

# **The Early Life Microbial Environment and Asthma**

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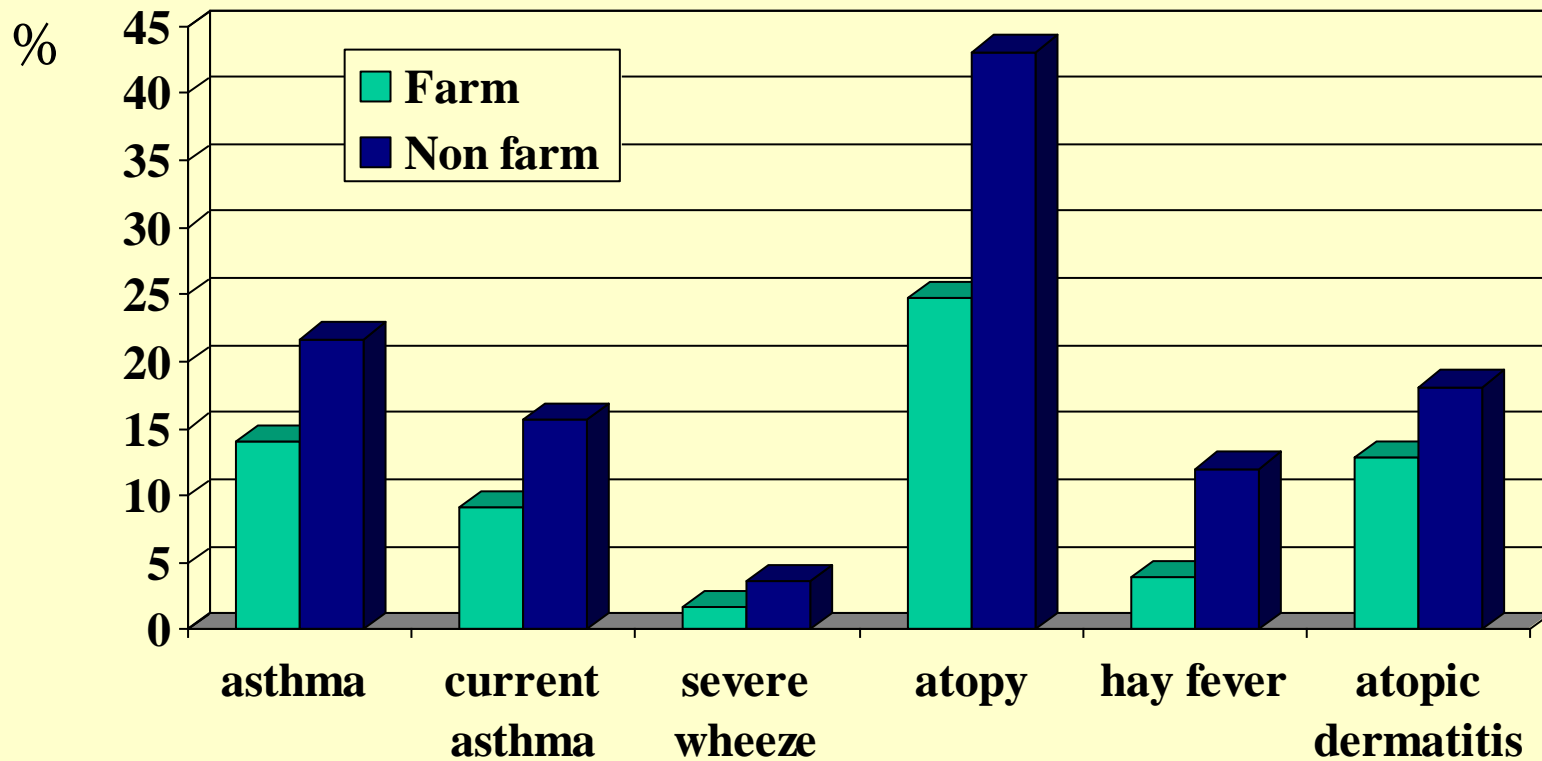
**Ludwig Maximilians University Munich, Germany**

**German Centre for Lung Research**



# GABRIEL Study: Prevalences between Farm and Non Farm Children.

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# Cow Shed and Milk Protect from Asthma and Atopy.

Asthma <sup>#</sup>	aOR*	95%-CI	p
- Contact with cows, - contact with straw	1.00	-	-
- Contact with cows, + contact with straw	1.00	0.76-1.32	1.00
+ Contact with cows, - contact with straw	0.94	0.73-1.21	0.63
+ Contact with cows, + contact with straw	0.68	0.54-0.85	<0.001
Consumption of farm milk	0.81	0.68-0.96	0.02
Farming	0.89	0.75-1.06	0.20

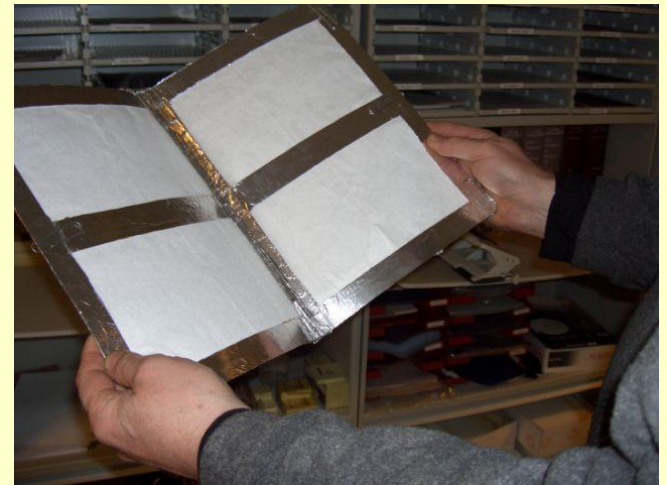
Atopic sensitization <sup>#</sup>	aOR*	95%-CI	p
Contact with straw	0.66	0.56-0.78	<0.001
Consumption of farm milk	0.77	0.67-0.88	<0.001
Farming	0.74	0.64-0.86	<0.001



What are protective factors in stables ?

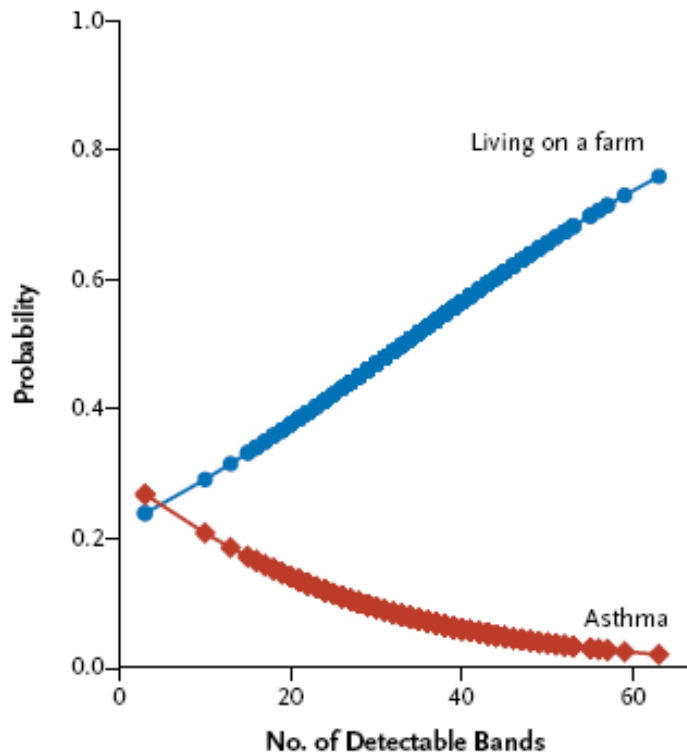
# Assessment of Environmental Microbial Exposures.

- Use of electrostatic dust collectors (EDCs)
- Indoor settled dusts from a nested case control among farm and non farm children in GABRIEL Advanced Studies
- Sequencing (16srRNA) for bacterial signals and conventional culture methods to assess fungi.

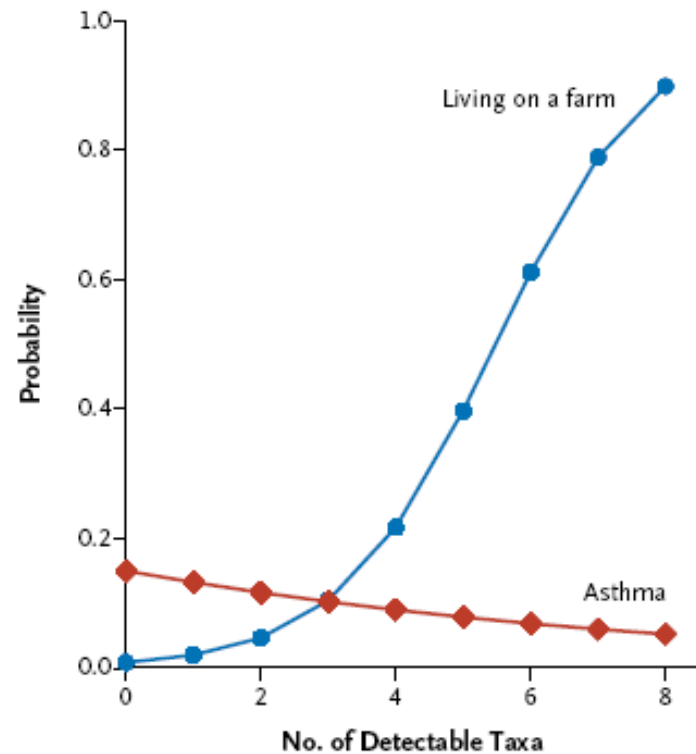


# The Diversity of Microbial Exposure is Inversely Related to Asthma.

**A** Bacteria (PARSIFAL)



**B** Fungi (GABRIELA)



**Figure 3.** Relationship between Microbial Exposure and the Probability of Asthma.

In both the PARSIFAL study and GABRIELA, the range of microbial exposure was inversely associated with the probability of asthma.

# Microbial Cocktail

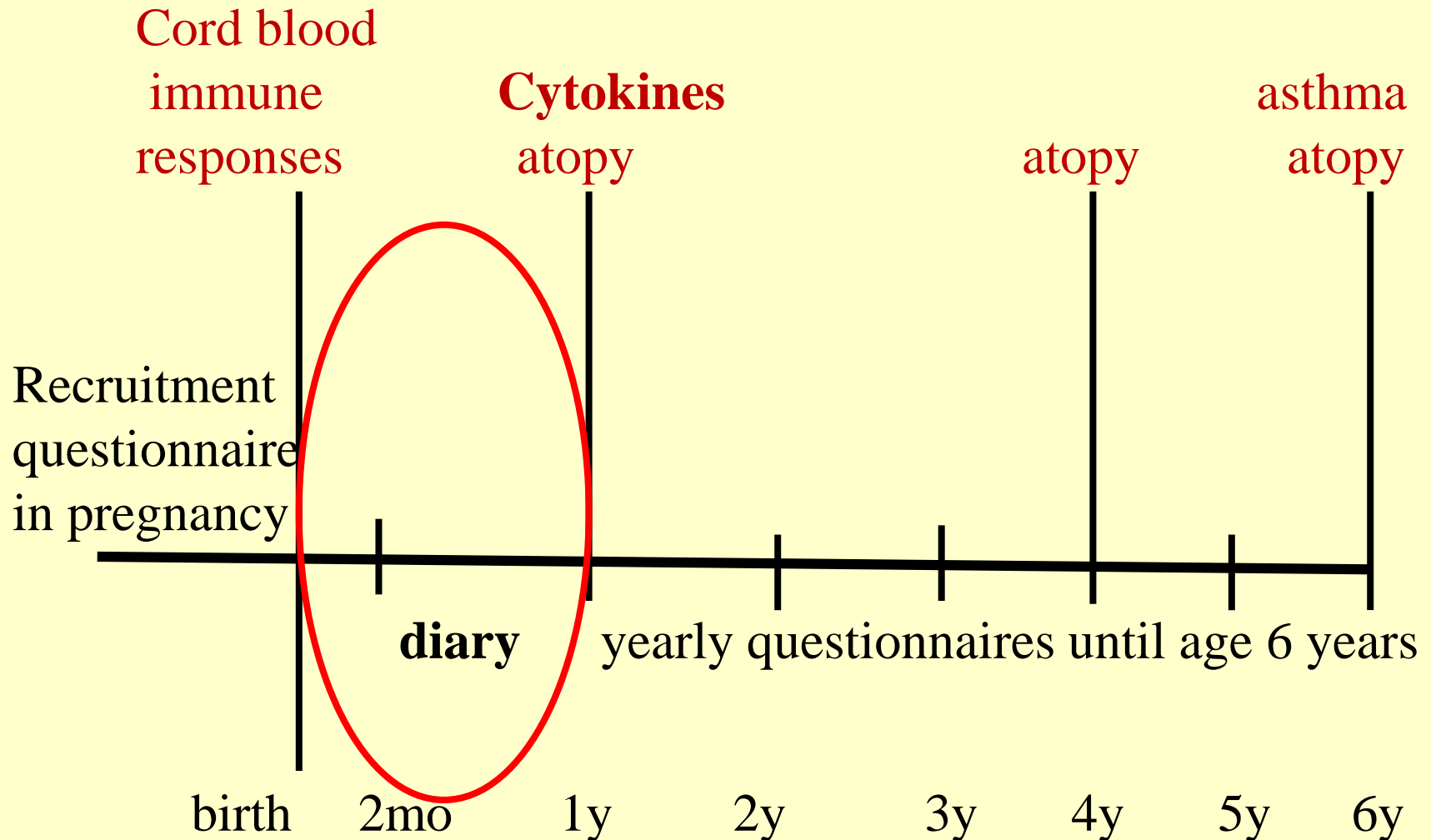
Bacteria: *Staphylococcus sciuri*, *Staphylococcus* sp., *Salinococcus* sp., *Macrococcus* sp., *Bacillus* sp., and *Jeotgalicoccus* sp., *Listeria monocytogenes*, *Bacillus licheniformis*, *Bacillus* sp., *Corynebacterium* sp., *Methylobacterium* sp., *Xanthomonas* sp., *Enterobacter* sp., *Pantoea* sp., *Acinetobacter lwoffii* and others.

Fungi: *Eurotium* sp; *Penicillium* sp

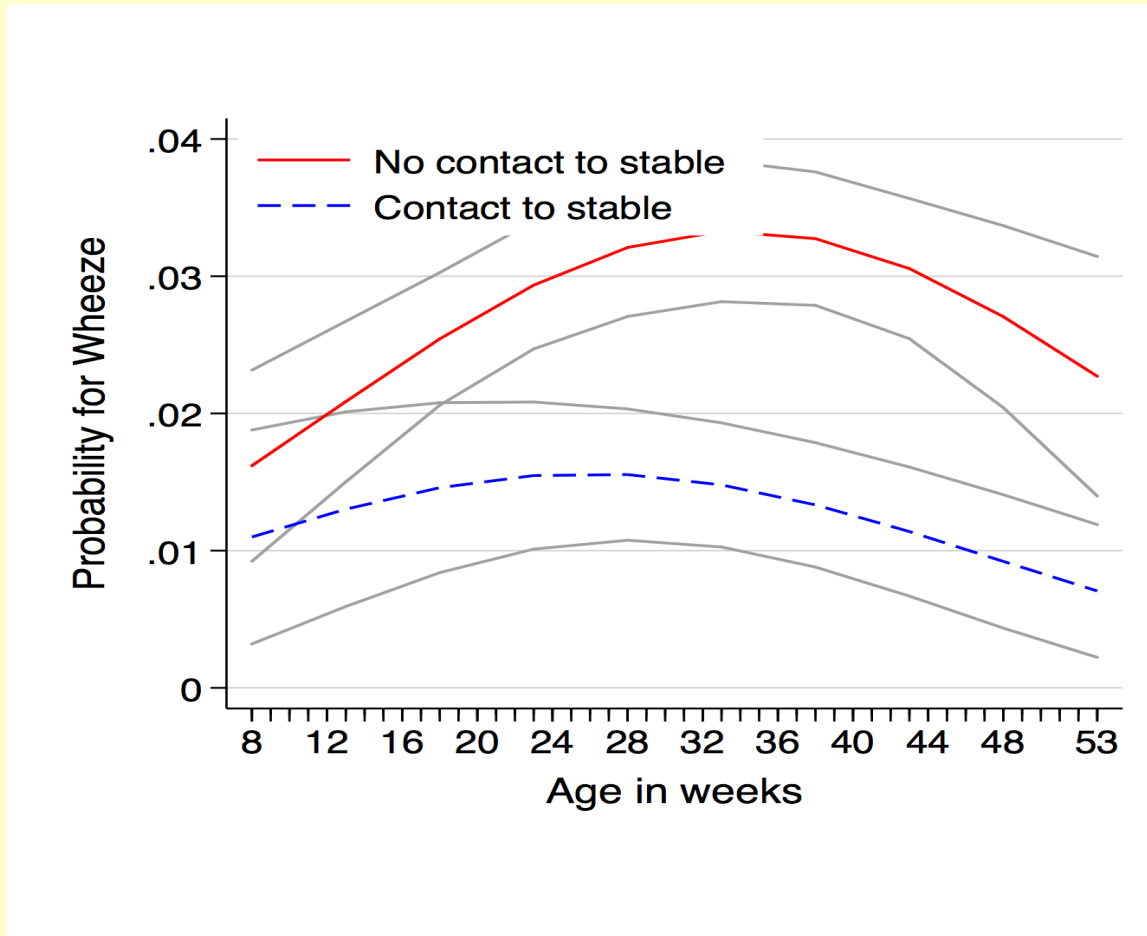




# PASTURE/EFRAIM Birth Cohort (N=1,133)



# Contact to Stable in 1. Year of Life and Wheeze Episodes.



**aOR from GEE model: 0.55 (95% CI: 0.43-0.71)**

# Contact to Stable in 1. Year of Life and Rhinitis Episodes.

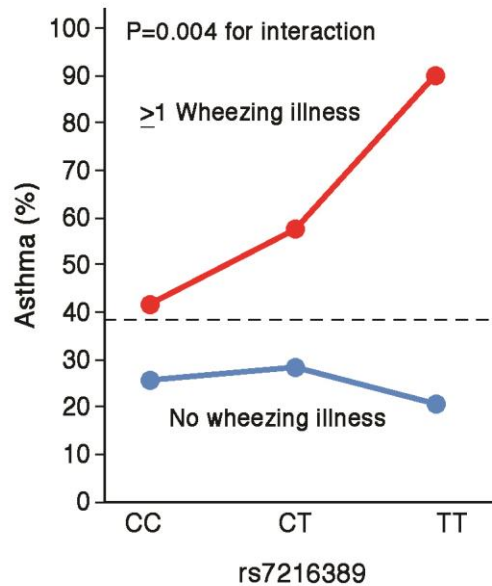
Similar effects on  
episodes of fever

Age in weeks

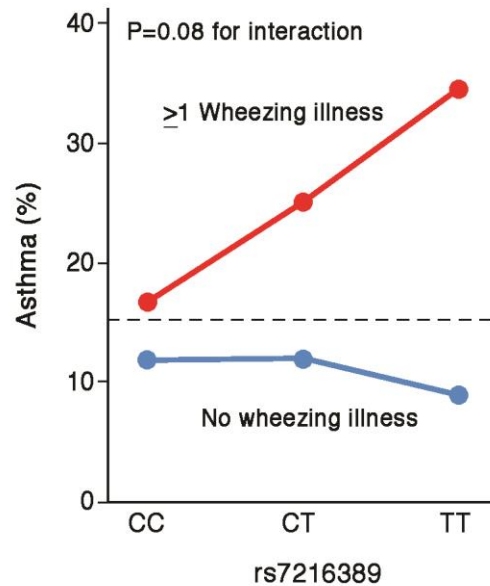
**aOR from GEE model: 0.65 (95% CI: 0.58-0.72)**  
(adjusted for confounders and wheeze)

# Chromosome 17 Locus: Association with Asthma and Rhinovirus Wheezing Illnesses.

**A) COAST**



**B) COPSAC**



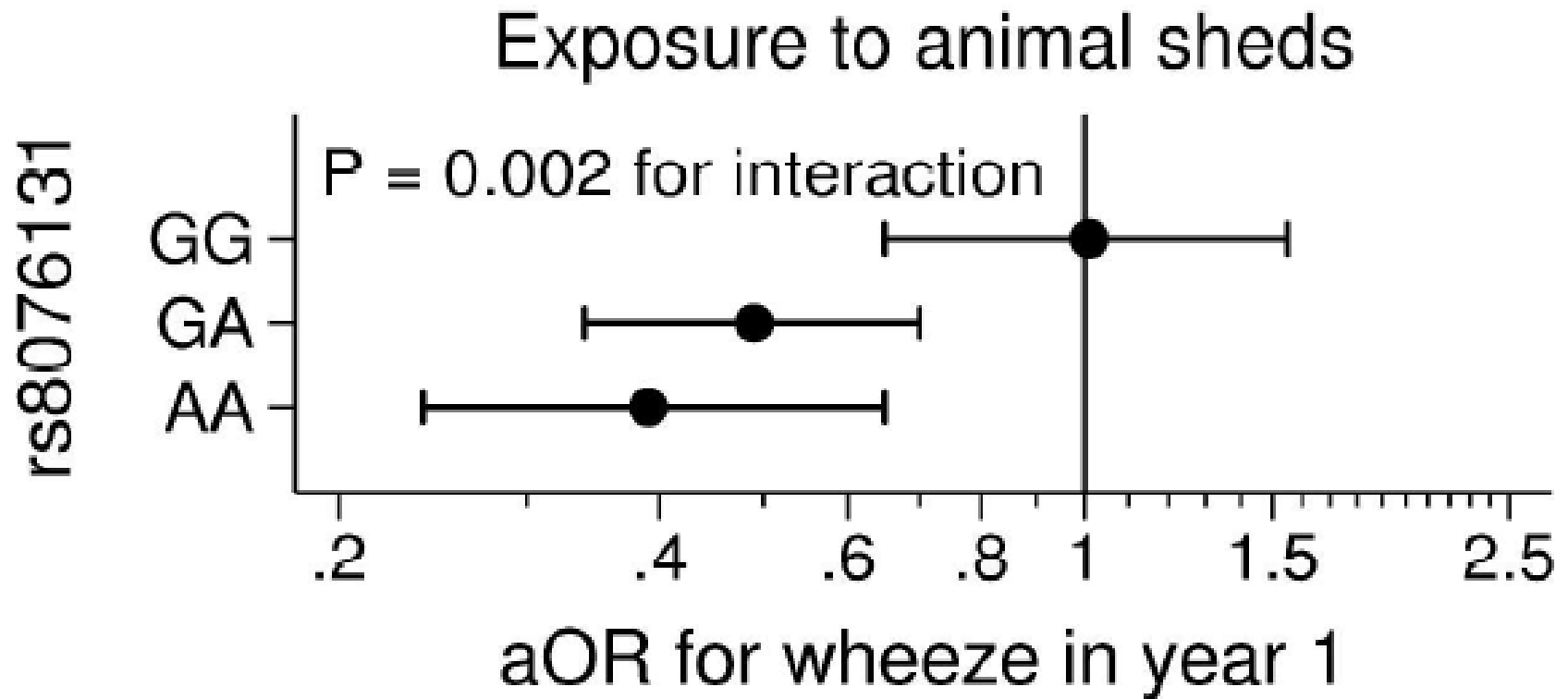
No. with Genotype  
 ≥1 Wheezing illness  
 No wheezing illness

	CC	CT	TT
≥1 Wheezing illness	12	33	20
No wheezing illness	39	67	29

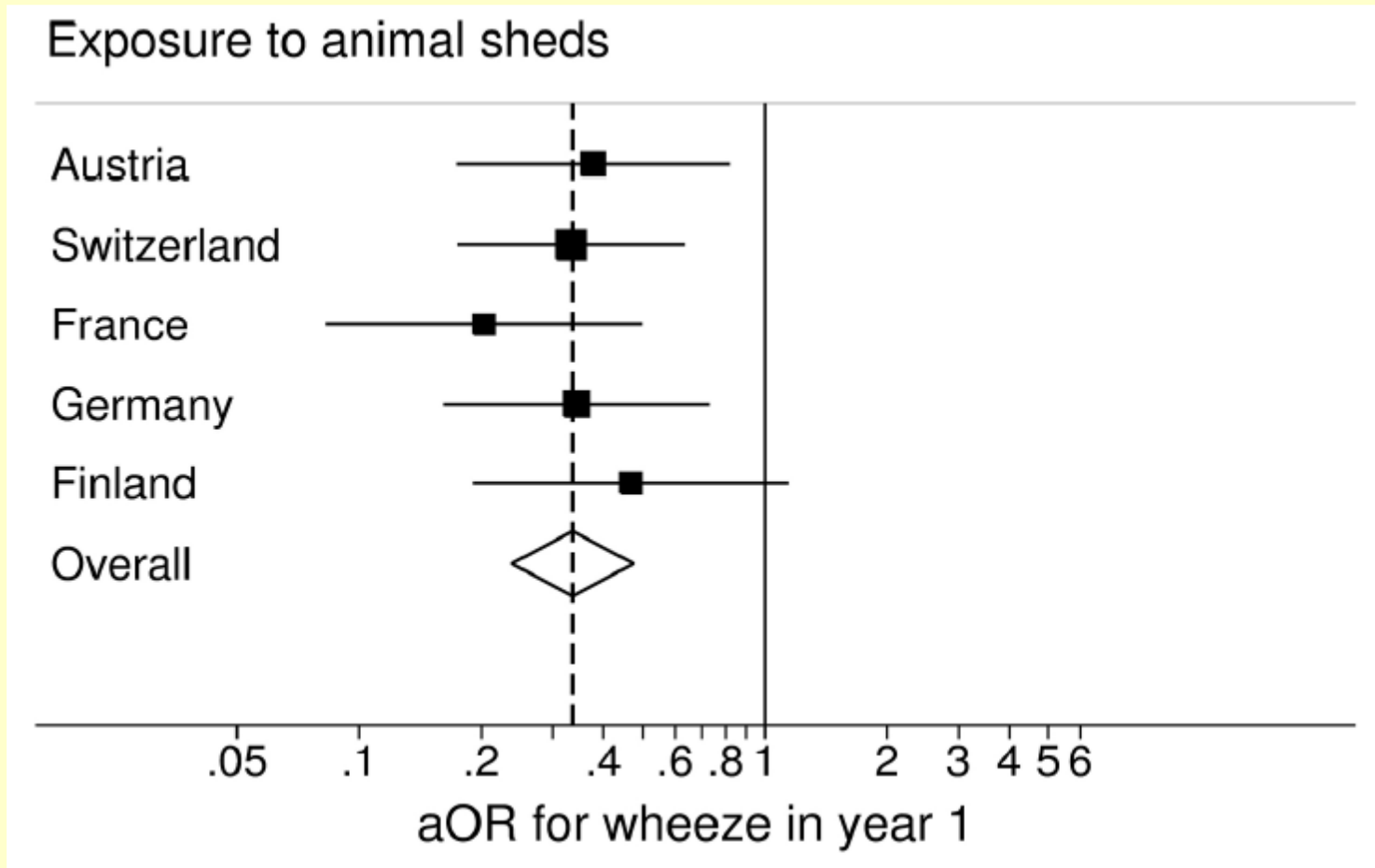
	CC	CT	TT
≥1 Wheezing illness	12	32	29
No wheezing illness	59	109	56

Is protection mostly in those at risk of developing asthma with virus induced wheezing, i.e. carriers of the chromosome 17q21 locus ?  
These account for 75% of the total population.

# Chromosome 17q21 Locus Interaction with Stay in Animal Sheds.

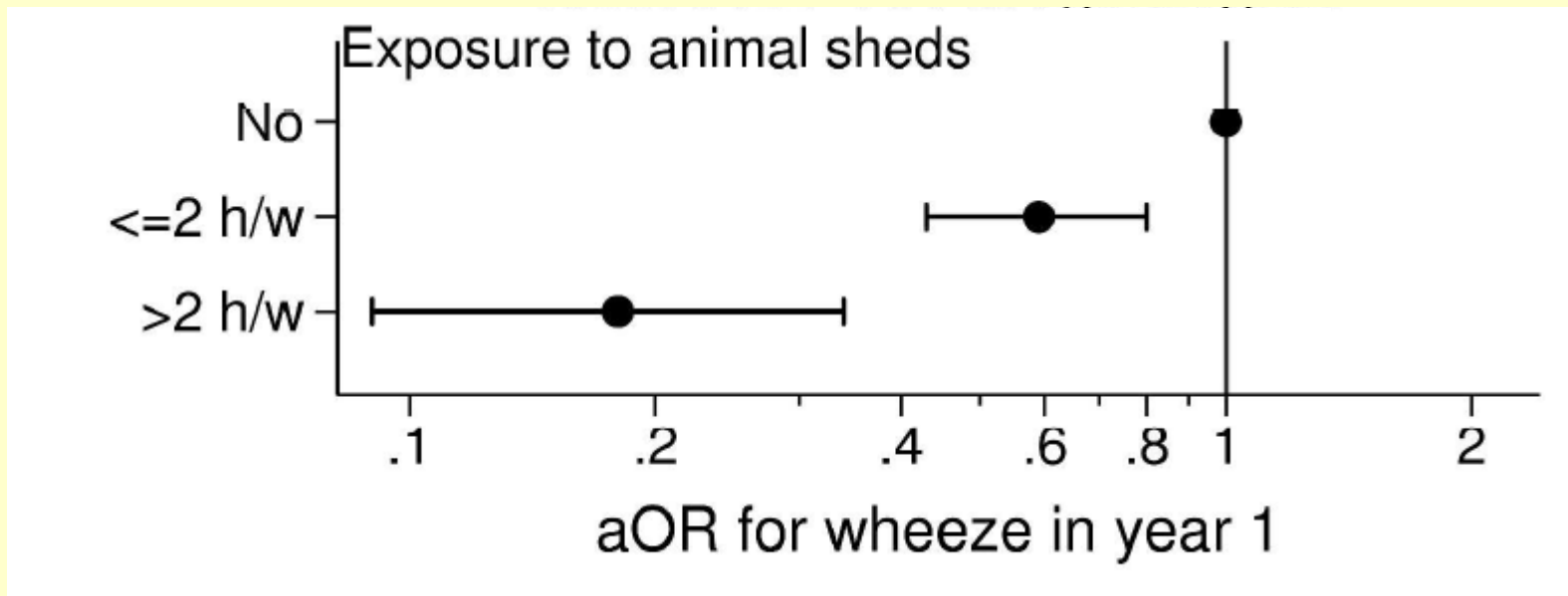


# Consistency of Effects in GA/AAs Across 5 PASTURE Populations.





# Dose Response Effect in GA/AAs.



# Amish People

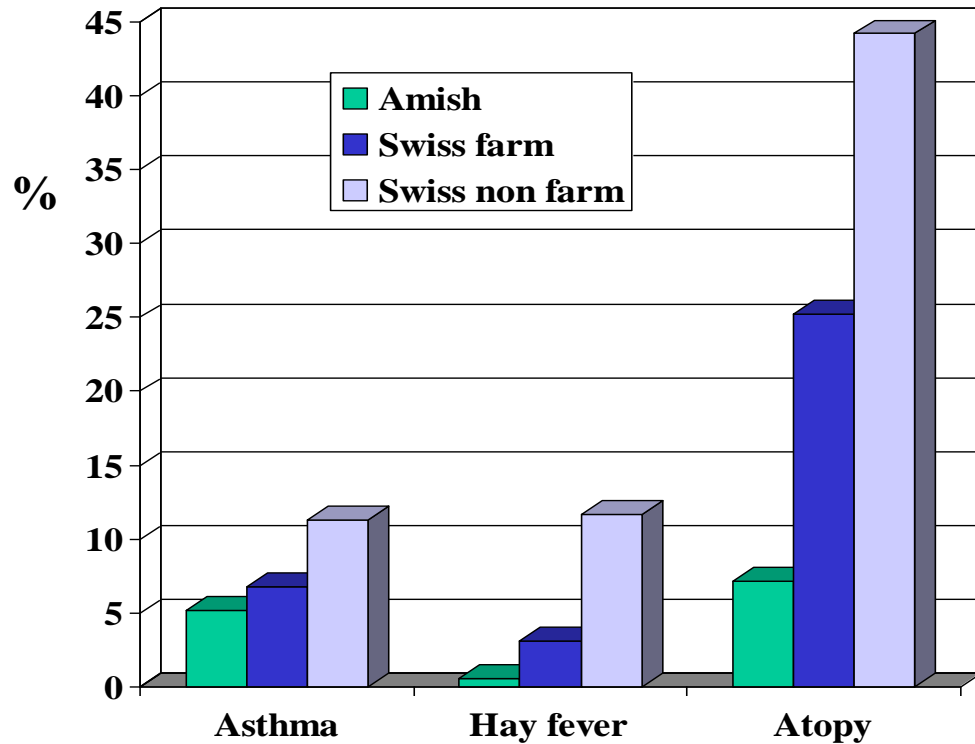


<https://reesephoto.files.wordpress.com/2012/01>





# Asthma and Atopy among Amish Children as Compared to Swiss Farm and Non Farm Children (GABRIEL Study)

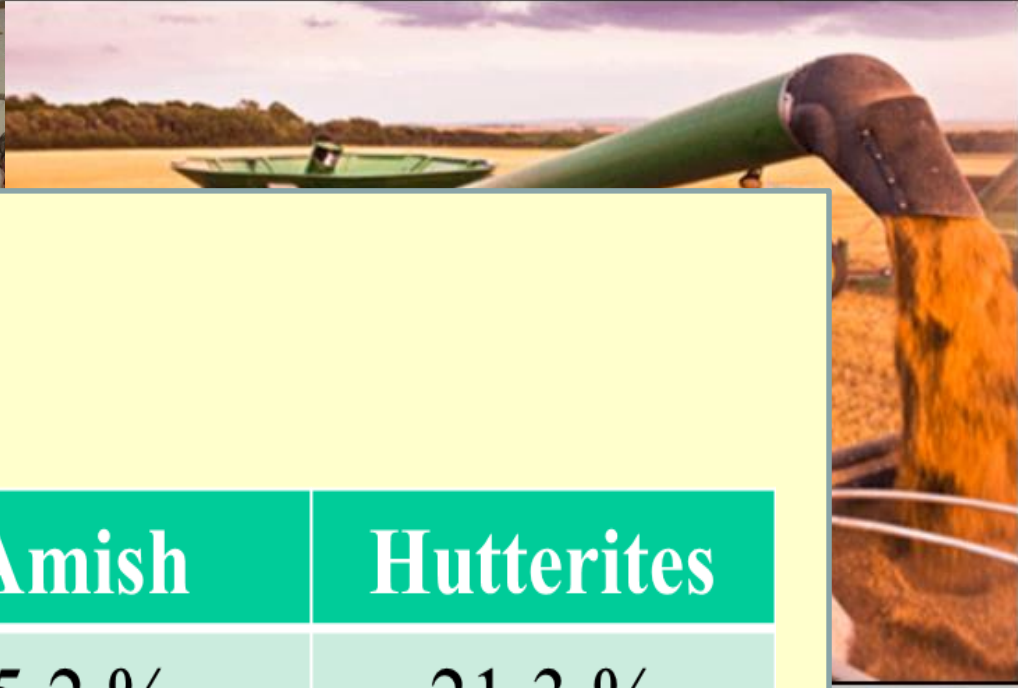


Holbreich et al, JACI 2012



	Amish	Hutterites
Asthma	5.2 %	21.3 %
Atopy	7.2%	33.3%

Stein et al, NEJM 2016

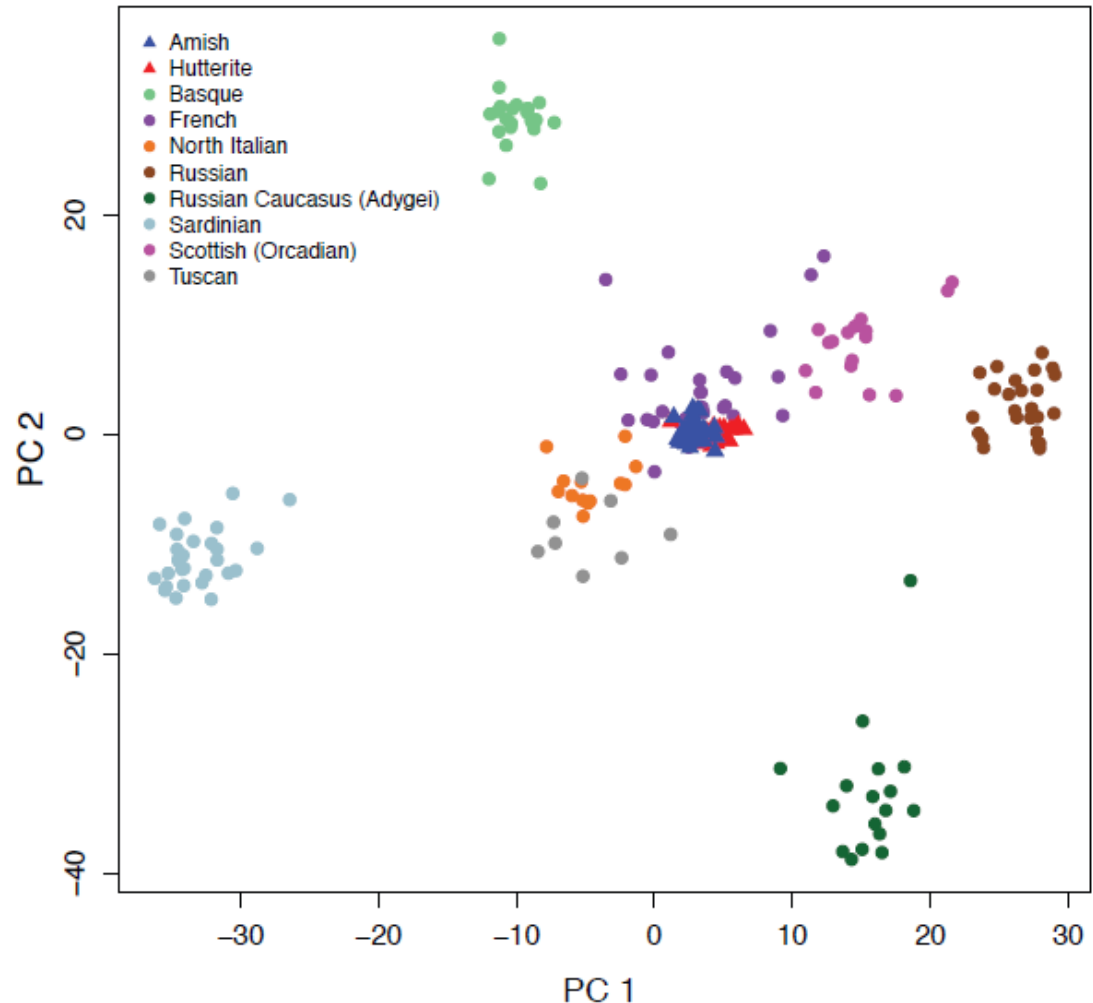


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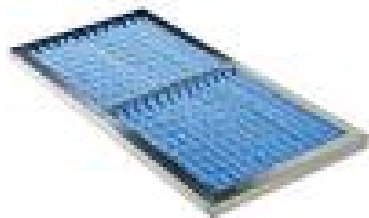
# Genetic Ancestry in Amish and Hutterites Compared to Other European Populations

118,789 SNPs  
genotyped or imputed;  
73,590 overlapping SNPs  
compared with the European  
populations in the Human  
Genome Diversity Project.

A



# The Environment in a Tube in a Mouse: Comparing Indoor Dust from Amish and Hutterite Homes



Electrostatic dust collectors

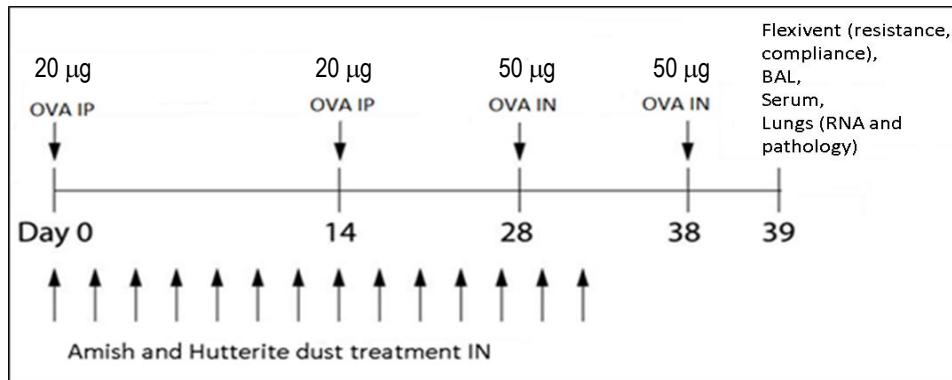
Place in children's bedrooms for 30 days



Extract dust



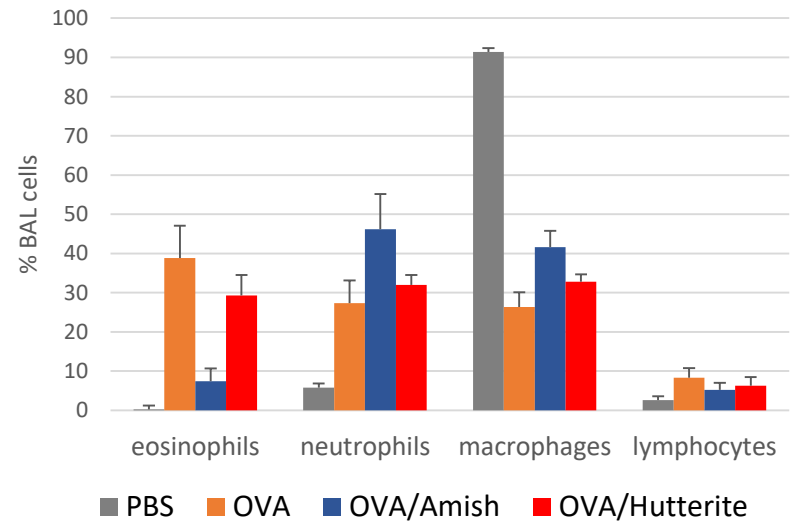
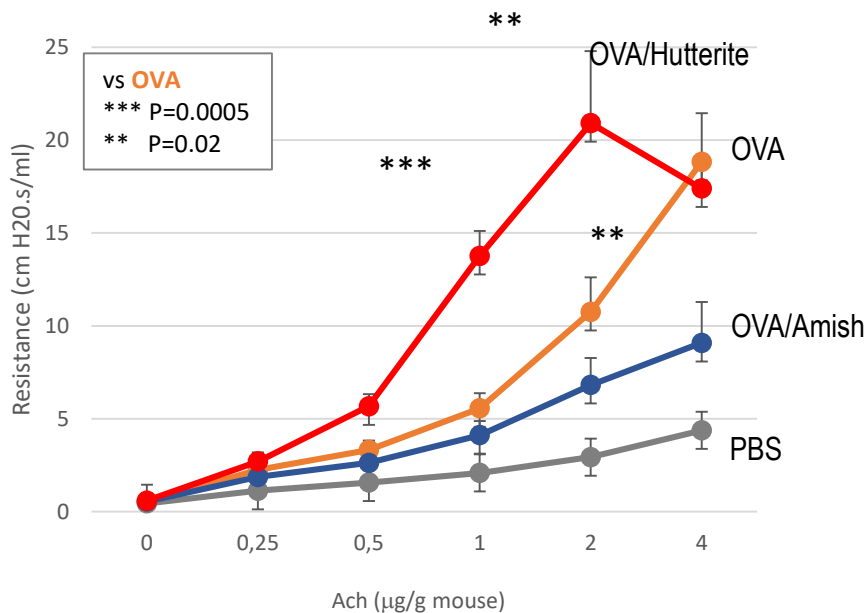
Administer dust extracts i.n. to allergen (OVA)-treated Balb/c mice



June 2015

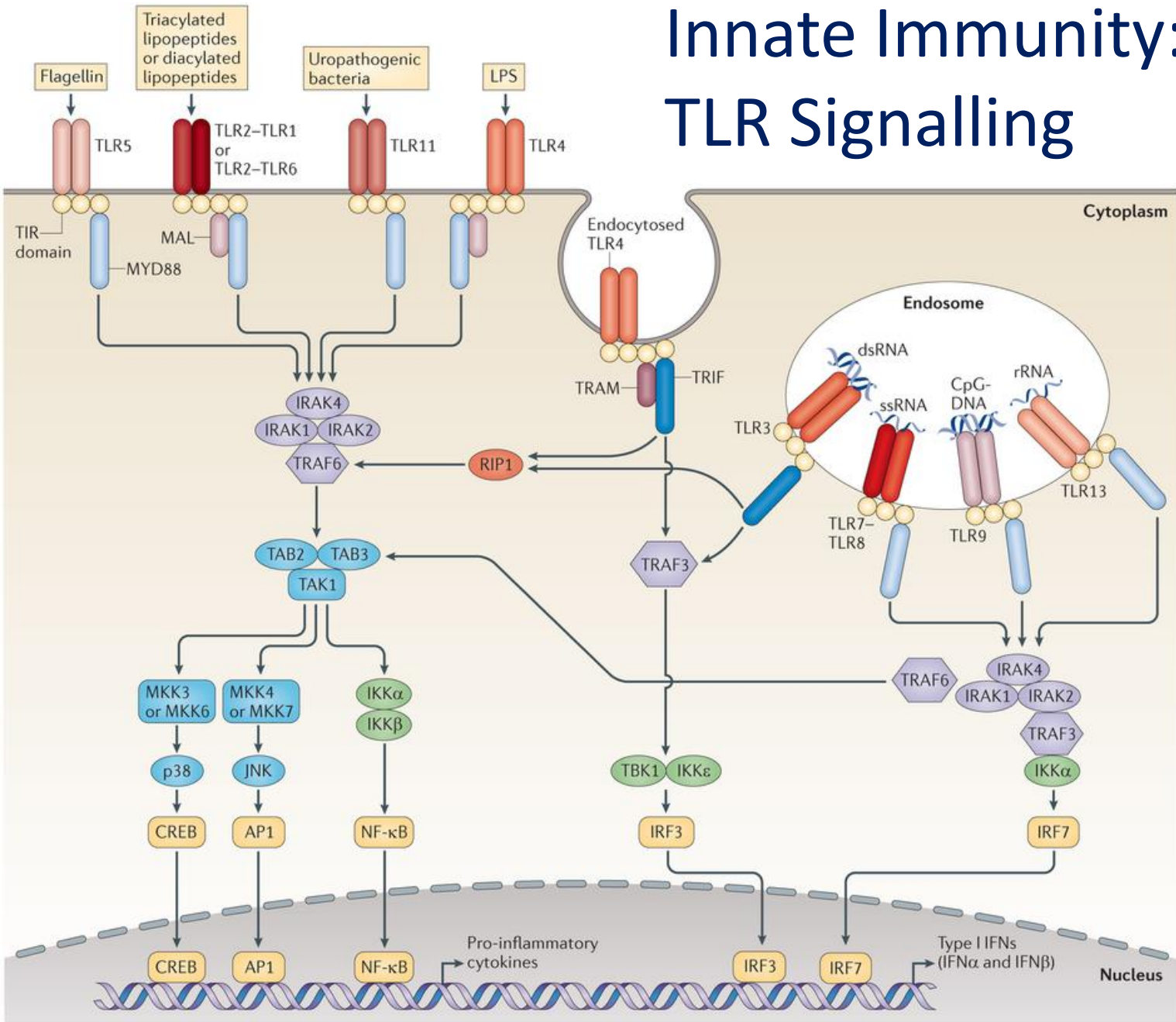
Courtesy of Donata Vercelli

# Strong suppression of OVA-induced airway hyperresponsiveness and Th2 inflammation in Amish<sub>home</sub> but not Hutterite<sub>home</sub> mice



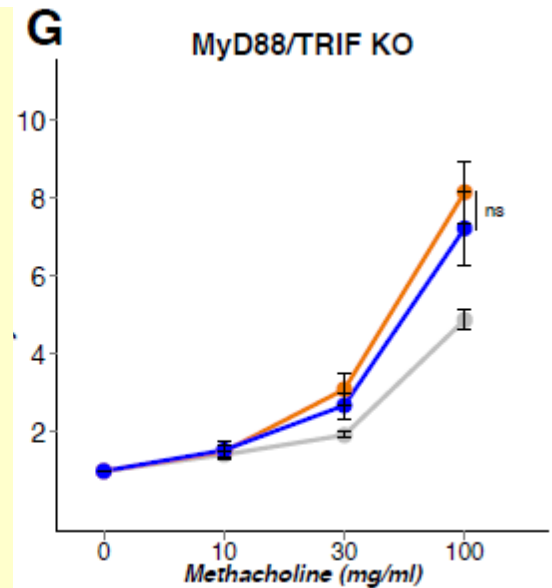
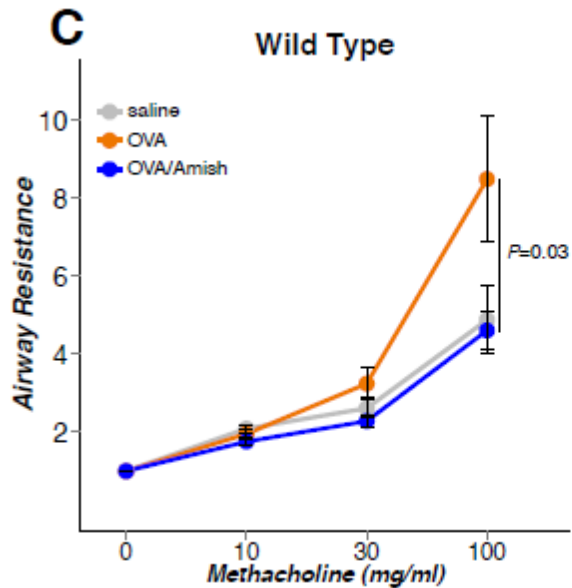


# Innate Immunity: TLR Signalling



O'Neill et al,  
Nat Rev  
Immunology  
2013

# Airway Hyperresponsiveness in Amish Mice: Wildtype and MyD88/TRIF Knockout



# The Early Life Microbial Environment and Asthma.

- Strong evidence that farming exposure protects from childhood asthma, wheeze and allergic sensitization.
- The relevant exposures are:
  - Stay in animal sheds
  - Consumption of raw cow's milk



# The Early Life Microbial Environment and Asthma.

- Early life exposure to cow sheds protects from the development of wheeze and later asthma.
- A microbial cocktail from cow sheds is most likely to confer this protection early in life.

# The Early Life Microbial Environment and Asthma

- In mice protection from allergic asthma by Amish dust extracts requires innate immune signalling.
- Increased innate immune signalling is also found among Amish and farm children.