The Microbiome and Asthma

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Update on Severe Asthma 2024

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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

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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.

Fecal Microbiome Beta Diversity (Bray-Curtis Dissimilarity) Over Early 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 antigenexperienced lymphocytes compared to SPF.
- However, wildling mice exhibit **increased** allergic airway inflammation after challenge with house dust mite, IL-33 or *A. alternata*.



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 \rightarrow 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.

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Hay fever, hygiene, and

fever has been described as a "post industrial

revolution epidemic," and successive morbidity

surveys from British general practice suggest that its

revalence has continued to increase over the past 30

ears.² Other evidence suggests a recent increase in the

revalence of asthma' and childhood eczema.' This

aper suggests a possible explanation for these trends

I studied the epidemiology of hay fever in a national

ample of 17 414 British children born during one week

March 1958 and followed up to the age of 23 years

the National Child Development Study). Three

nes were investigated; (a) self reported "hay

household size

ubjects, methods, and result

David P Strachan

CIE 7HT

ccurring in initiants seven years previously might be differenced by total family size, it is less likely to have seen affected specifically by the number of older hildren in the household. Similar gradients in high fore, a peri adamid readsing preduce of periods and seven an

months" at age 11; (c) parental recall of "eczema ir

nodels were fitted with the LR program in the BMD

factors studied the most striking associations with hav

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 hav fever was inversely related to

the number of children in the household at age 1

persisted. These trends in adjusted prevalence were

ndependent of one another and each was significant

children were significantly steeper (γ = 11.6, df = 1

p<0.01 at age 11; $\chi^2=19.5$, df=1, p<0.01 at age 23). A further analysis of hav fever occurring at 23 by birth

<0.01, see table), but the trends by numbe

(when it is assumed most families were complete). When prevalence figures were adjusted by multiple logistic regression for other significant determinants of hav fever in this cohort (see table) the associations with

statistical nackage

Of the 16 perinatal,

numbers of older and younger childr

he first year of life" elicited when the child was 7. Cross tabulations were performed with the SAS statistical package, and multiple logistic regression

These observations do not support suggestions that origin line(tons, particularly of the respiratory transmission of atopy here could, however, be explained if allerized issues of atopy here could, however, be explained if allerized issues and atoms. Cal & JA (and B (1981) 1.8 between the support of the support of atopy here were the support of allerized issues and atoms of a barrier of barrier to a support here and the support of the support of atopy here were the support of all allerized issues atoms for a support atoms for a support of the support of the support of the support here a support of the support of the support of the support atoms for a support of the support of the support of the support atoms for a support of the support of the support of the support atoms for a support of the support of the support of the support of the support atoms for a support of the support of the support of the support of the support atoms for a support of the support of the support of the support of the support atoms for a support of the support of the support of the support of the support atoms for a support of the suppor

hood, (Accepted 14 September 1989)

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



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



- 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.



Age (d)

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.

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 <i>Lachnospira</i> ; higher <i>Clostridium neonatale</i> (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 paper²⁹ 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
 - Environmental microbiome
 - 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 CRISPRbased 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





- 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.