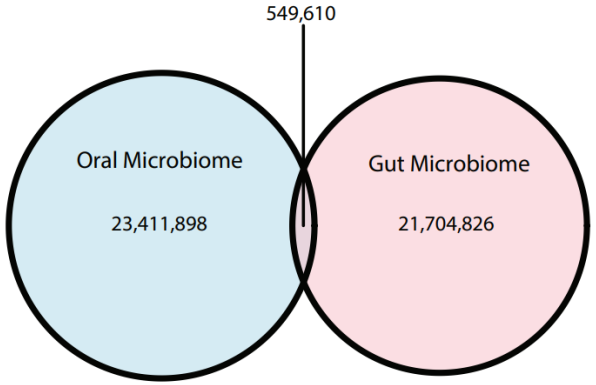
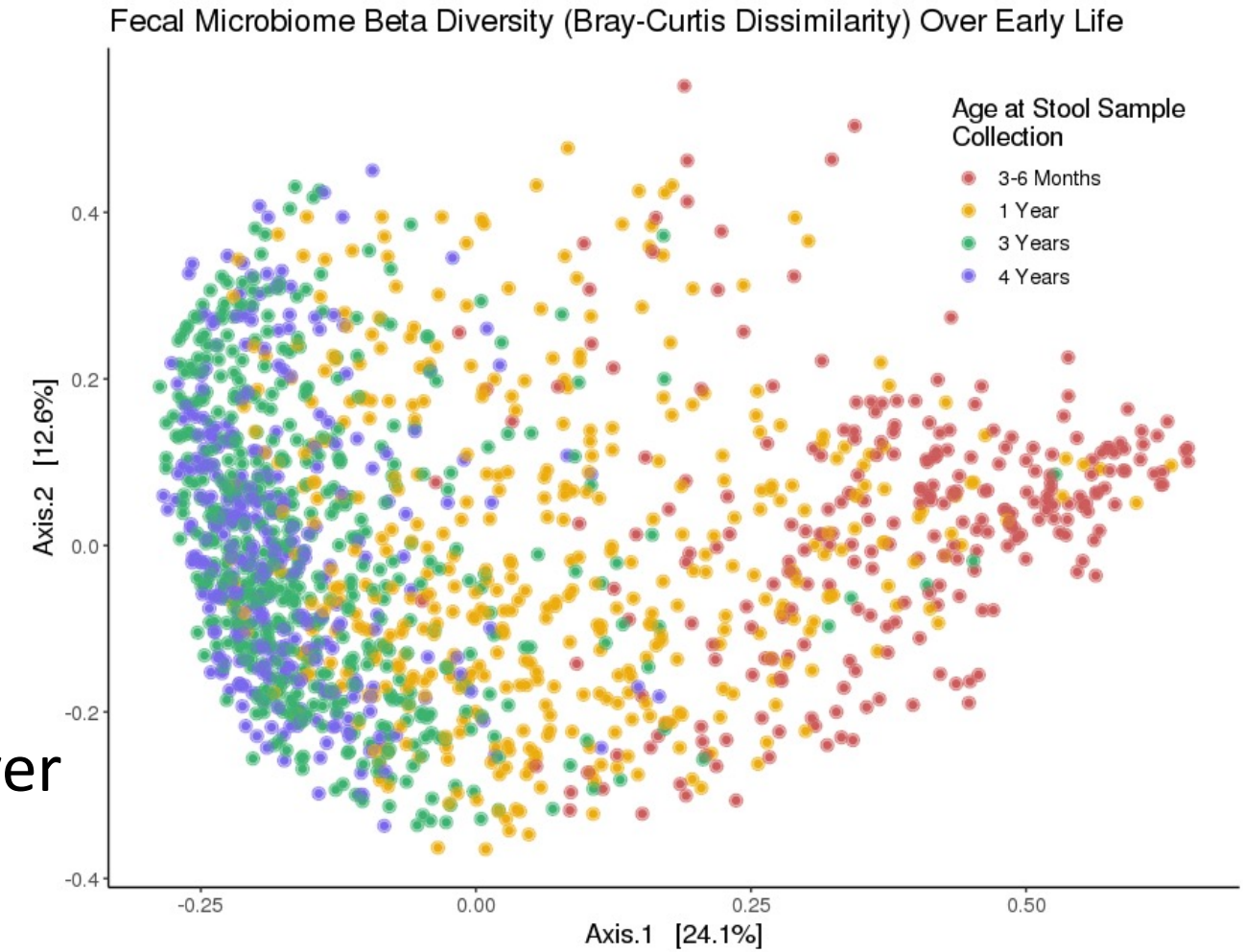
3. Potential microbiome-based interventions

The Microbiome

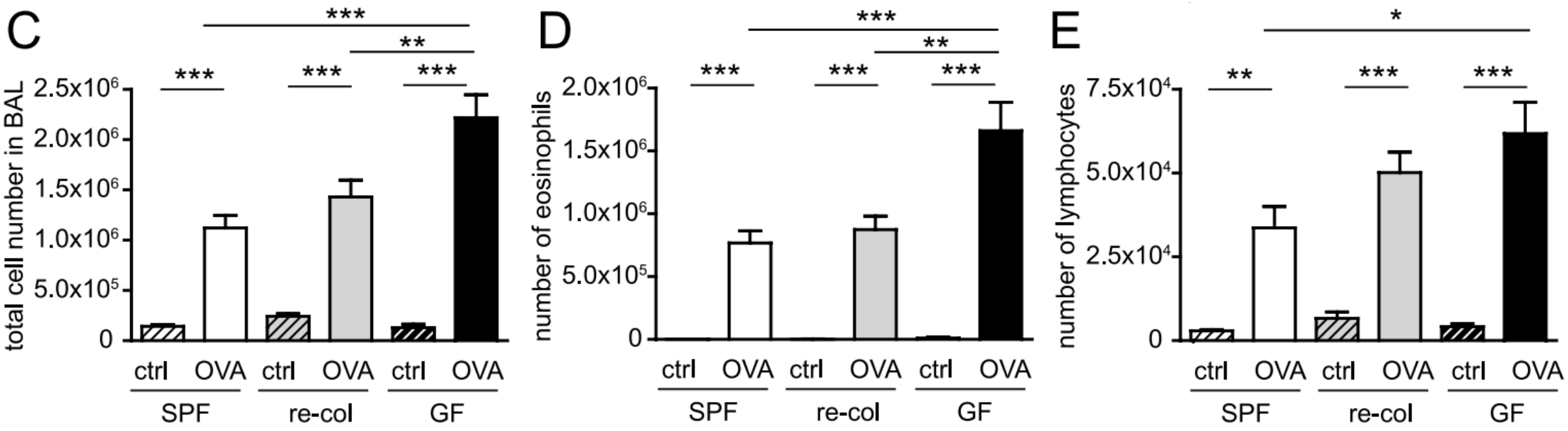
- The microbiome (collective genomic contents) of the trillions of microbes resident on the human body comprises **~45 million non-redundant genes**.



- Essential functions include nutrient harvest, vitamin synthesis, development & maintenance of immune function.
- The microbiome develops rapidly over the first few years of life.



Tierney BT, et al. Cell Host Microbe 2019.



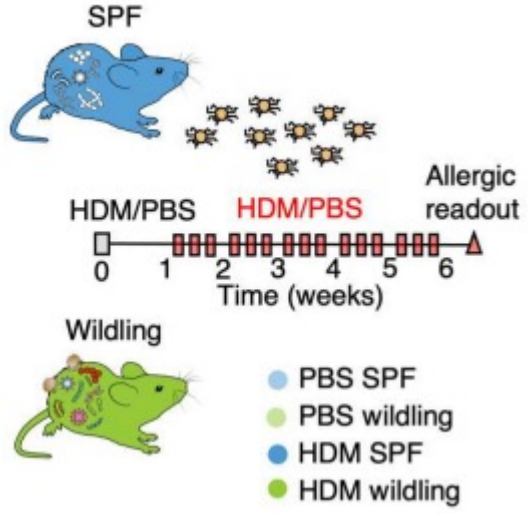
Experimental evidence of the importance of the microbiome in allergic disease:

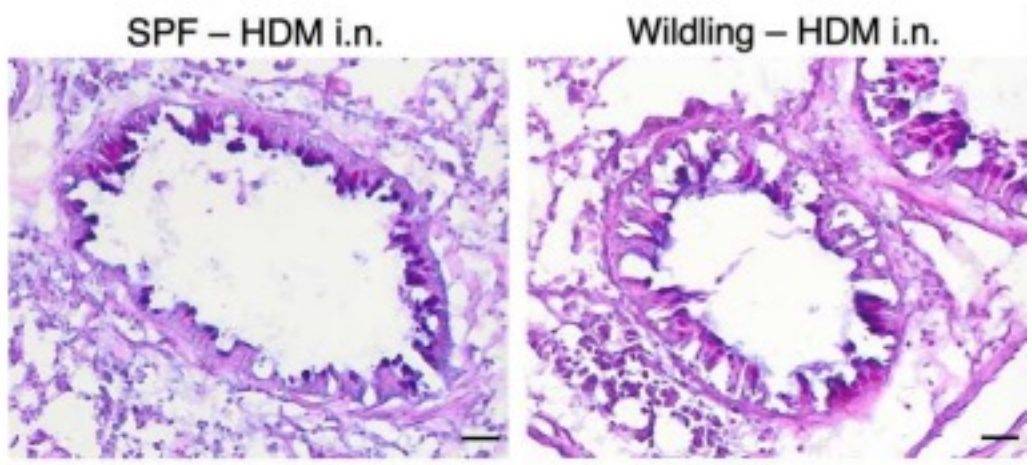
Germ-free mice have reduced T regulatory cells, elevated IgE, and increased susceptibility to anaphylaxis and allergic airway inflammation.

Herbst T, et al. Am J Respir Crit Care Med 2011.

Effects of microbial diversity on allergy development is complex

- Wildling mice, which more closely resemble free-living mice, exhibit more diverse microbiota and larger populations of antigen-experienced lymphocytes compared to SPF.
- However, wildling mice exhibit **increased** allergic airway inflammation after challenge with house dust mite, IL-33 or *A. alternata*.

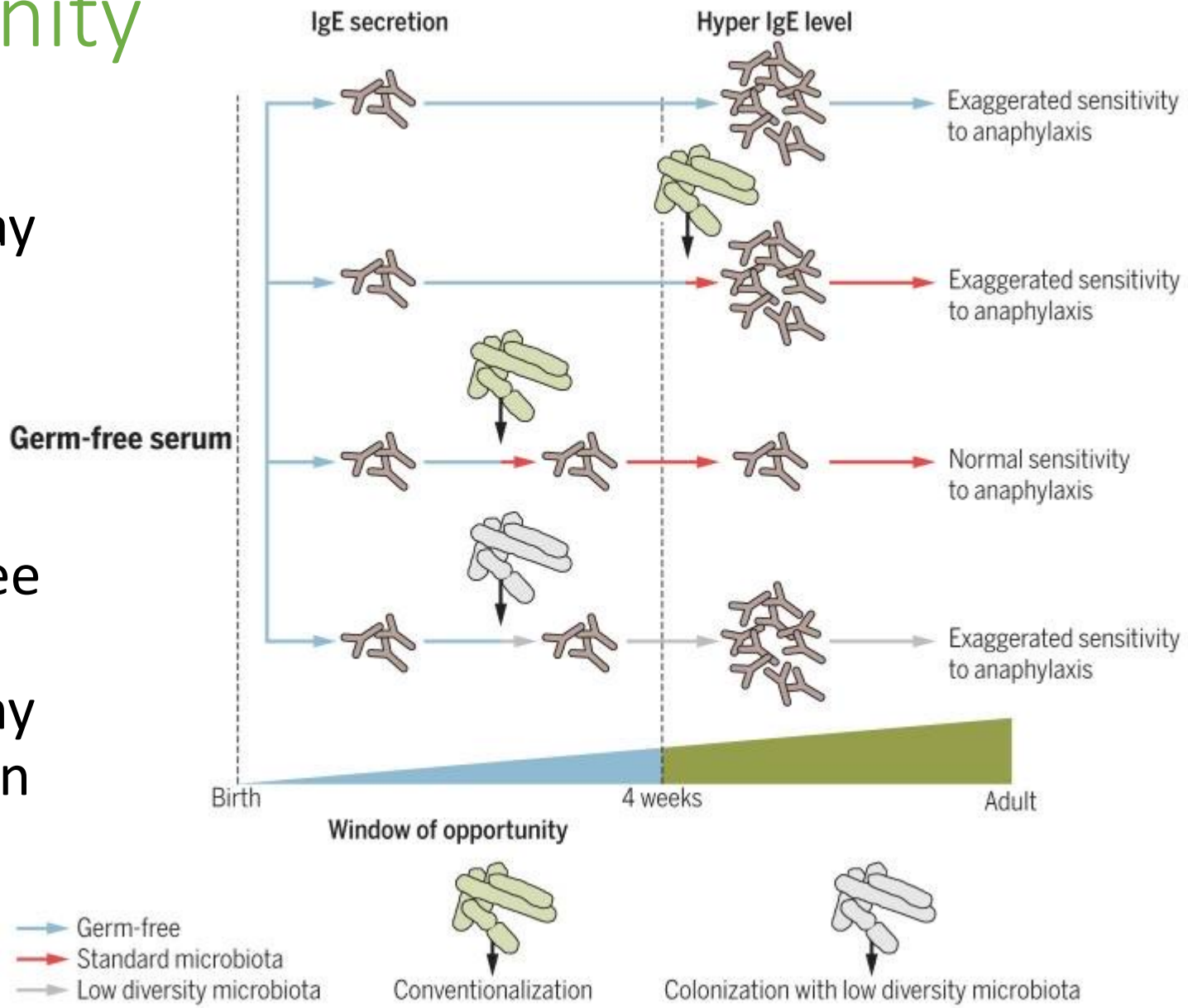




Ma J, et al. Sci Immunol 2023.

Windows of Opportunity

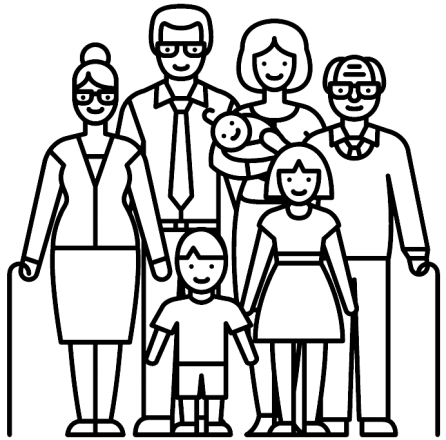
- The first few weeks of life require tolerance to a vast array of new stimuli, including microbial colonization.
- Although many defects associated with being germ-free in animal models can be corrected by colonization at any time, some require colonization early in life.

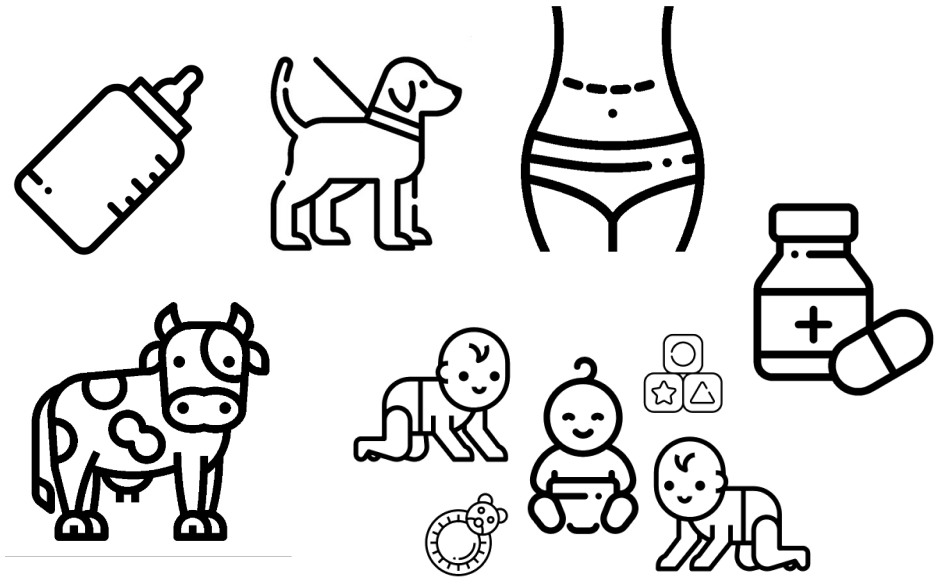


Cahenzli J, Cell Host Microbe 2013.
Fig: Gensollen T, Science 2016.

Epidemiologic evidence of the importance of the microbiome in asthma

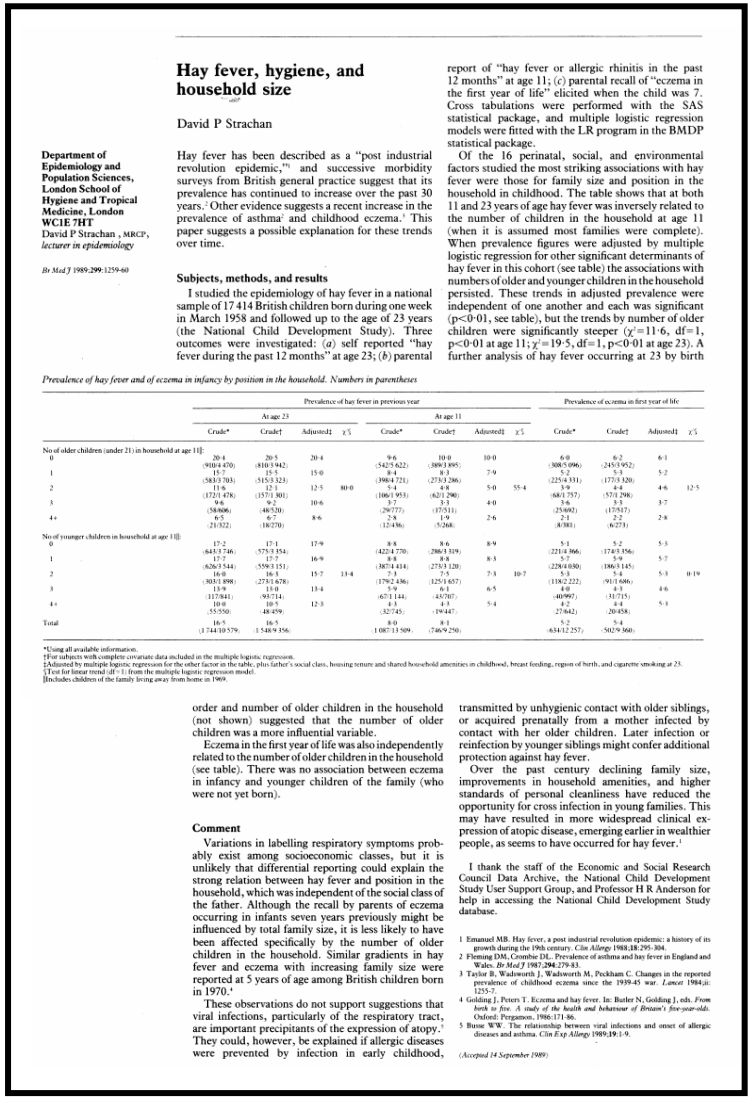
Hygiene hypothesis: reduced microbial exposure
→ rising prevalence of allergic disease





Several asthma and allergy risk factors impact microbial exposures.

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



Hay fever, hygiene, and household size

David P Strachan

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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[3] and childhood eczema.[4] 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 ($p<0{\cdot}01$, see table), but the trends by number of older children were significantly steeper ($\chi^2_1=11{\cdot}6$, df=1, $p<0{\cdot}01$ at age 11; $\chi^2_1=19{\cdot}5$, df=1, $p<0{\cdot}01$ 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

	Prevalence of hay fever in previous year								Prevalence of eczema in first year of life			
	At age 23				At age 11							
	Crude*	Crude†	Adjusted‡	χ^2_1§	Crude*	Crude†	Adjusted‡	χ^2_1§	Crude*	Crude†	Adjusted‡	χ^2_1§
No of older children (under 21) in household at age 11‖:												
0	20·4 (910/4 470)	20·5 (810/3 942)	20·4		9·6 (54/25 622)	10·0 (389/3 895)	10·0		6·0 (308/5 096)	6·2 (245/3 952)	6·1	
1	15·7 (583/3 703)	15·5 (515/3 323)	15·0		8·4 (398/4 721)	8·3 (273/3 286)	7·9		5·2 (225/4 331)	5·3 (177/3 320)	5·2	
2	11·6 (172/1 478)	12·1 (157/1 301)	12·5	80·0	5·4 (106/1 953)	4·8 (62/1 290)	5·0	55·4	3·9 (68/1 757)	4·4 (57/1 298)	4·6	12·5
3	9·6 (58/606)	9·2 (48/520)	10·6		3·7 (29/777)	3·3 (17/511)	4·0		3·6 (25/692)	3·5 (17/517)	3·7	
4+	2·8 (21/322)	6·7 (18/270)	8·6		2·8 (12/436)	1·9 (5/268)	2·6		2·1 (8/381)	2·2 (6/273)	2·8	
No of younger children in household at age 11‖:												
0	17·2 (643/3 746)	17·1 (575/3 354)	17·9		8·8 (422/4 770)	8·6 (286/3 319)	8·9		5·1 (221/4 366)	5·2 (174/3 356)	5·3	
1	17·7 (626/3 544)	17·7 (559/3 151)	16·9		8·8 (387/4 414)	8·8 (273/3 120)	8·3		5·7 (228/4 030)	5·9 (186/3 145)	5·7	
2	16·0 (303/1 898)	16·3 (273/1 678)	15·7	13·4	7·3 (179/2 436)	7·5 (125/1 657)	7·3	10·7	5·3 (118/2 222)	5·4 (91/1 686)	5·3	0·19
3	13·9 (117/841)	13·0 (93/714)	13·4		5·9 (67/1 144)	6·1 (45/707)	6·5		4·0 (40/997)	4·3 (31/715)	4·6	
4+	10·0 (55/550)	10·5 (48/459)	12·3		4·3 (32/745)	4·3 (19/447)	5·4		4·2 (27/642)	4·4 (20/458)	5·3	
Total	16·5 (1 744/10 579)	16·5 (1 548/9 356)			8·0 (1 087/13 509)	8·1 (746/9 250)			5·2 (634/12 257)	5·4 (502/9 360)		

*Using all available information.
†For subjects with complete covariate data included in the multiple logistic regression.
‡Adjusted by multiple logistic regression for the other factor in the table, plus father's social class, housing tenure and shared household amenities in childhood, breast feeding, region of birth, and cigarette smoking at 23.
§Test for linear trend (df = 1) from the multiple logistic regression model.
‖Includes children of the family living away from home in 1969.

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.

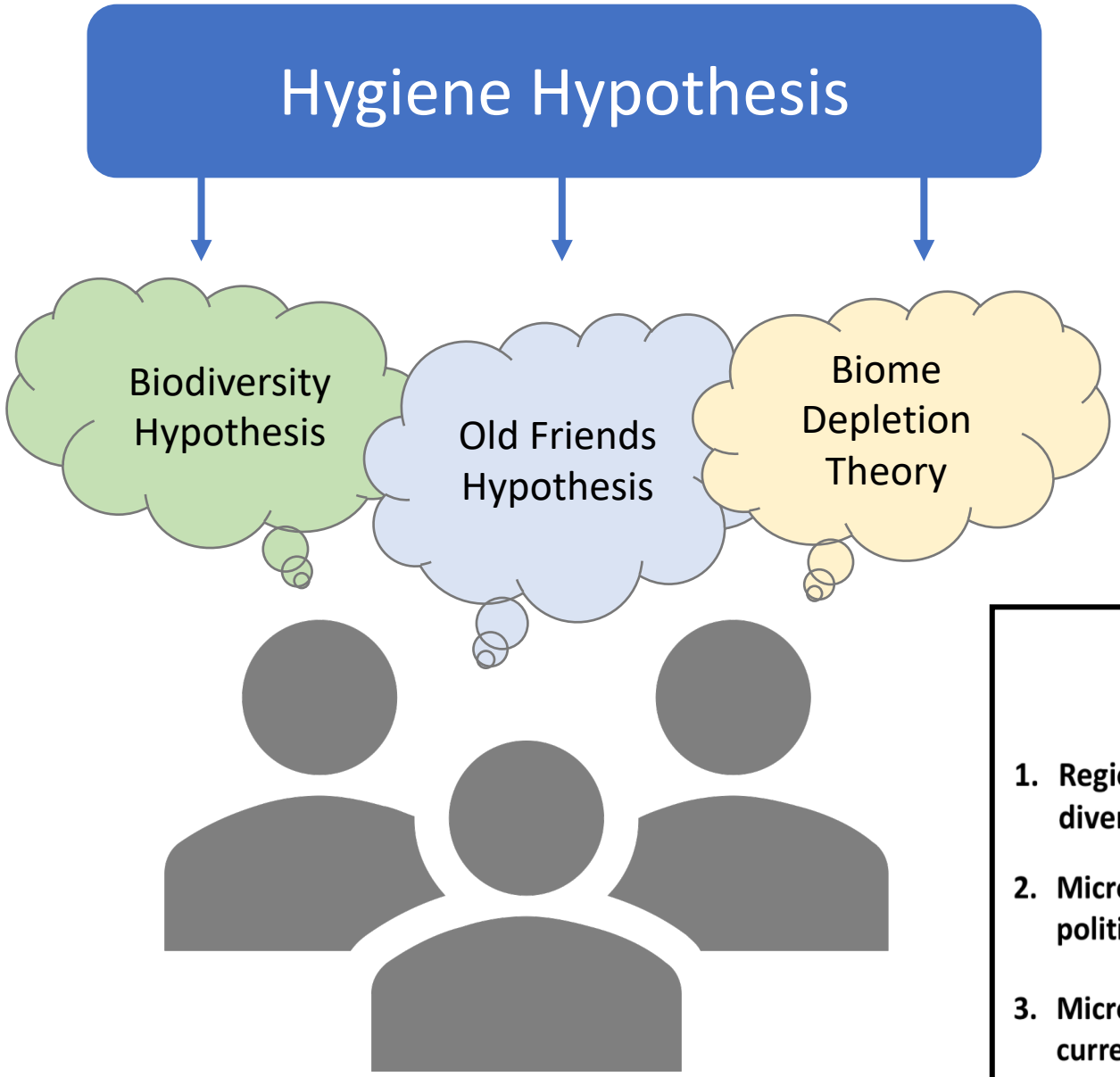
Over the past century declining family size, improvements in household amenities, and higher standards of personal cleanliness have reduced the opportunity for cross infection in young families. This may have resulted in more widespread clinical expression of atopic disease, emerging earlier in wealthier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

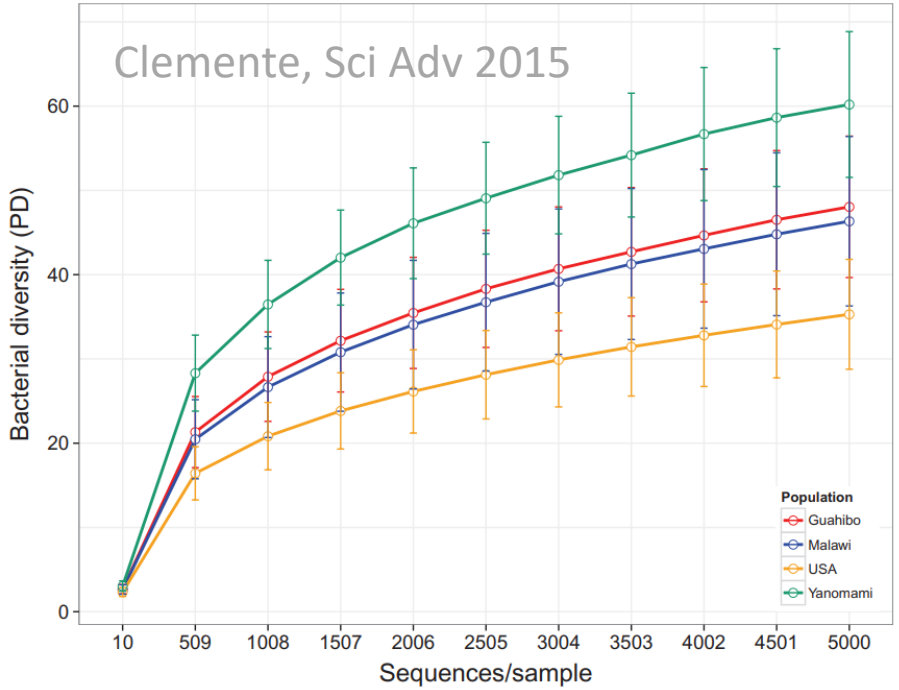
I thank the staff of the Economic and Social Research Council Data Archive, the National Child Development Study User Support Group, and Professor H R Anderson for help in accessing the National Child Development Study database.

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 Burne WW. The relationship between viral infections and onset of allergic diseases and asthma. *Clin Exp Allergy* 1989;19:1-9.

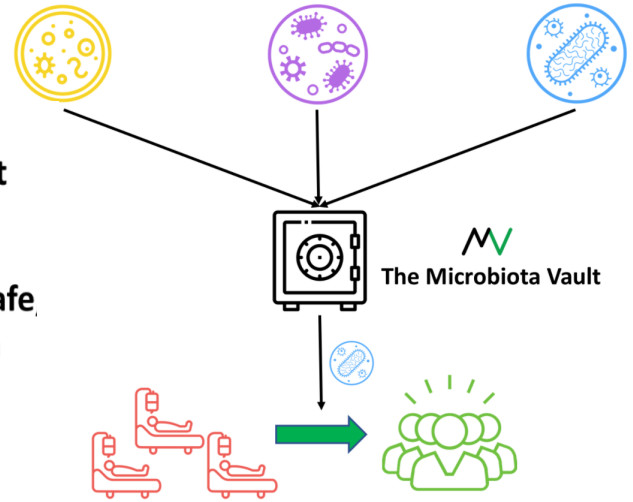
(Accepted 14 September 1989)

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





1. **Regional working collections submit diverse microbiota samples**
2. **Microbiota samples are stored in a safe, politically neutral and stable location**
3. **Microbiota restoration may reverse current Western health trends**

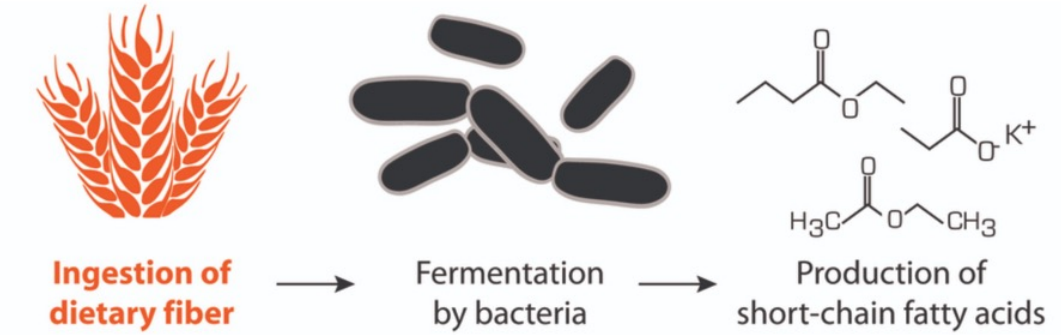


Pfefferle, et al. The Hygiene Hypothesis – Learning From but Not Living in the Past. Front Immunol 2021.

Mechanisms whereby the microbiome may influence risk of asthma

Production or modification of **metabolites**

- Short-chain fatty acids
- Tryptophan metabolites
- Polyunsaturated fatty acid metabolites
- Bile acids



Engagement of host receptors such as Toll-like receptors

Colonization resistance & other **interactions with other microbes**

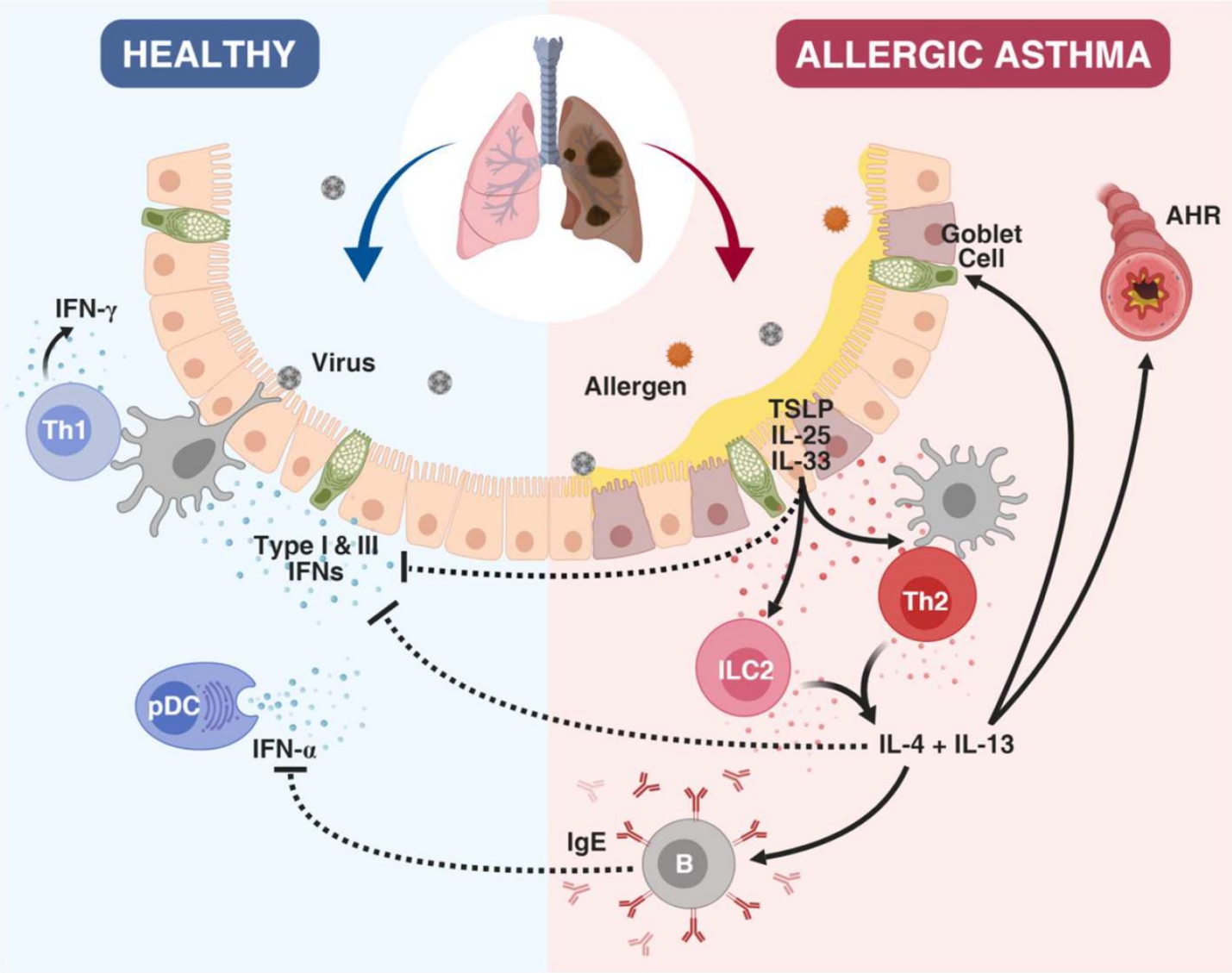
Koh A, Cell 2016.
Stein MM, NEJM 2016.

1. Microbiome & how it could influence asthma

2. **Associations between the microbiome & asthma**
   - **Airway microbiome**
   - **Environmental microbiome**
   - **Gut microbiome**

3. Potential microbiome-based interventions

The Airway Microbiome: Viruses



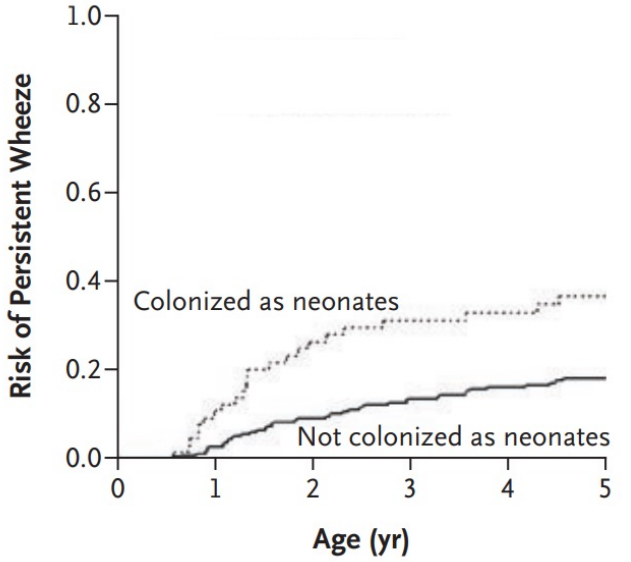
RSV and rhinovirus are important causes of wheezing in early life.

Wheezing with infection by these viruses is associated with elevated risk of subsequent asthma.

Children with pre-existing atopy are at highest risk of asthma after a rhinovirus wheezing illness.

Reviewed in: Altman M, et al. JACI 2020.

The Airway Microbiome: Bacteria



No. at Risk						
Colonized	66	58	46	42	37	33
Not colonized	255	244	218	200	185	178

- Colonization of the hypopharynx at age 1 month with ***S. pneumoniae, M. catarrhalis*** **or** ***H. influenzae*** associated with asthma at age 5 years.
- These genera are also associated with RSV, rhinovirus, and lower airway symptoms during respiratory infections.

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

The Airway Microbiome:
Bacteria

Microbiome Utrecht Infant Study

de Steenhuijsen Piters WAA, et al. Early-life viral infections are associated with disadvantageous immune and microbiota profiles and recurrent respiratory infections. Nat Microbiol 2022.

1st viral infection in infancy

↓

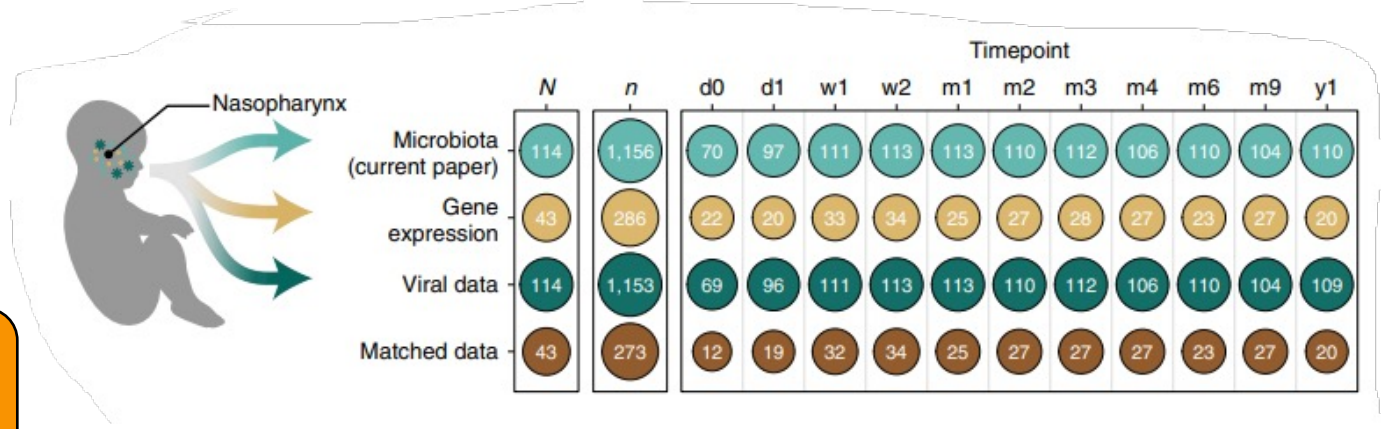
IFN-associated pro-inflammatory nasal environment

↓

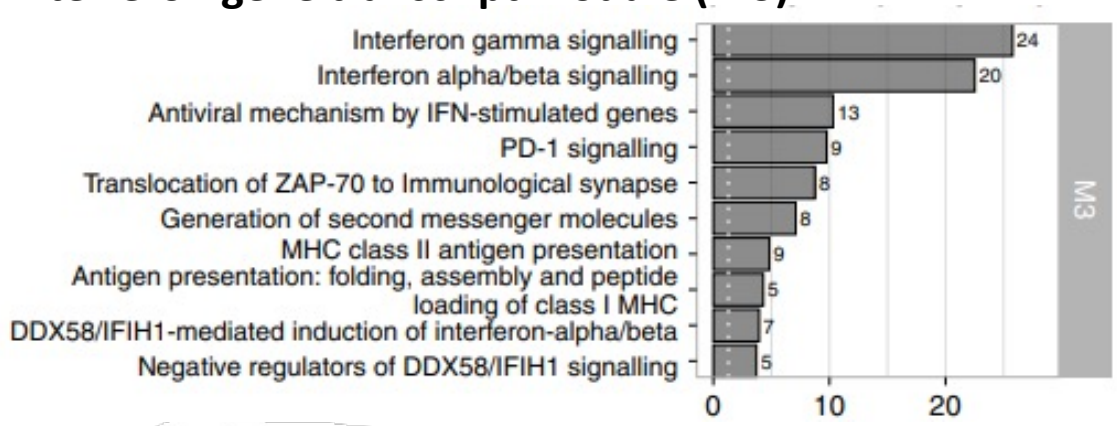
Selection for bacterial pathobionts

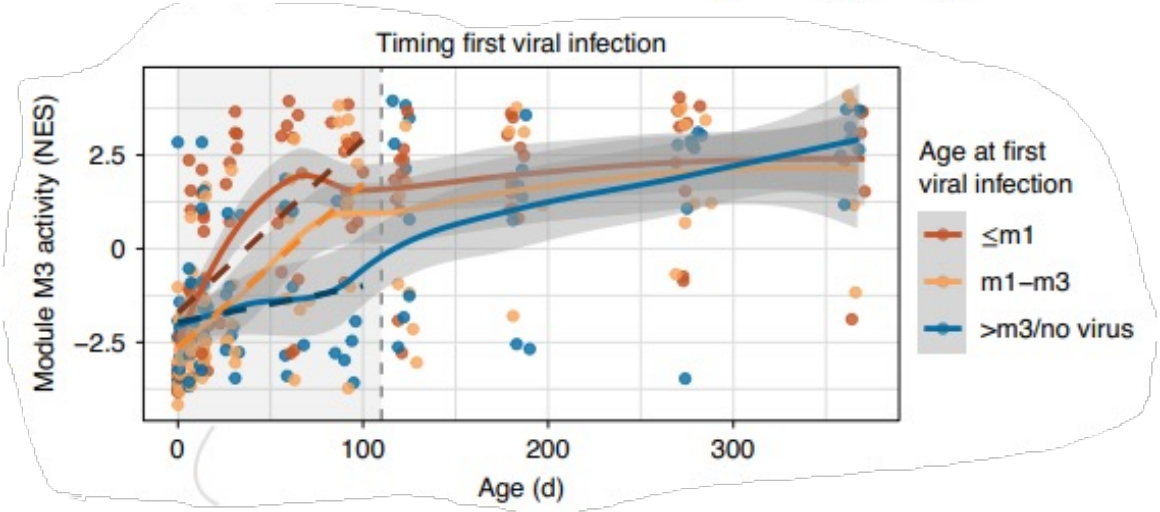
↓

Increased respiratory tract infection risk



Interferon gene transcript module (M3)



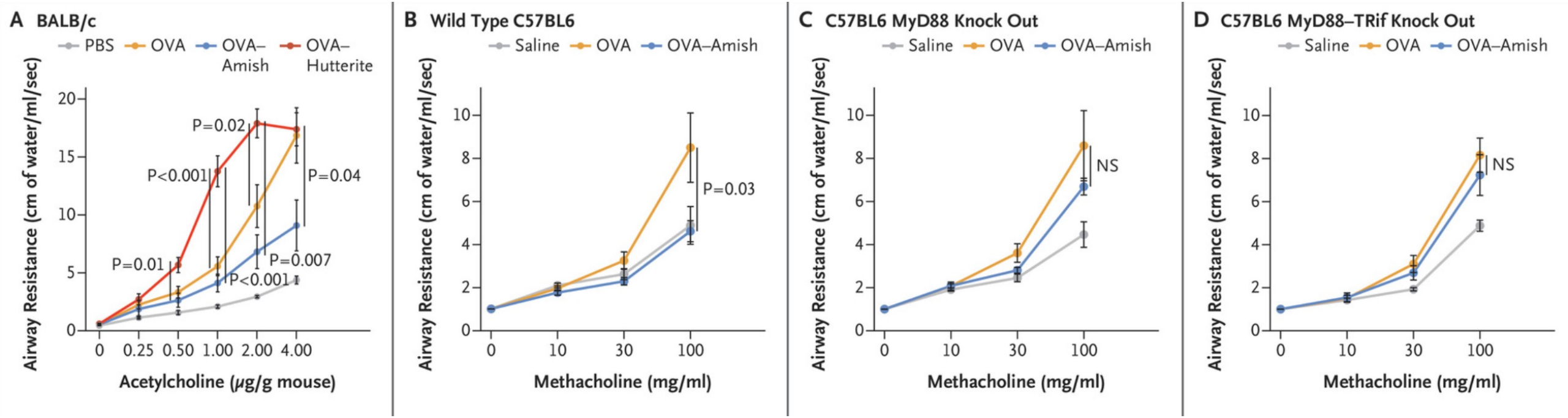


The Environmental Microbiome:
Amish & Hutterite Study

- Amish & Hutterites are genetically similar, but Amish live in **closer proximity to cow stables** and have 4x **lower asthma prevalence**.
- Dust collected from homes of n=10 in each group: higher perennial allergens, endotoxin & different bacterial composition in Amish
- Cytokine levels including **IL-33 and IL-25** were higher in supernatants of LPS-treated peripheral blood leukocytes from Hutterite children.

Stein MM, *et al*. NEJM 2016.

The Environmental Microbiome: Amish & Hutterite Study



In an OVA mouse model of allergic asthma, inhalation of dust from Amish but not Hutterite homes was protective.

Stein MM, *et al*. NEJM 2016.

The Gut Microbiome in Asthma: Birth cohort studies

	Age at gut microbiota determination	α-diversity (respiratory disease *vs* no respiratory disease)	Relative abundance of bacteria taxa (or fungal taxa) in respiratory disease versus no respiratory disease	Age of participants at respiratory disease determination (outcome)	AHRQ rating
Fujimura et al (2016)[29]	≤1 month	Not reported	Lower *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*, and *Akkermansia*; lower Malassezia; higher *Candida* and *Rhodotorula*	4 years (high risk of asthma)	Poor
Stockholm et al (2018)[32]	≤1 month	No difference	No difference	5 years (asthma)	Good
Arrieta et al (2015)[27]*	3 months	No difference	Lower *Faecalibacterium*, *Lachnospira*, *Rothia*, *Veillonella*, and *Peptostreptococcus*	1 year (atopic wheeze)	Poor
Boutin et al (2020)[35]*	3 months	α-diversity decreased	Lower *Faecalibacterium*, *Lachnospira*, *Coprococcus*, *Roseburia*, *Blautia*, *Parabacteroides*, and *Ruminococcus*	1 year (atopic wheeze)	Poor
Stiemmsa et al (2016)[30]*	3 months	No difference	Lower Clostridiales and *Lachnospira*; higher *Clostridium neonatale* (species), Clostridiaceae (family), and Firmicutes (phylum)	4 years (asthma)	Good
Arrieta et al (2018)[31]	3 months	No difference	Lower *Bifidobacterium*; higher *Streptococcus*, *Veillonella*, and *Pichia kudriavzevii*	5 years (atopic wheeze)	Fair
Arrieta et al (2015)[27]*	1 year	No difference	Lower *Oscillospira*	1 year (atopic wheeze)	Poor
Stiemmsa et al (2016)[30]*	1 year	No difference	Lower *Clostridium neonatale*; higher Lachnospiraceae and *Rothia*	4 years (asthma)	Good
Stockholm et al (2018)[32]	1 year	No difference	Lower *Roseburia*, *Alistipes*, and *Flavonifractor*; higher *Veillonella*	5 years (asthma)	Good
Patrick et al (2020)[36]*	1 year	α-diversity decreased	Lower *Faecalibacterium prausnitzii*, *Ruminococcus bromii*, and Rikenellaceae (family); higher *Dialister*	5 years (asthma)	Good
Depner et al (2020)[37]	1 year	α-diversity decreased	Lower *Faecalibacterium*, *Roseburia*, and *Ruminococcus*	6 years (non-atopic asthma)	Good

*Studies from the same cohort. AHRQ=Newcastle-Ottawa Quality assessment for cohort and case-control studies converted to the Agency for Healthcare Research and Quality scale. One paper[29] did not report results independently by time of stool sample collection, but the authors reported consistent decreases in relative abundance of certain bacteria genera in gut microbiota (*Lachnobacterium*, *Lachnospira*, and *Dialister*) at all timepoints examined (5 weeks, 3·3 months, 5·3 months, and 7·8 months) in children who developed asthma (parent-reported doctor diagnosis of asthma at age 6–11 years) compared with children who did not develop asthma.

Alcazar CG, et al. The association between early-life gut microbiota and childhood respiratory diseases: a systematic review. Lancet Microbe. 2022.

1. Microbiome & how it could influence asthma

2. Associations between the microbiome & asthma
   - Airway microbiome
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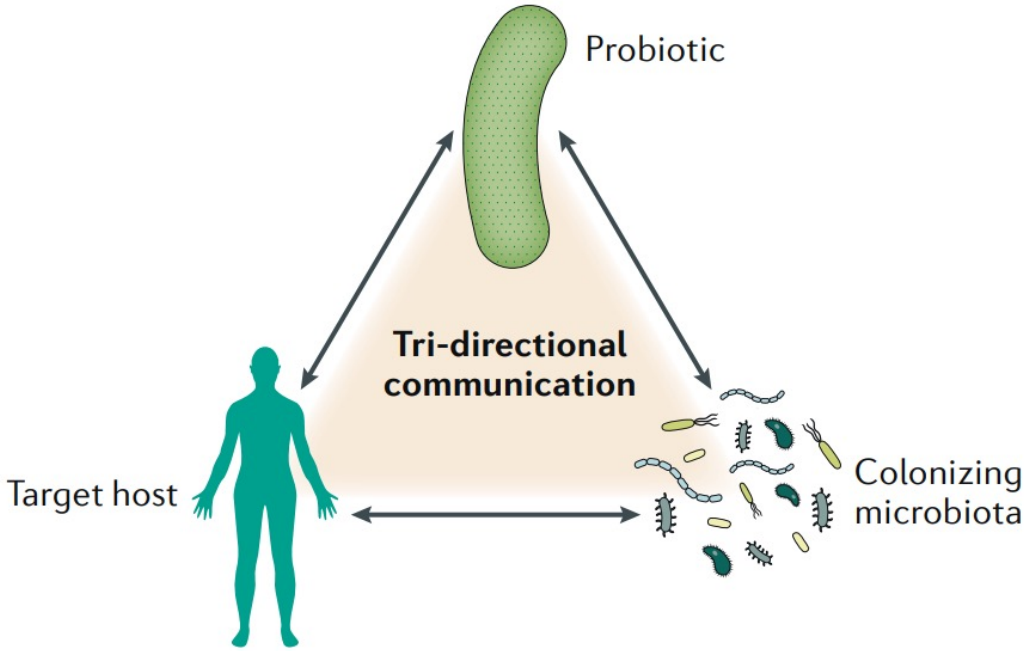
   - Gut microbiome

3. **Potential microbiome-based interventions**

Probiotic: live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.

Potential mechanisms of health effects

- Production of metabolites and enzymes
- Effects on overall microbiota composition
- Altered IgA production
- T regulatory cell induction
- Improved epithelial health



"At present, practicing clinicians can avail themselves of intestinal flora modulators as an adjunct in the prevention of atopic dermatitis but not of other forms of allergic diseases."

Fiocchi A, Cabana MD, Mennini M. Current Use of Probiotics and Prebiotics in Allergy. J Allergy Clin Immunol Pract. 2022.

Sanders ME, et al. Nat Rev Gastroenterol Hepatol 2019. Suez J, et al. Nat Med 2019.

Campus News • April 17, 2023

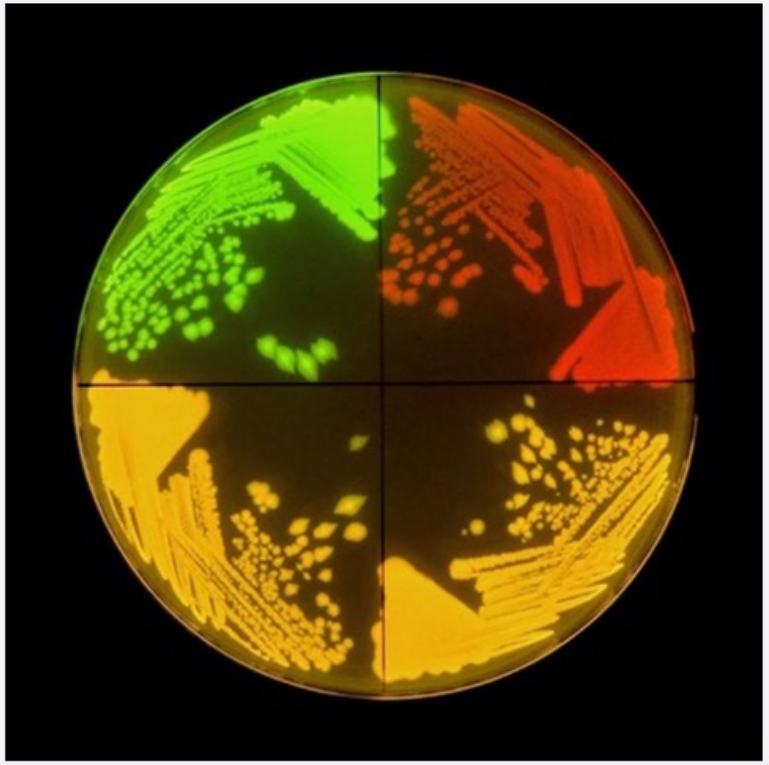
Editing Genes in the Microbiome to Prevent Disease

TED Audacious Grant Combines CRISPR Gene Editing with a Genomic Understanding of the Human Microbiome to Address Asthma and Other Conditions

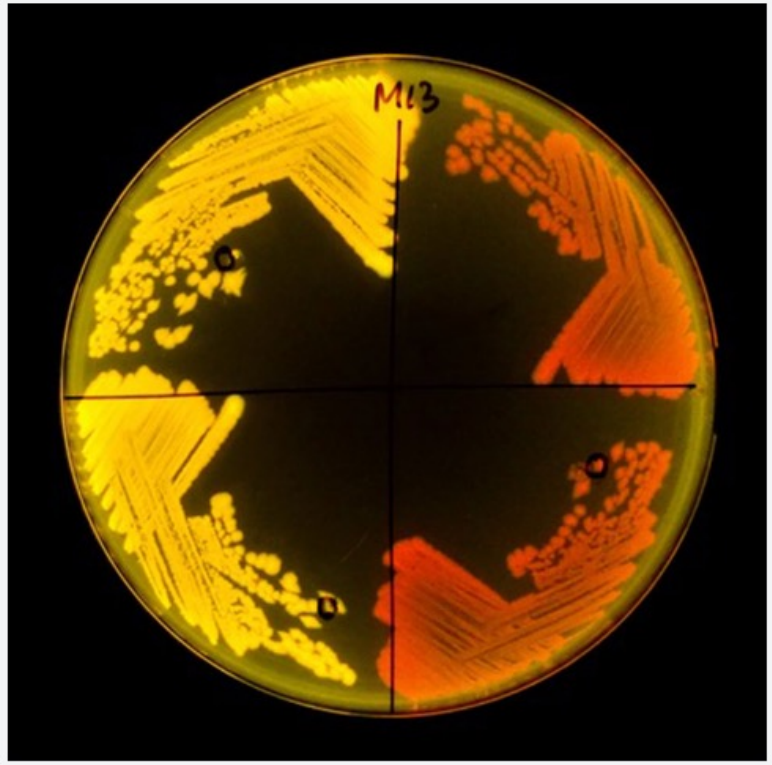
"UCSF's Sue Lynch, will use CRISPR-based gene editing tools customized for the task by some of the world's premier gene editing scientists at the Innovative Genomics Institute (IGI) – namely Nobel Laureate Jennifer Doudna, PhD, and microbiome specialist Jill Banfield, PhD, at UC Berkeley.

Their **goal will be to perform precise edits to the genomes of microbial cells associated with asthma** and move these modifications towards clinical trials in humans."

Plates of E. coli strains in the mouse gut, demonstrating Turnbaugh's success editing a single gene:

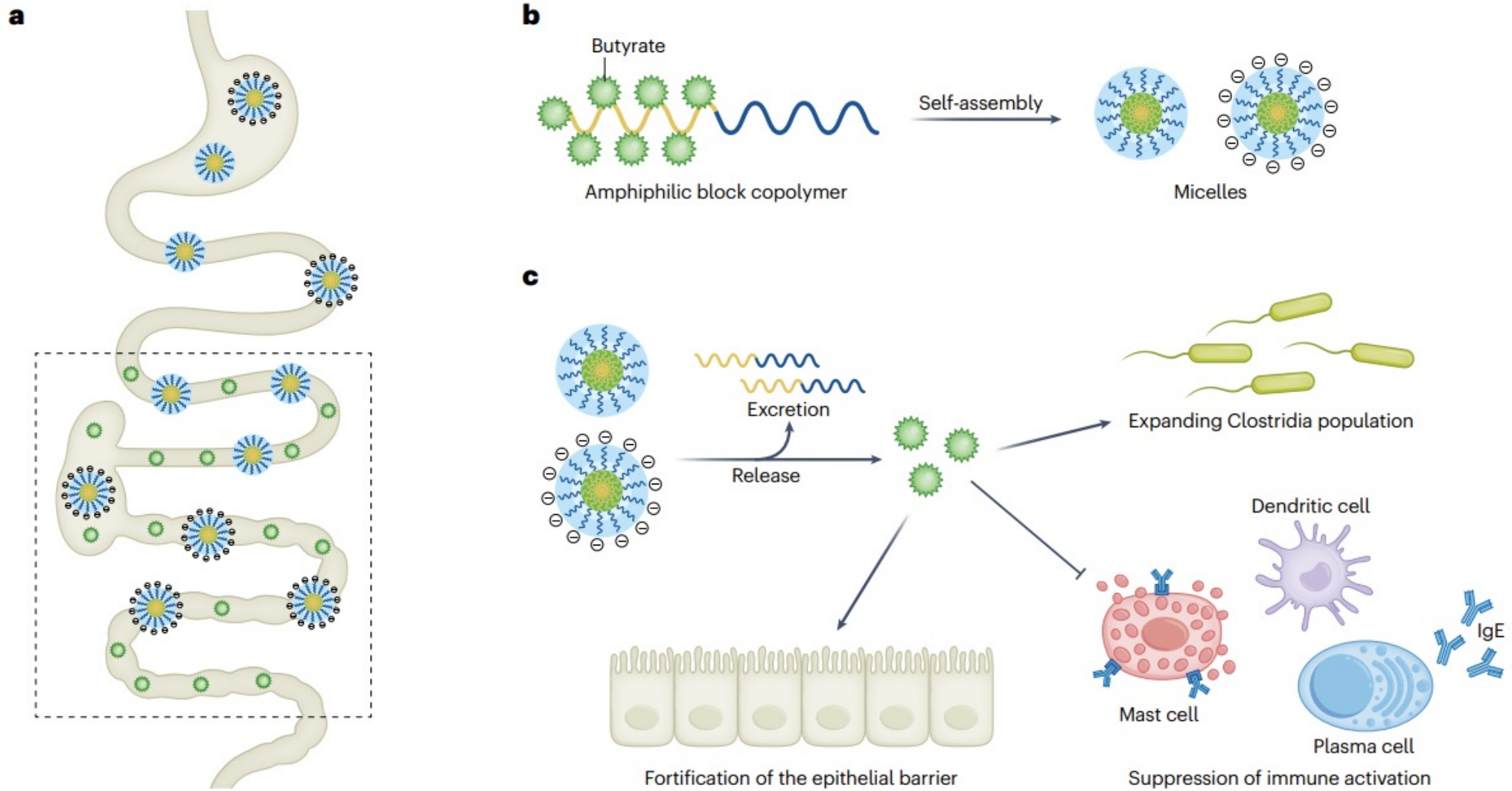


Three separate E. coli strains that express green, red, and both (yellow).



Here, CRISPR gene editing machinery was delivered to the mouse's gut using a virus, editing out the gene responsible for the green color.

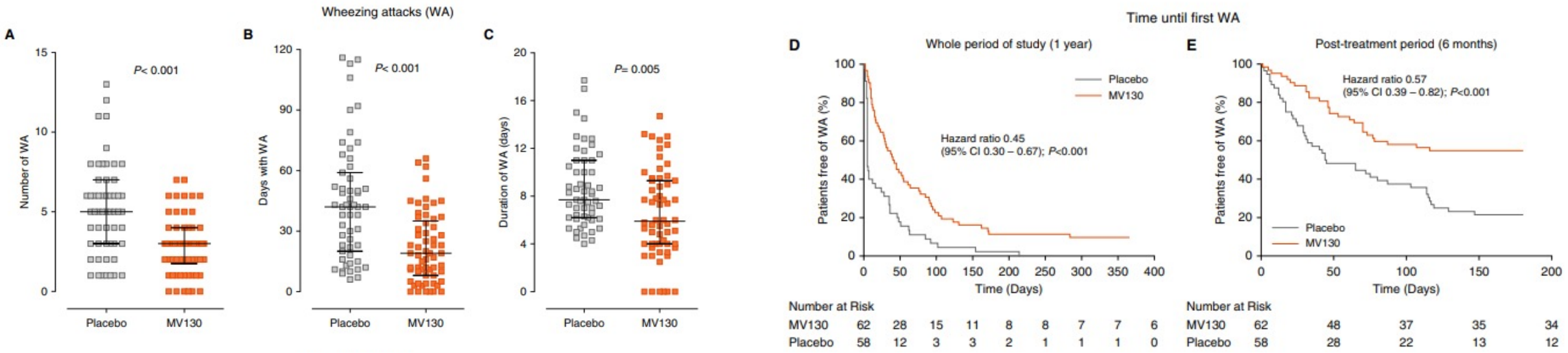
Local Butyrate Delivery



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

Bacterial Lysates: Immunoregulatory cellular extracts

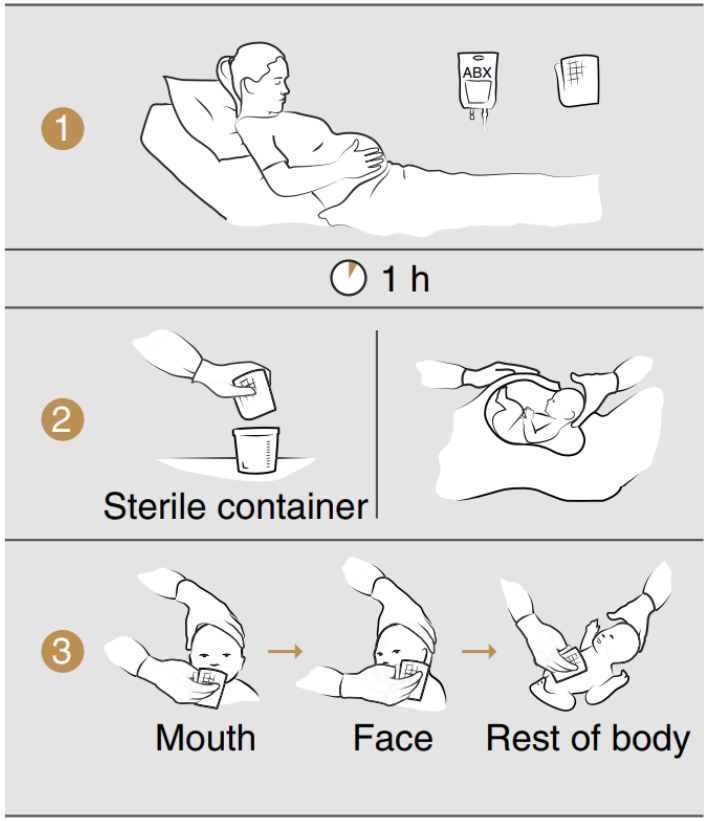
- **MV130:** sublingual suspension of heat-inactivated whole-cell bacteria: *S epidermidis, S aureus, S pneumoniae, H influenzae, M catarrhalis, K pneumoniae*
- RCT in n=120 children < 3 years old with 3+ wheezing attacks in prior year and no aeroallergen sensitization.



Nieto A, et al. Am J Respir Crit Care Med 2021.

ORBEX trial underway (NCT02148796):

OM-85 BV to prevent wheezing lower respiratory tract infection in high-risk infants



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

"Eating dirt or moving to a farm are at best theoretical rather than practical clinical recommendations for the prevention of asthma"

Scott T. Weiss, NEJM Editorial 2002

Under development: a door mat packed with microbe-rich soil for use in entries of urban homes

Martin Täubel, Finnish institute for health and welfare

Key Points

- The microbiome changes dramatically over the first few years of life and this process is critical to immune development.
- The microenvironment of the airway, the gut and the environment surrounding an individual all influence risk of asthma.
- Look out for emerging microbiome-based interventions for preventing and treating asthma and other allergic diseases.