Enfant allergique, la faute à l'environnement?

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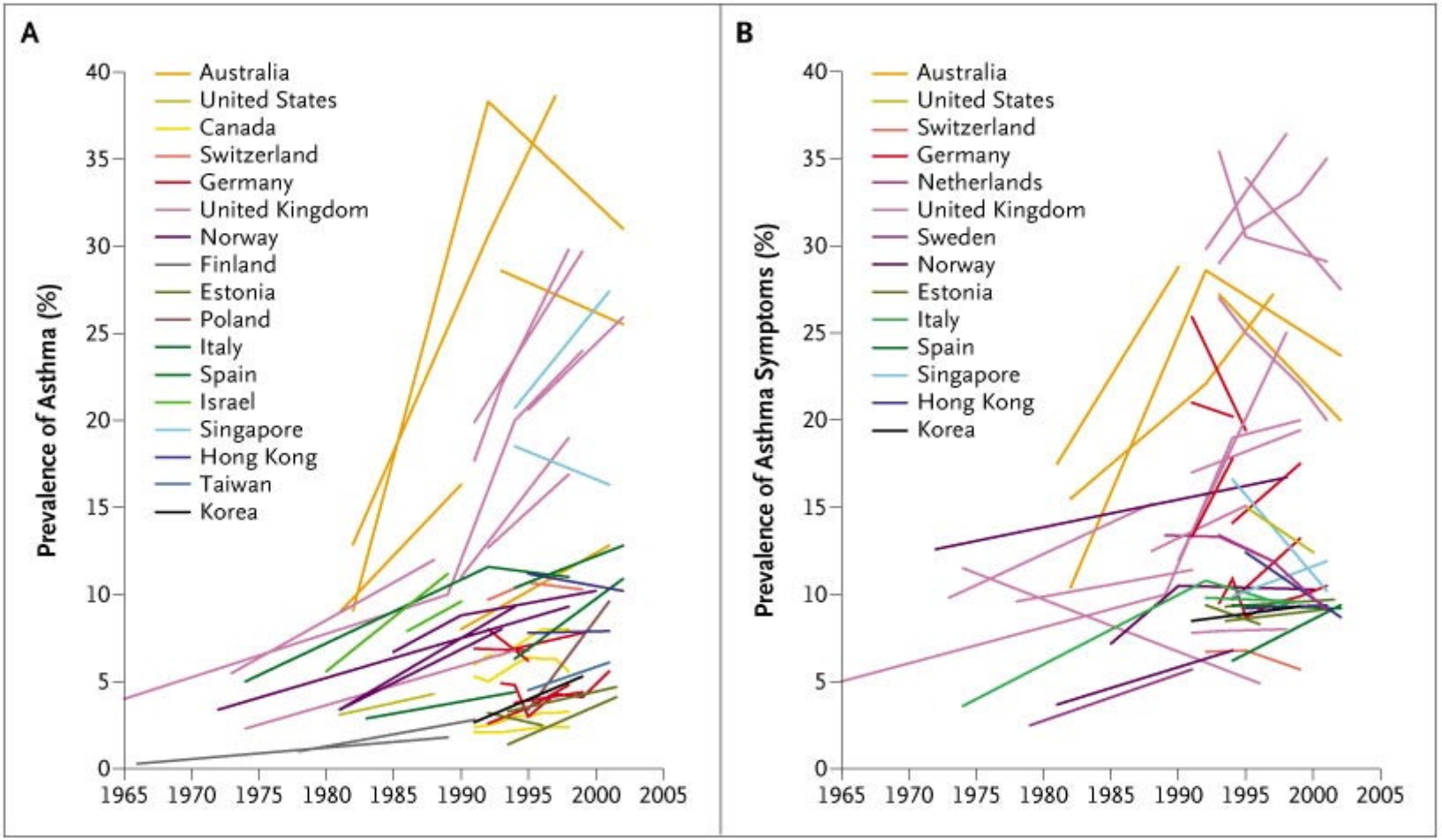
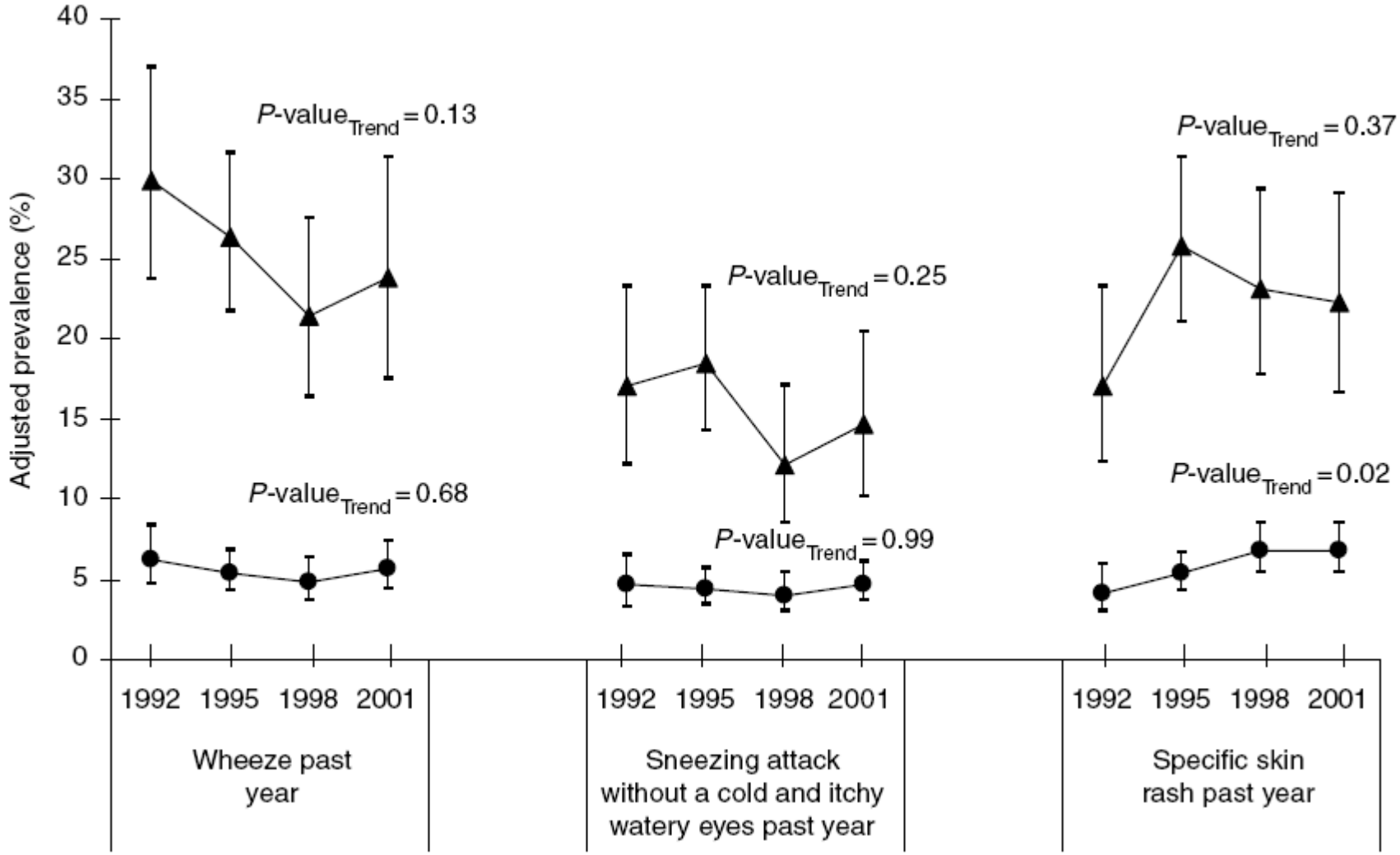
Changes in the Prevalence of Diagnosed Asthma and Asthma Symptoms over Time in Children and Young Adults.



Eder W et al. N Engl J Med 2006;355:2226-2235.

Trends for allergic symptoms in 5-7 yr old in CH



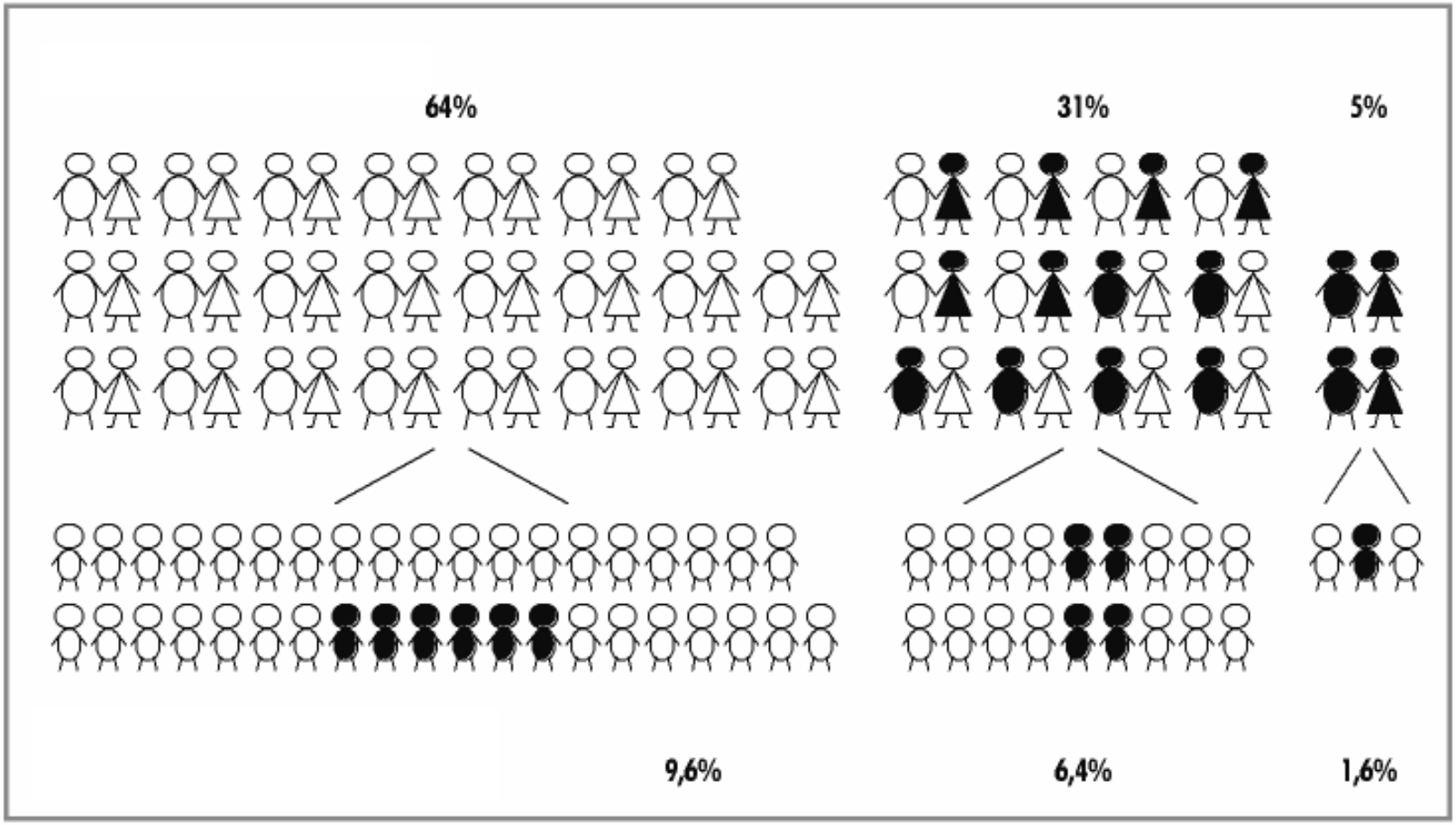
[▲] when polution was perceived, [●] or not as a risk factor

Grize L. Allergy 2006;61:556-62

The two major factors to develop an allergic disease:

- Genetics
- The environment

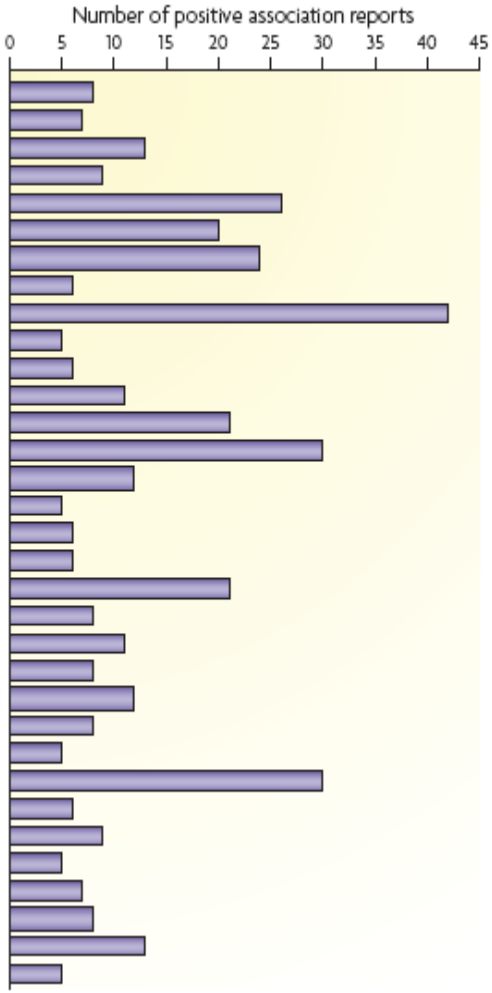
Prevalence of atopy in the first 2 years of life and cumulative prevalence in parents.



Source: MAS 90

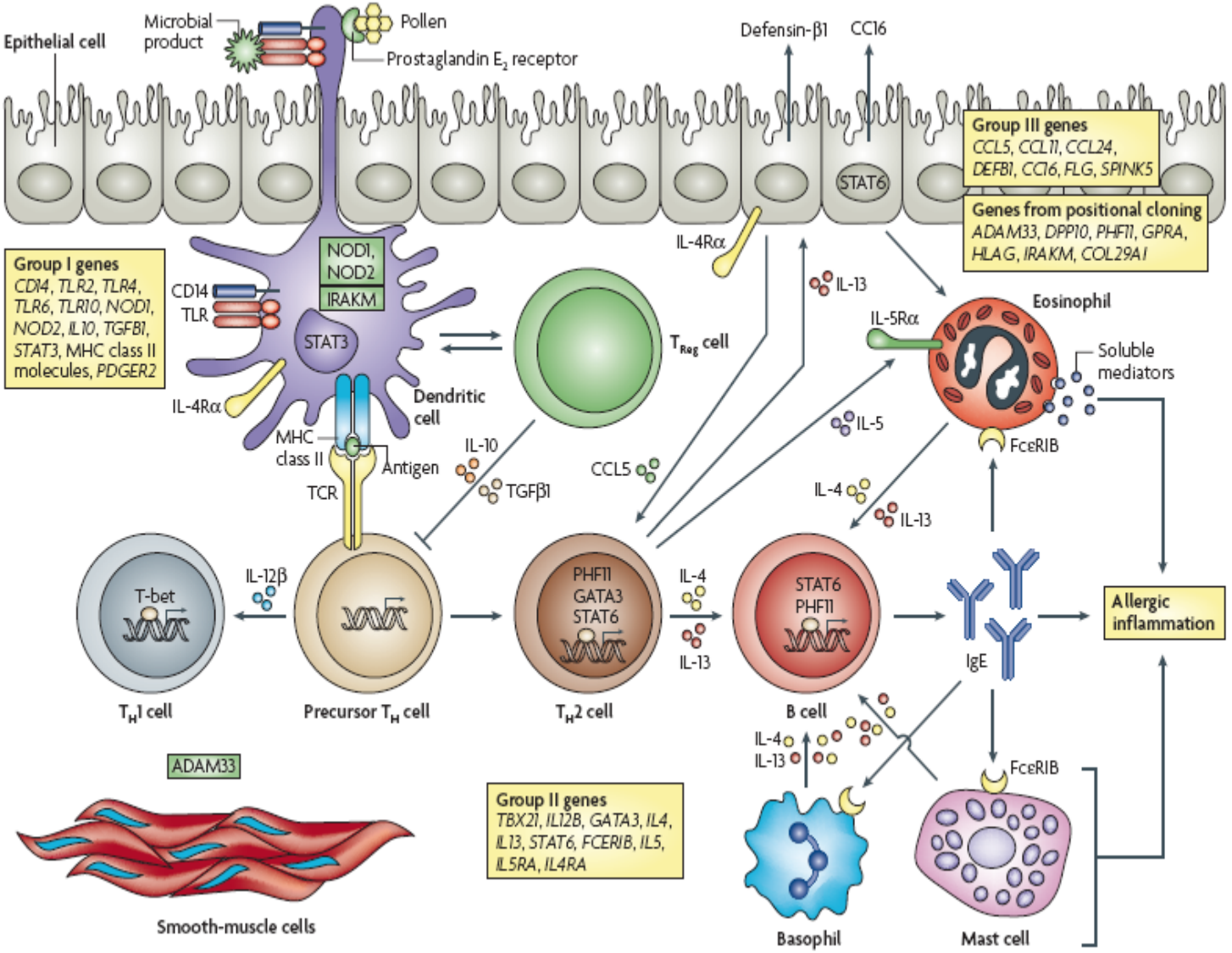
Susceptibility genes for asthma and asthma-related traits

Gene	Chromosome	Function and pathway	Common variants
GSTM1	1p13.3	Environmental and oxidative stress — detoxification	+/null
FLG	1q21.3	Epithelial barrier integrity	Arg510X, 2282del4
IL10	1q31-q32	Immunoregulation	–1082A/G, –571C/A
CTLA4	2q33	T-cell-response inhibition and immunoregulation	–318C/T, 49A/G
IL13	5q31	T_H2 effector functions	–1112C/T, Arg130Gln
IL4	5q31.1	T_H2 differentiation and IgE induction	–589C/T, +33C/T
CD14	5q31.1	Innate immunity — microbial recognition	–1721G/A, –260C/T
SPINK5	5q32	Epithelial serine protease inhibitor	Glu420Lys
ADRB2	5q31-q32	Bronchial smooth-muscle relaxation	Arg16Gly, Gln27Glu
HAVCR1	5q33.2	T-cell-response regulation — HAV receptor	5383_5397del
LTC4S	5q35	Cysteinyl leukotriene biosynthesis — inflammation	–444A/C
LTA	6p21.3	Inflammation	*Nco*I (intron 1)
TNF	6p21.3	Inflammation	–308G/A, –857C/T
HLA-DRB1	6p21	Antigen presentation	Multi-SNP alleles
HLA-DQB1	6p21	Antigen presentation	Multi-SNP alleles
HLA-DPB1	6p21	Antigen presentation	Multi-SNP alleles
GPRA	7p14.3	Regulation of cell growth and neural mechanisms	Haplotypes
NAT2	8p22	Detoxification of drugs and carcinogens	Slow acetylation SNPs
FCERIB	11q13	High-affinity Fc receptor for IgE	Ile181Leu, Gly237Glu
CC16	11q12.3-q13.1	Epithelium-derived anti-inflammatory protein	38A/G
GSTP1	11q13	Environmental and oxidative stress — detoxification	Ile105Val
IL18	11q22.2-q22.3	Induction of IFNγ and TNF	–656T/G, –137G/C
STAT6	12q13	IL-4 and IL-13 signalling	2964G/A, (GT)n exon 1
NOS1	12q24.2-q24.31	Nitric oxide synthesis — cell–cell communication	3391C/T, 5266C/T
CMA1	14q11.2	Mast-cell chymotryptic serine protease	*Bst*X1, –1903G/A
IL4R	16p12.1-p12.2	α-chain of the IL-4 and IL-13 receptors	Ile50Val, Glu551Arg
CCL11	17q21.1-q21.2	Epithelium-derived eosinophil chemoattractant	Ala23Thr, –1328G/A
CCL5	17q11.2-q12	Monocyte, T-cell and eosinophil chemoattractant	–403A/G, –28C/G
ACE	17q23.3	Inactivation of inflammatory mediators	In/del
TBXA2R	19p13.3	Smooth-muscle contraction, inflammation	924T/C, 795T/C
TGFB1	19q13.1	Immunoregulation, cell proliferation	–509C/T
ADAM33	20p13	Cell–cell and cell–matrix interactions	Multiple SNPs
GSTT1	22q11.23	Environmental and oxidative stress — detoxification	A/null



Vercelli D. Nat Rev Immunol. 2008 Mar;8(3):169-82.

Susceptibility genes for asthma and asthma-related traits



Vercelli D. Nat Rev Immunol. 2008 Mar;8(3):169-82.

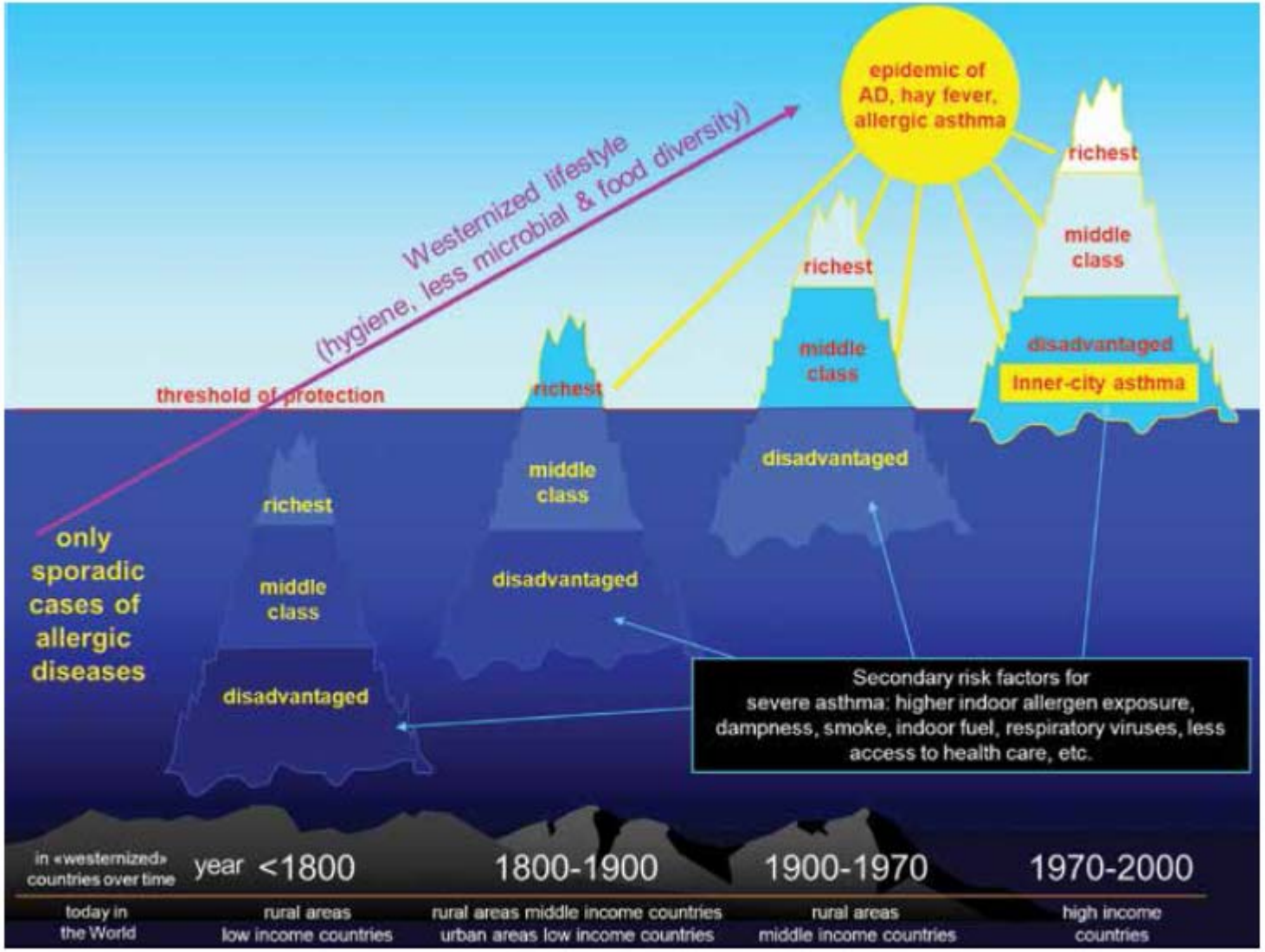


Figure 1 The spread of hay fever and allergic asthma according to socio-economic status and westernization level. (*Reproduced with permission from Annals of Allergy, Asthma & Immunology, Vol. 89(S1). Matricardi PM, Bouygue GR, Tripodi S. Inner-city asthma and the hygiene hypothesis, 69–74. Copyright Elsevier 2002.*)

More allergies, any definite cause?

- Our environment?
- Genetics?
- Perception?
- Erroneous preventive measures?
- A media powered marketing?
- A little of everything???

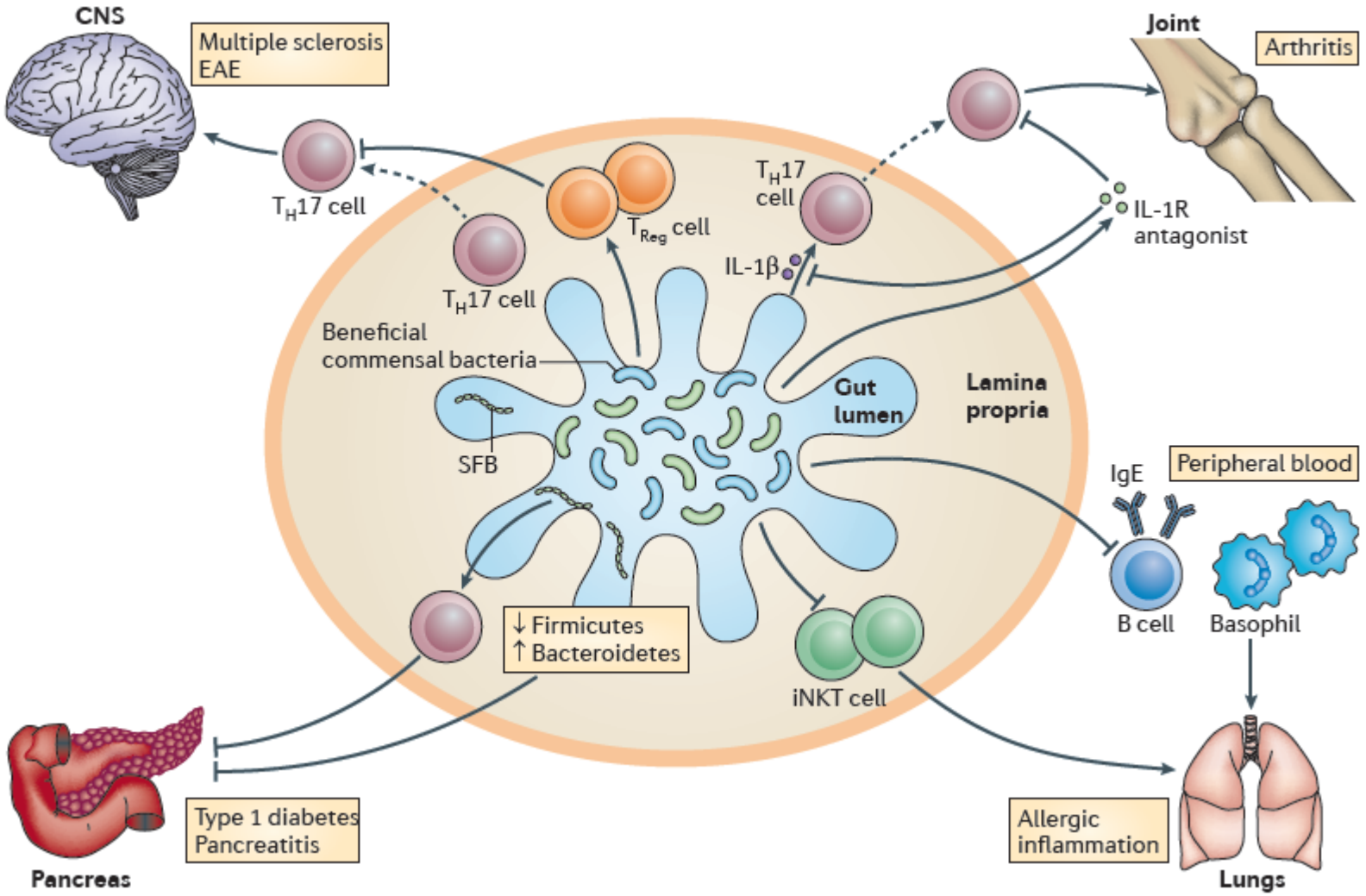
The environment

"You're allergic to the environment. We've got to get you off the planet."

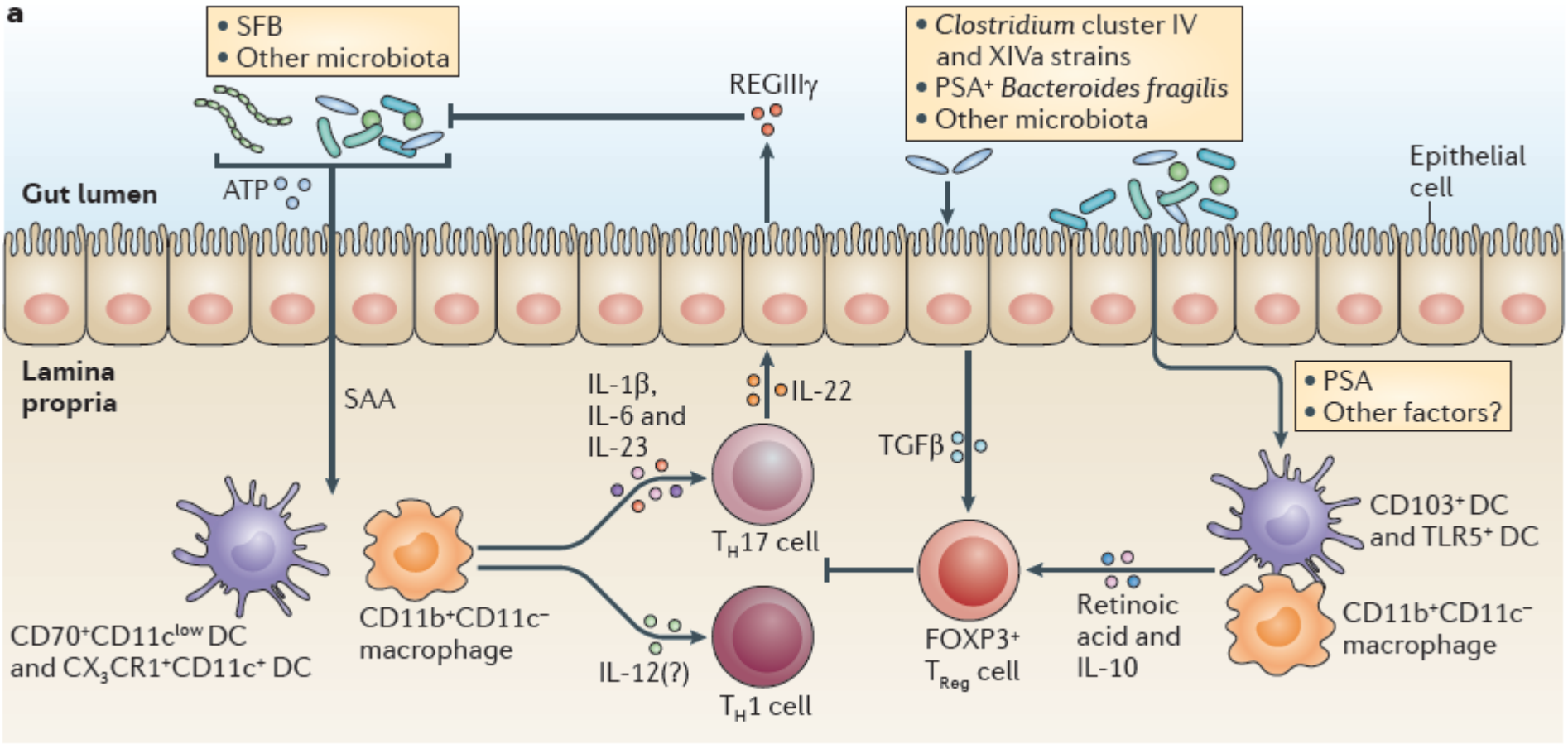
The intestinal microbiota,

A life besides or in interaction with the immune system?

Influences of the microbiota on diseases



Kamada *et al.* Nature Reviews Immunol 2013;13:321



Kamada *et al.* Nature Reviews Immunol 2013;13:321

Modulation of allergy and the role of the microbiota

Farming and allergies

	Stables and farm milk in the 1st year of life (n=218)	Stables, but no farm milk in the 1st year of life (n=48)	Farm milk, but no stables in the 1st year of life (n=189)	Farm milk, stables, or both after the 1st year of life (n=138)	Neither stables nor farm milk exposure (n=170)
Asthma diagnosis	1% (3) 0·14 (0·04–0·48)	6% (3) 0·51 (0·14–1·86)	6% (11) 0·48 (0·21–1·1)	11% (15) 0·88 (0·42–1·86)	12% (20) Reference
At least one wheeze attack in past 12 months	3% (6) 0·17 (0·07–0·45)	6% (3) 0·43 (0·12–1·52)	6% (12) 0·43 (0·20–0·92)	9% (12) 0·60 (0·28–1·28)	15% (25) Reference
Hay fever	3% (7) 0·20 (0·08–0·50)	4% (2) 0·25 (0·05–1·13)	4% (8) 0·24 (0·10–0·56)	13% (18) 0·88 (0·44–1.74)	16% (27) Reference
Runny nose and itchy eyes in past 12 months	5% (11) 0·27 (0·13–0·57)	8% (4) 0·44 (0·14–1·37)	7% (14) 0·42 (0·21–0·86)	12% (16) 0·65 (0·33–1·30)	20% (34) Reference
Atopic sensitisation†	12% (27) 0·32 (0.17–0·62)	21% (10) 0·56 (0·25–1·27)	15% (29) 0·43 (0·24–0·77)	29% (40) 0·99 (0·58–1·69)	33% (56) Reference

*Adjusted for age, sex, study area, parental education, family history of asthma and hay fever, number of older siblings and farming status. †Any reaction to inhalent allergens (house dust and storage mites, cat dander, grass and birch pollen, cow epithelium) of ⩾3·5 kU/L.

Table 2: **Frequency and risk (adjusted* odds ratio, 95% CI) of asthma, hay fever, and atopic sensitisation in relation to exposure to stables and farm milk in the 1st year of life**

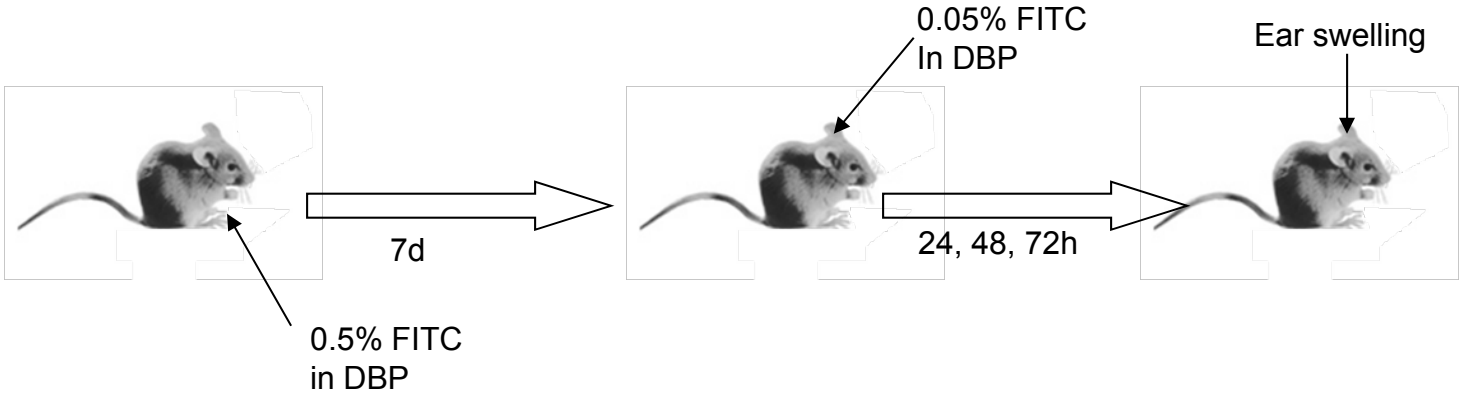
- **Best prevention, exposed to the barn dust and drinking non-pasteurized farm milk**

Riedler *et al.* Lancet 2001;358:1129

For allergy modulation

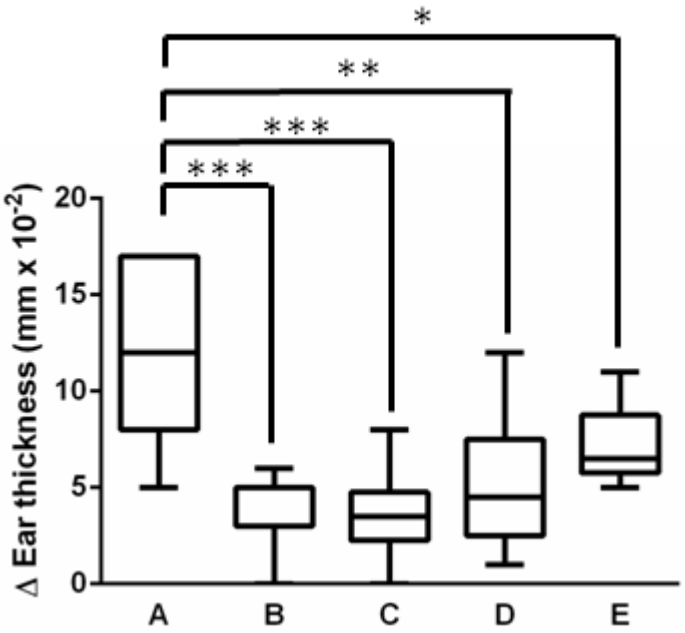
Mice in the protective « farm environment »

Skin Alergy Model by contact hypersensitivity (Th 2 type)

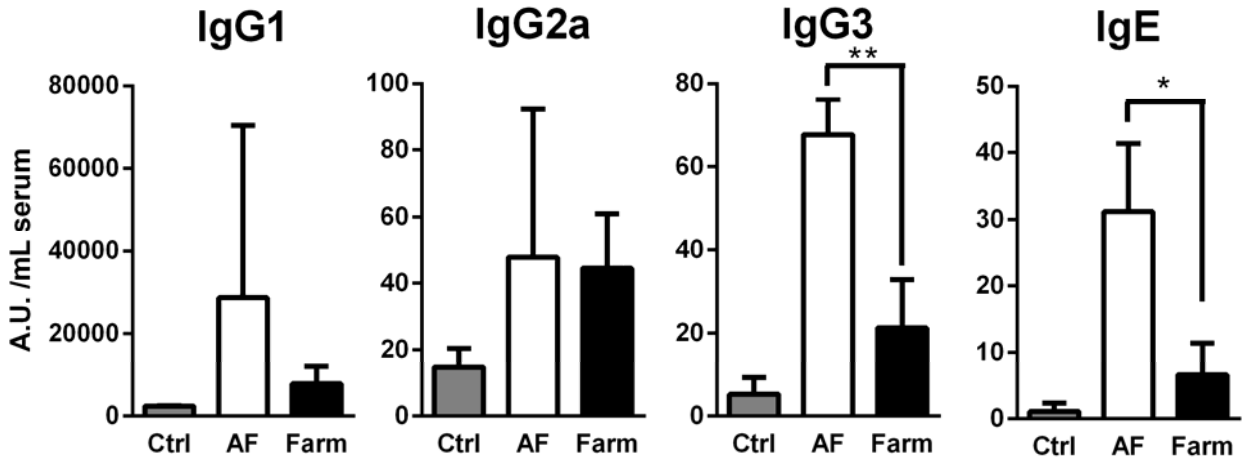


Frossard *et al.* Clin Exp Allergy *in press*

Skin allergy: contact hypersensitivity to FITC

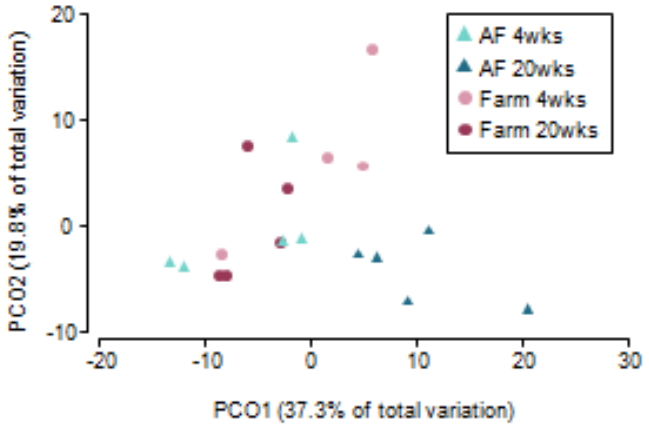


Group	Born at	Transferred	Sensitized at
A	AF	No	8 wks of life
B	Farm	No	8 wks of life
C	AF	To Farm at 48h of life	8 wks of life
D	AF	To Farm at 4 wks of life	8 wks of life
E	AF	To Farm at 8 wks of life	12 wks of life



Frossard *et al.* Clin Exp Allergy *in press*

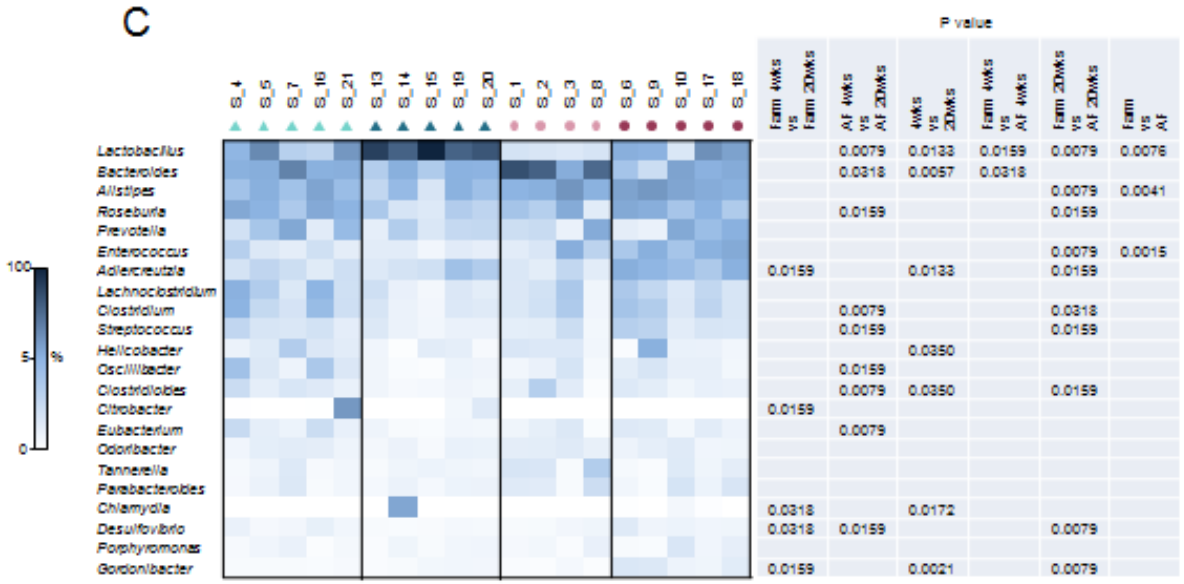
A



B

	Farm 4wks	Farm 20wks	AF 4wks
Farm 20wks	0.0575		
AF 4wks	0.067	0.0926	
AF 20wks	**0.0073**	**0.0075**	**0.0076**

C



P value

Farm 4wks vs Farm 20wks	AF 4wks vs AF 20wks	4wks vs 20wks	Farm 4wks vs AF 4wks	Farm 20wks vs AF 20wks	Farm vs AF
	0.0079	0.0133	0.0159	0.0079	0.0076
	0.0318	0.0057	0.0318		
				0.0079	0.0041
	0.0159			0.0159	
				0.0079	0.0015
0.0159		0.0133		0.0159	
	0.0079			0.0318	
	0.0159			0.0159	
		0.0350			
	0.0159				
	0.0079	0.0350		0.0159	
0.0159					
	0.0079				
0.0318		0.0172			
0.0318	0.0159			0.0079	
0.0159		0.0021		0.0079	

Frossard *et al.* Clin Exp Allergy *in press*

Microbiota and allergic diseases in humans

Allergy development and the intestinal microflora during the first year of life

Bengt Björkstén, MD, PhD,[a,b] Epp Sepp, MD, PhD,[c] Kaja Julge, MD, PhD,[d] Tiia Voor, MD,[d] and Marika Mikelsaar, MD, PhD[c] *Stockholm and Linköping, Sweden, and Tartu, Estonia* (J Allergy Clin Immunol 2001;108:516-20.)

TABLE I. Prevalence of certain species of fecal microorganisms in allergic (n = 18) and healthy (n = 26) children during the first year of life

	Prevalence (%)									
	1 week		1 mo		3 mo		6 mo		12 mo	
Microorganisms	Healthy	Allergic	Healthy	Allergic	Healthy	Allergic	Healthy	Allergic	Healthy	Allergic
S aureus	62	56	65	56	50¶	50	23*¶	61*	27	39
Enterococci	96*	67*	96†	72†	96	89	96	100	96	89
Lactobacilli	8*|	39*	46|	56	34	56	38	39	38	44
Bifidobacteria	50†	17†	69	39	62‡	28‡	42	28	69§	22§
Bacteroides	46	61	62	72	65	83	81	94	96	89
Clostridia	27	50	27	28	46	28	65	50	54	67

Prevalence of microorganisms in allergic infants vs healthy infants at a given age: *P = .02; †P = .03; ‡P = .04; §P = .05.
Prevalence of microorganisms in healthy children at different ages: \|P = .02; ¶P = .05.

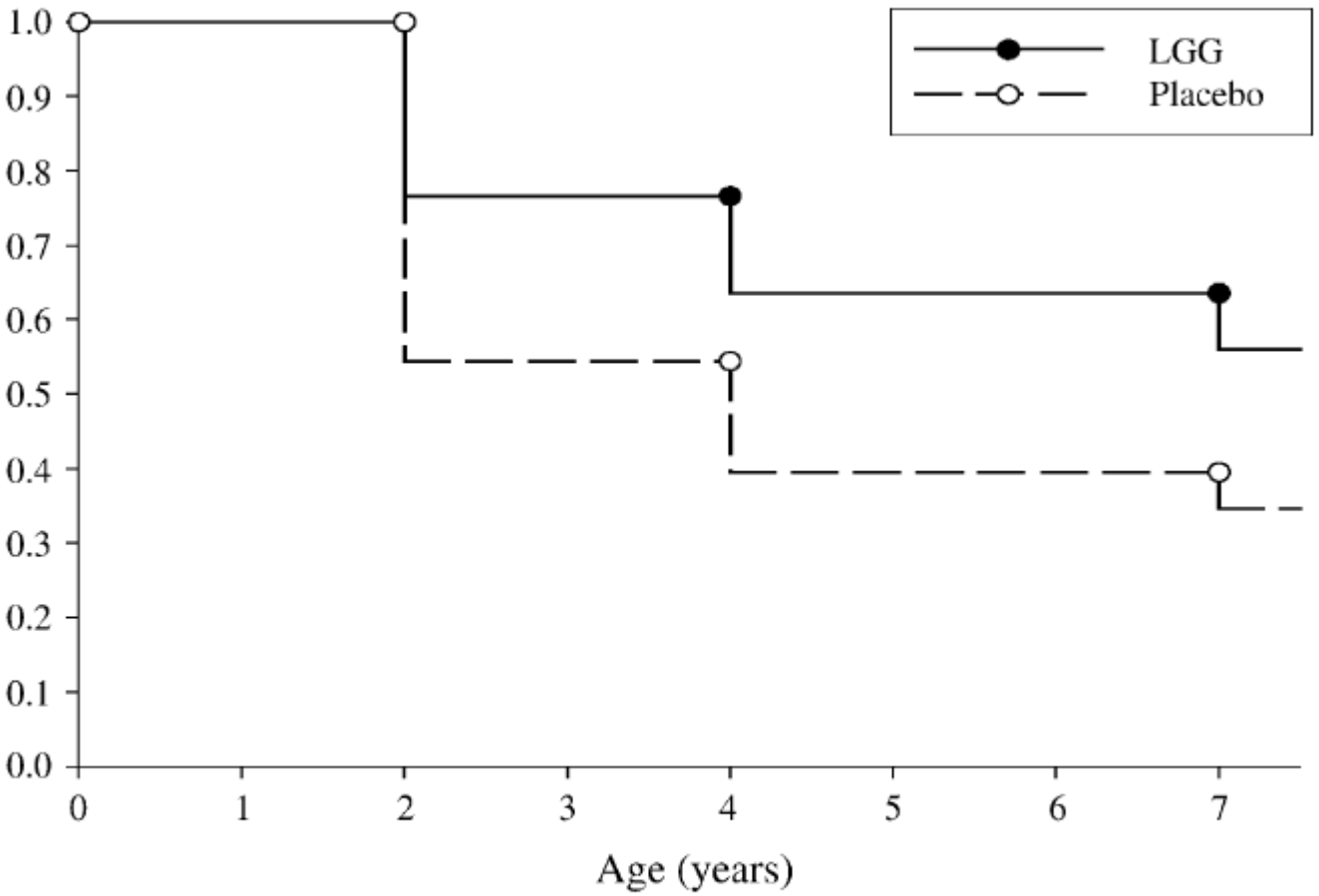
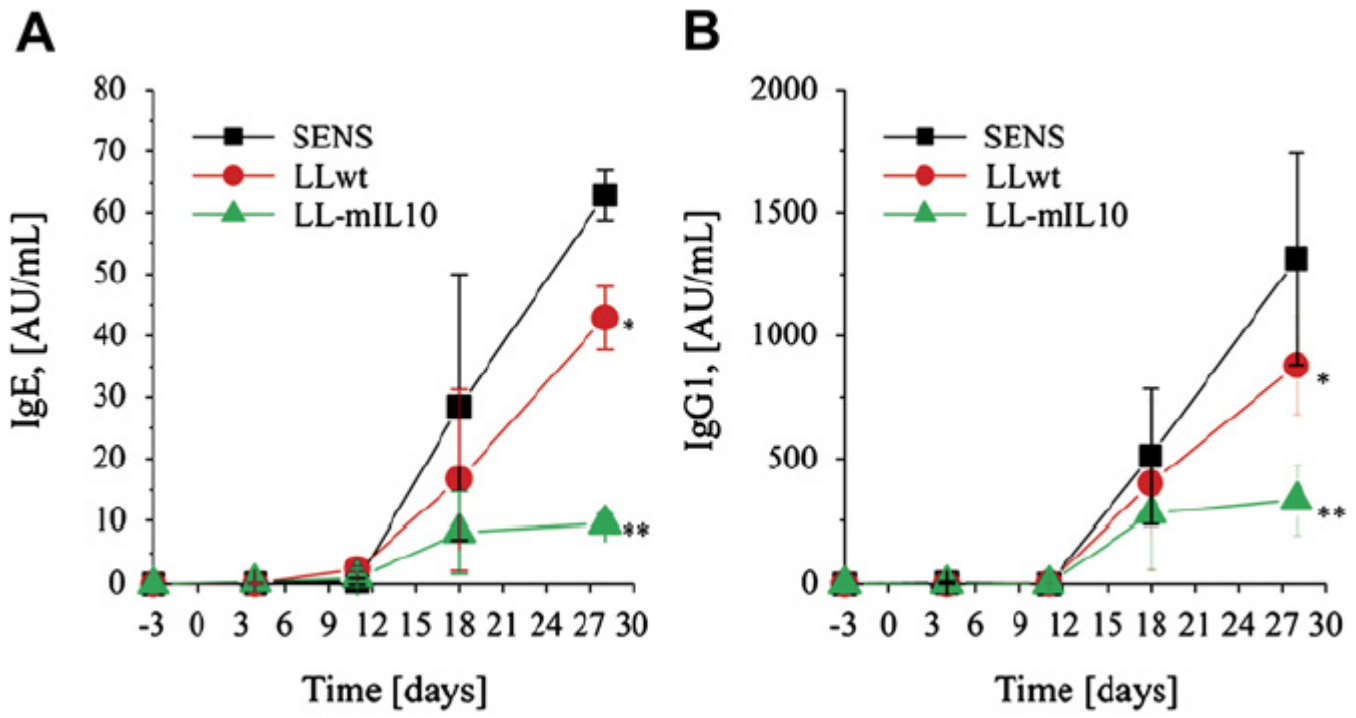


FIG 1. Kaplan-Meier curves for children without eczema at the ages of 2, 4, and 7 years in *Lactobacillus* GG (*LGG;* n = 64) and placebo (n = 68) groups; *P* = .008 by log-rank test.

Kalliomäki et al Lancet 2001;357; 1076 & 2003;361:1869 & JACI 2007;119:1019

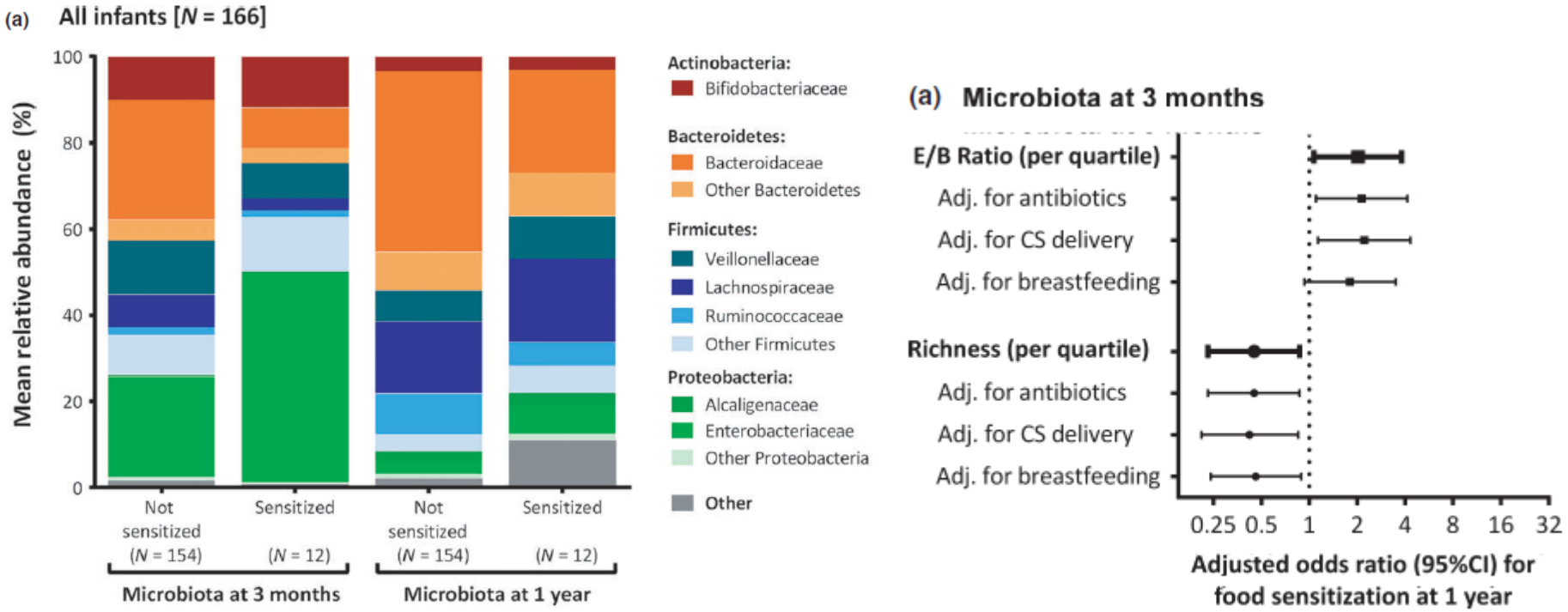
Food allergies and microbiota

Mice fed with Lactococcus Lactis transfected with a rmIL-10 gene are protected from food allergies



Frossard *et al.* J Allergy Clin Immunol 2007;119:952

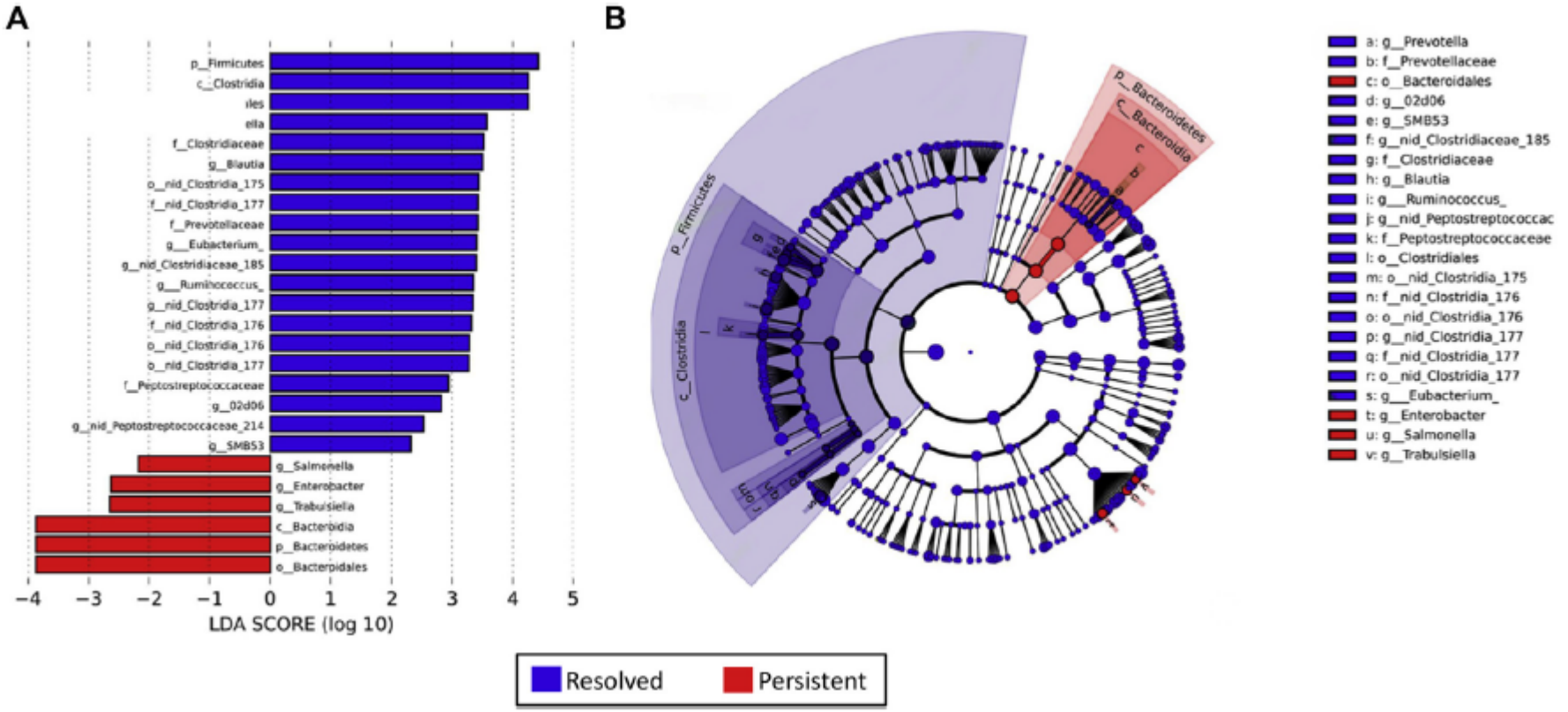
Lower richness of microbiota diversity and modified ratio of Enterobacteriacea/Bacteroidaceae ratio in food sensitized children



Azad MB *et al* Clin Exp Allergy 2015; 45: 632.

Early-life gut microbiome composition and milk allergy resolution (J Allergy Clin Immunol 2016;138:1122-30.)

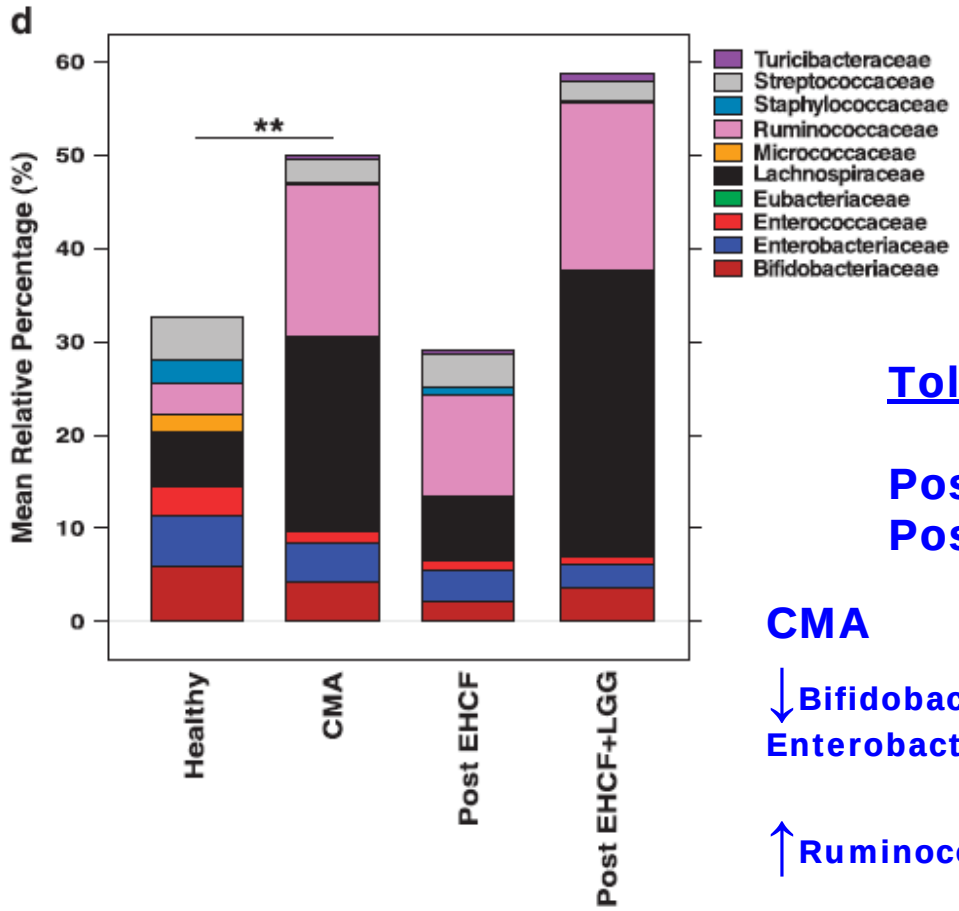
Supinda Bunyavanich, MD, MPH,[a,b] Nan Shen, MS,[a] Alexander Grishin, PhD,[b] Robert Wood, MD,[c] Wesley Burks, MD,[d] Peter Dawson, PhD,[e] Stacie M. Jones, MD,[f] Donald Y. M. Leung, MD, PhD,[g] Hugh Sampson, MD,[b] Scott Sicherer, MD,[b] and Jose C. Clemente, PhD[a,h] *New York, NY, Baltimore and Rockville, Md, Chapel Hill, NC, Little Rock, Ark, and Denver, Colo*



Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants

The ISME Journal (2016) **10**, 742–750

Roberto Berni Canani[1,8], Naseer Sangwan[2,8], Andrew T Stefka[3,8], Rita Nocerino[1], Lorella Paparo[1], Rosita Aitoro[1], Antonio Calignano[4], Aly A Khan[5], Jack A Gilbert[2,6,7] and Cathryn R Nagler[3]



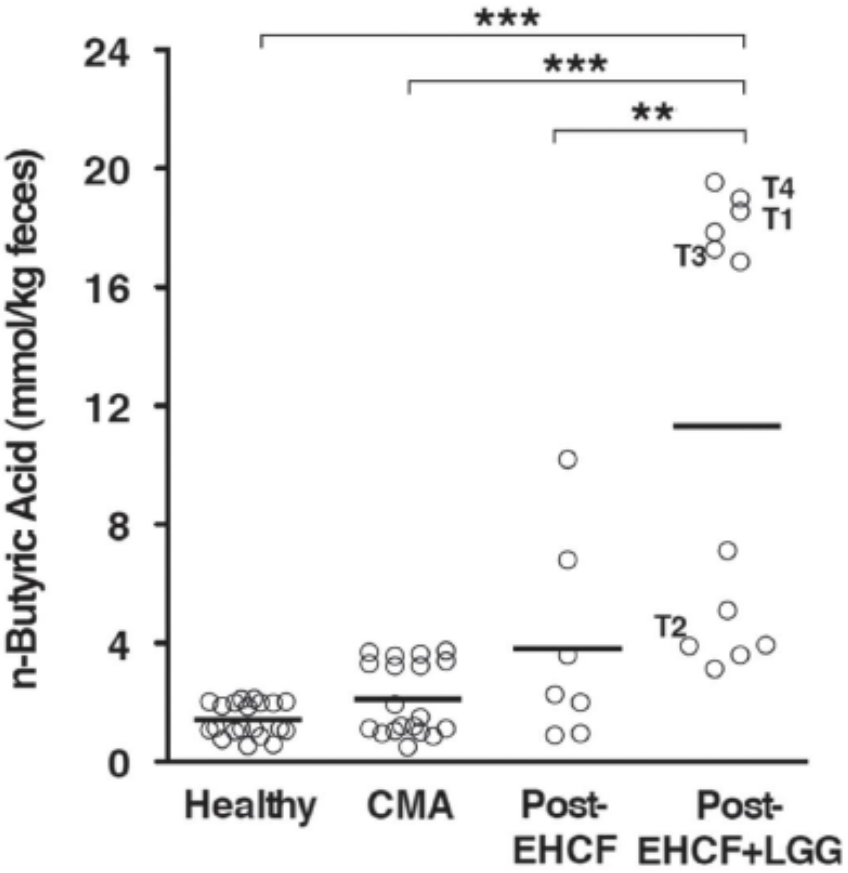
Tolerance after 12 mo treatment

Post EHCF: 0 / 7
Post EHCF+LGG: 5 / 12

CMA

↓**Bifidobacteriaceae, Streptococcaceae, Enterobacteriaceae and Enterococcaceae**

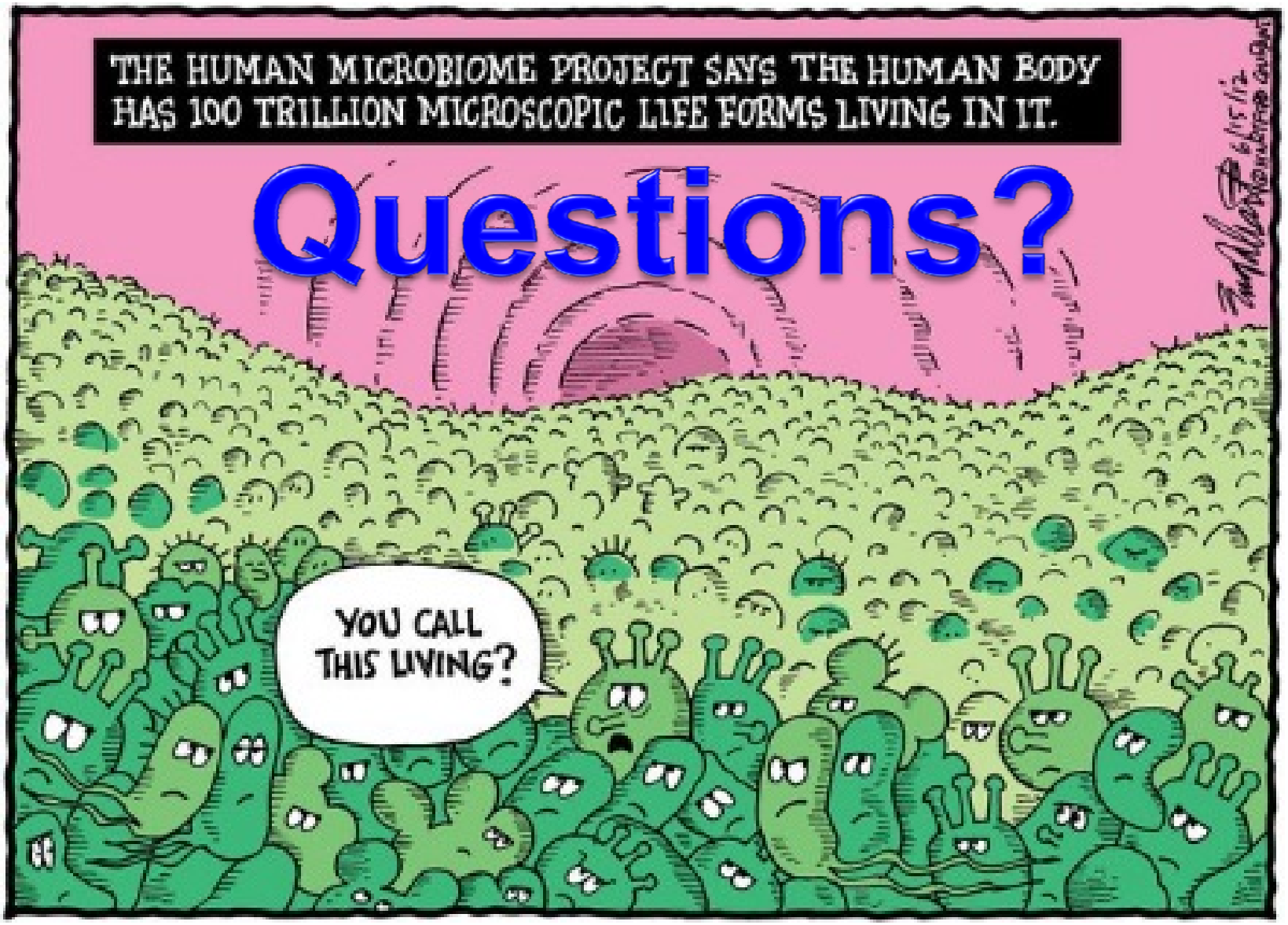
↑**Ruminococcaceae and Lachnospiraceae**



The ISME Journal (2016) **10**, 742–750

Microbiota and allergies – perspectives –

- We need a better comprehension of the role of the environment in allergy
- Can the a specific microbiome predict allergy?
- Can the microbiota be manipulated for primary / secondary prevention of allergy?


THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.
Questions?
YOU CALL THIS LIVING?