

대한 결핵 및 호흡기 학회

# Hygiene hypothesis in Asthma

2019-JULY-13 천식 연구회 Workshop

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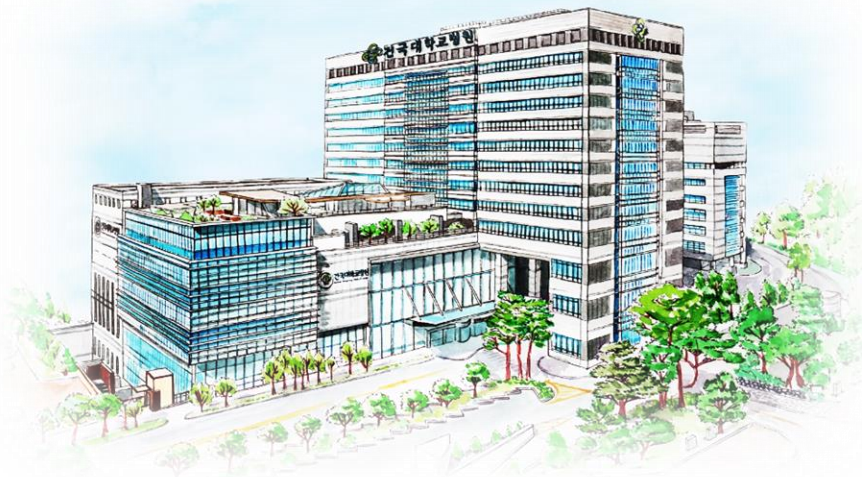
4. Hygiene hypothesis을 뒷받침하는 근거들

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# 1. Hygiene hypothesis

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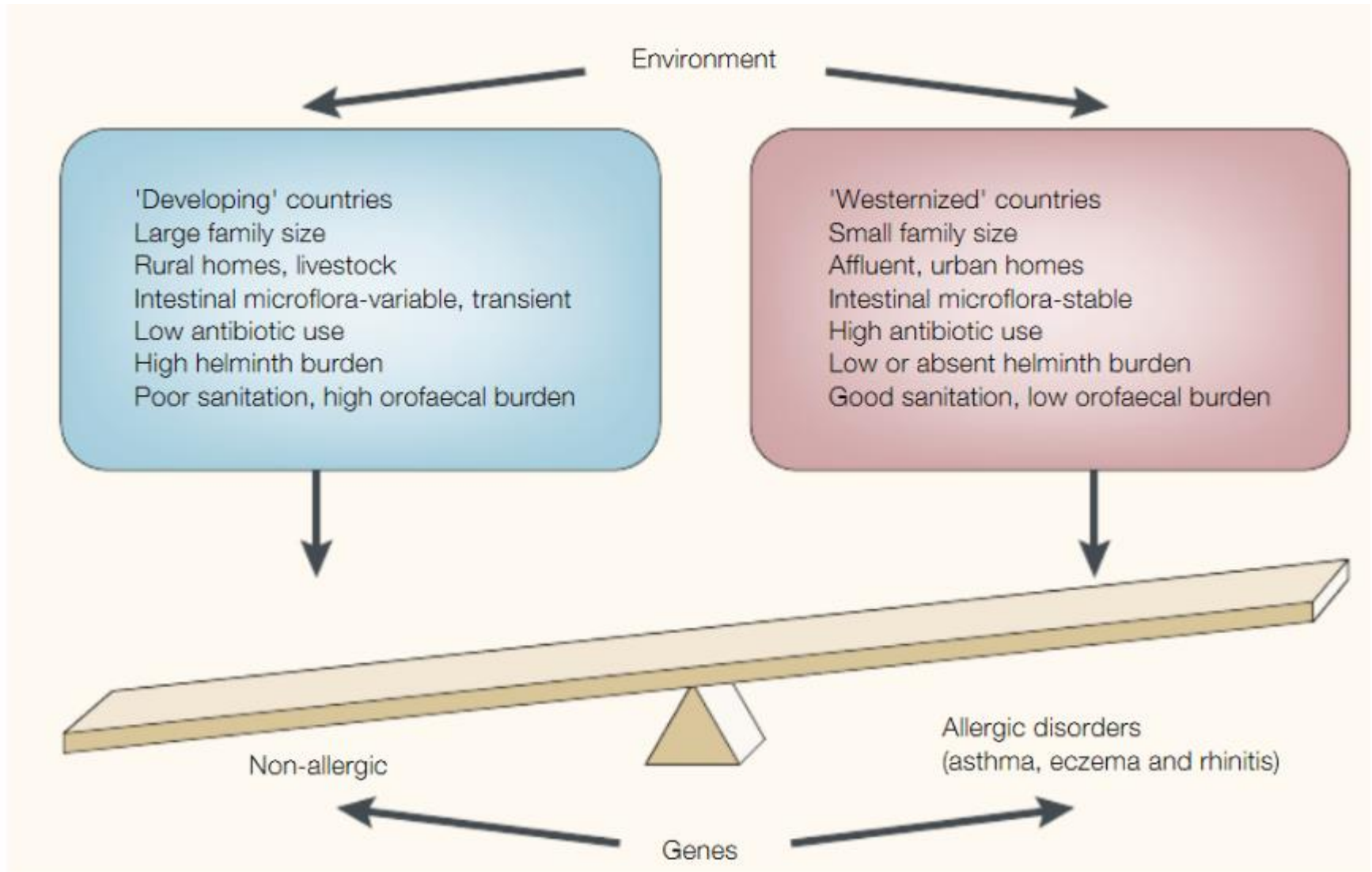


# Hygiene hypothesis (위생 가설)의 이해

“ 우리 어린 시절에는 흙먹고, 지렁이도 먹고 자랐어 ”  
“ 옛날에는 아토피라는 게 없었잖아 ”  
“ 우리는 흙먹고 자라서 아토피가 없었던 것 같아 ”



# Hygiene hypothesis (위생 가설)의 이해





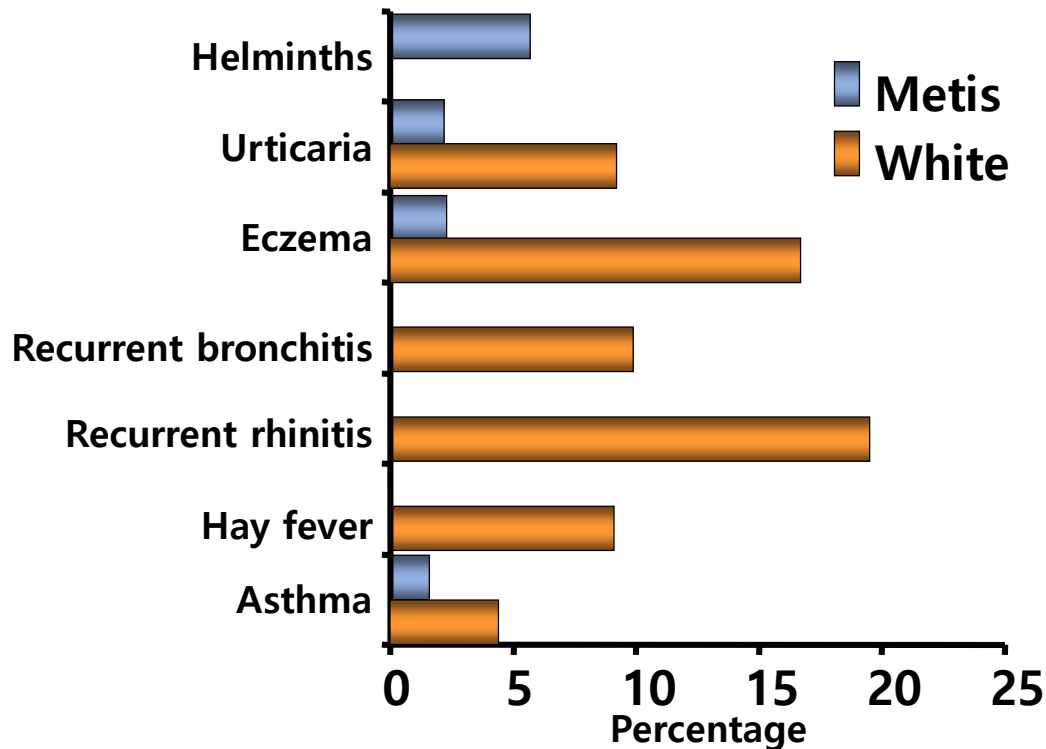
## 2. Hygiene hypothesis 배경



# 1976' Gerrard "The allergy epidemic"



"Metis" : Native American Community  
Neighbouring white community



"It is suggested that atopic disease is the price paid by some members of the white community for their relative freedom from diseases due to viruses, bacteria and helminths"

# 1989' Hay fever, hygiene, and household size

핵가족화, 개인 위생 증가, 생활 환경의 발전이 진행하면서  
알레르기 질환이 증가함

1958년 3월 생, 총 17414 명

→ 11세, 23세에 설문

(지난 1년간 알레르기 질환이 있었나?)

→ 7세 때 출생 1년 동안 eczema 발생 여부



총 16가지의 perinatal, social, environmental factors와의 연관성 분석

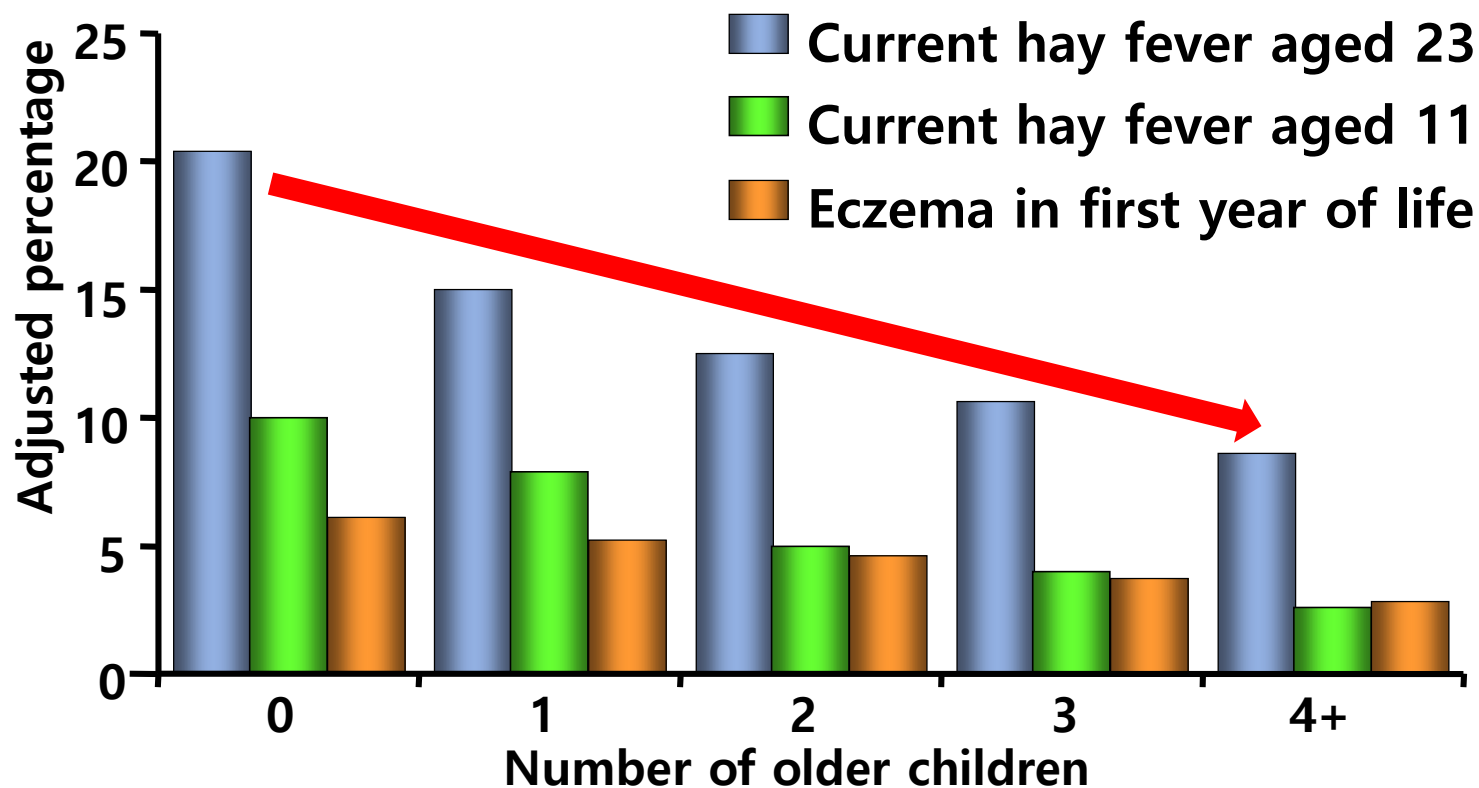
Hay fever in this cohort the associations with numbers of older and younger children in the household persisted.

→ 알레르기 질환 및 증상은 형제의 수(total family size) 와 연관성이 높았는데 형제 수가 많으면 알레르기가 적었음

→ **Unhygienic contact with older siblings** or acquired infection by contact with older children **protection against hay fever (Suggestions)**

# 1989' Hay fever, hygiene, and household size

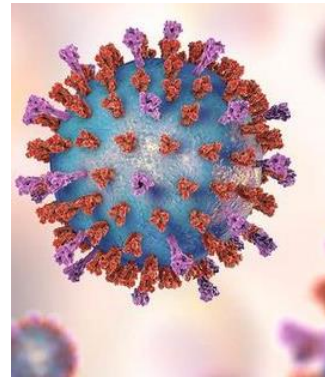
From the 1958 birth cohort,  
decrease in hay fever with increasing family size



# 1993' measles virus infection and atopic dermatitis



5명 아토피 피부염 환자

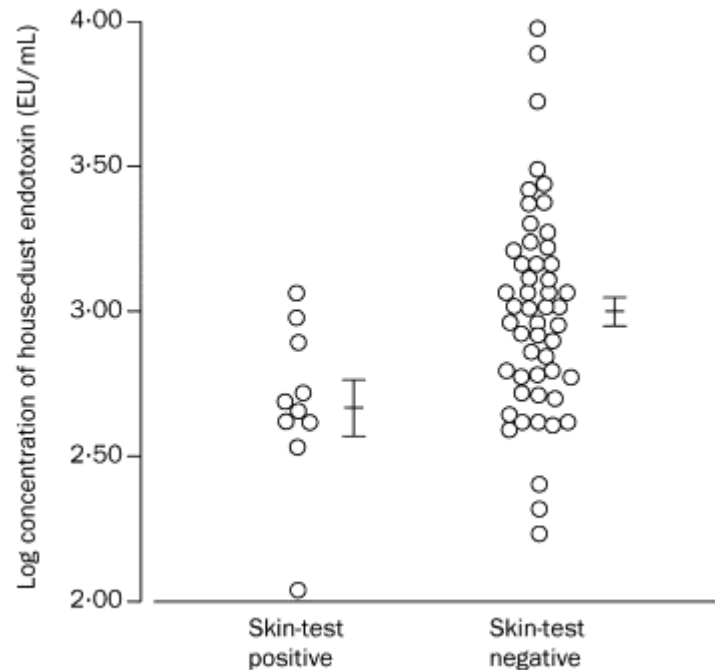
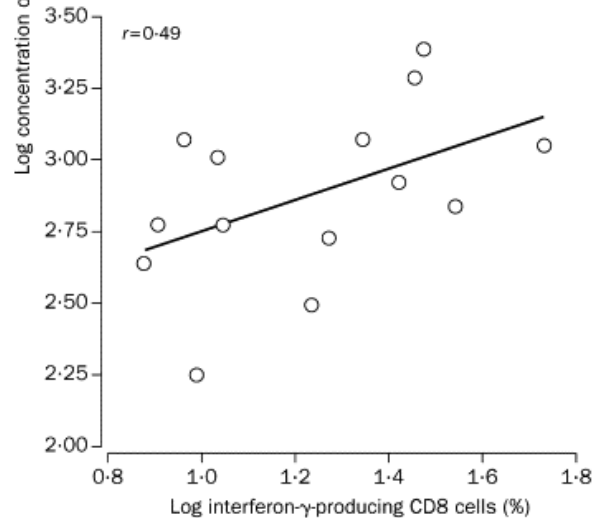
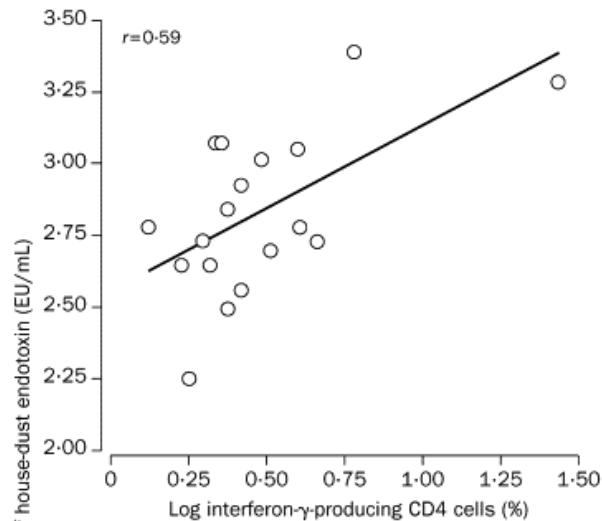


Natural measles infection

- 4주 내에 5명 중 4명이 steroid, 식이제한 등의 intervention 없이 Eczematous lesion이 clear 하게 호전됨
- 1명에서는 RAST score 가 의미 있게 감소함
- PBMCs의 ovalbumin 자극에 반응이 감소함

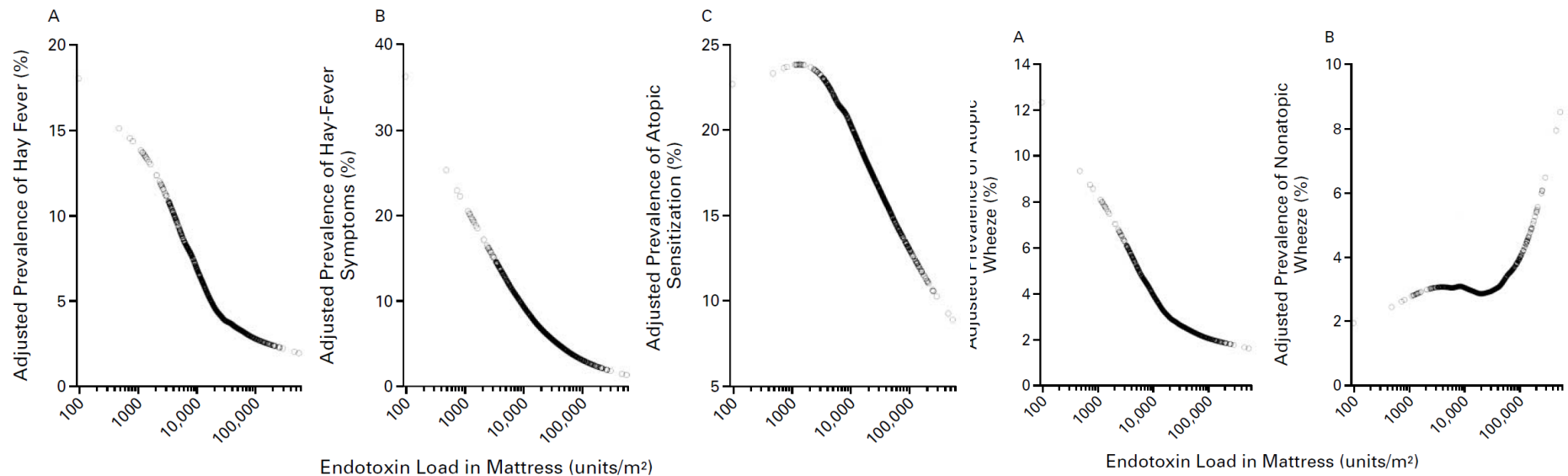
# 2000' Liu AH - Endotoxin exposure and allergy

First direct in-vivo evidence that indoor endotoxin exposure early in life may protect against allergen sensitization by enhancing type 1 immunity



# 2002' Endotoxin exposure and its relation to asthma

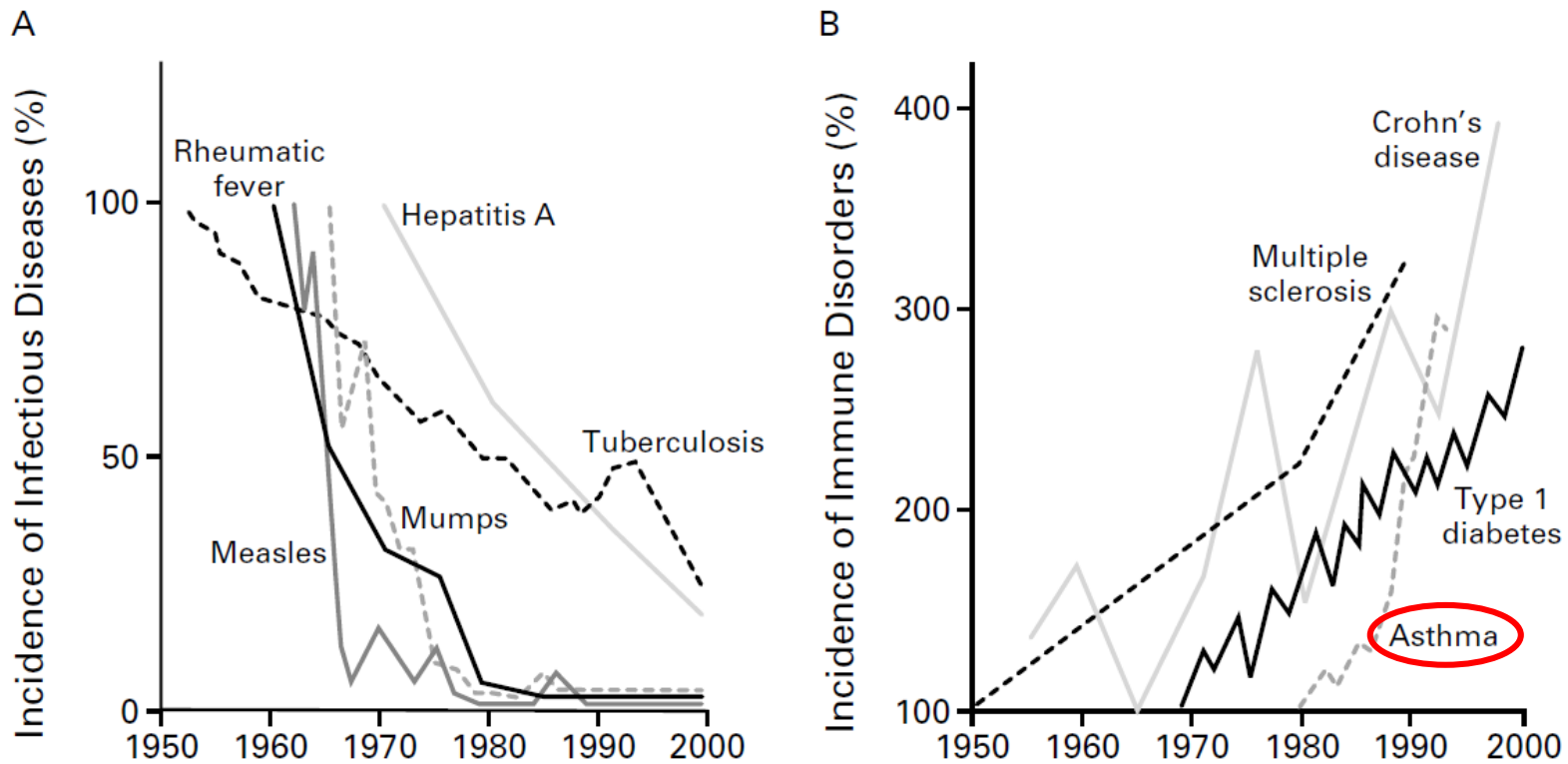
A subject's environmental exposure to endotoxin may have a crucial role in the development of tolerance to ubiquitous allergens found in natural environments



Children 6-13세 812명 (독일, 오스트리아, 스위스)  
Blood sample – sensitization, cytokine evaluation  
Endotoxin levels in bedding

# 2002' The effect of infections on susceptibility to autoimmune and allergic diseases

Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000



**“The **Hygiene Hypothesis** was the first to suggest that exposure to germs and bacteria is not a bad thing as it helps the child’s immune system develop”**

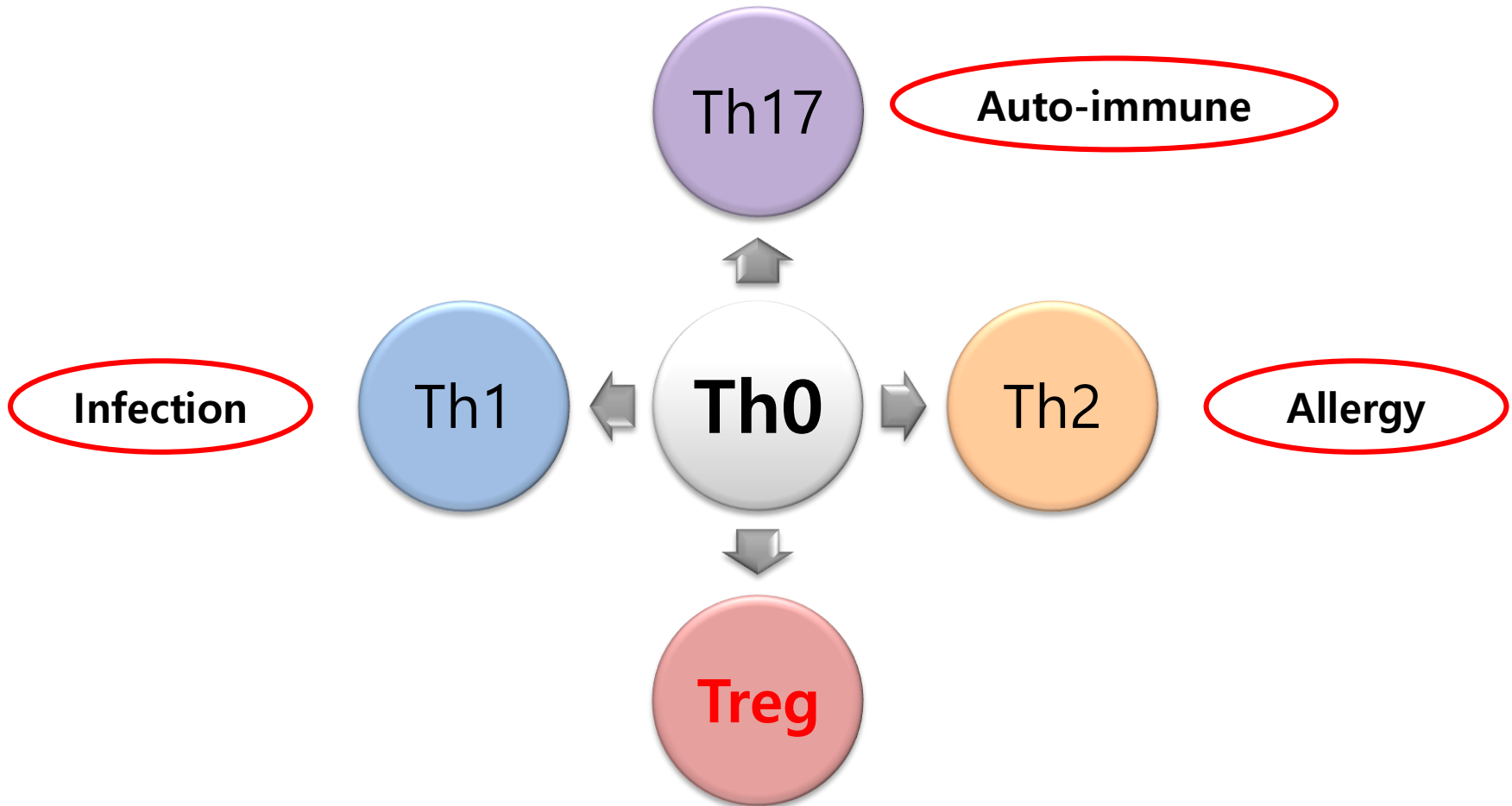


### 3. Underlying mechanisms



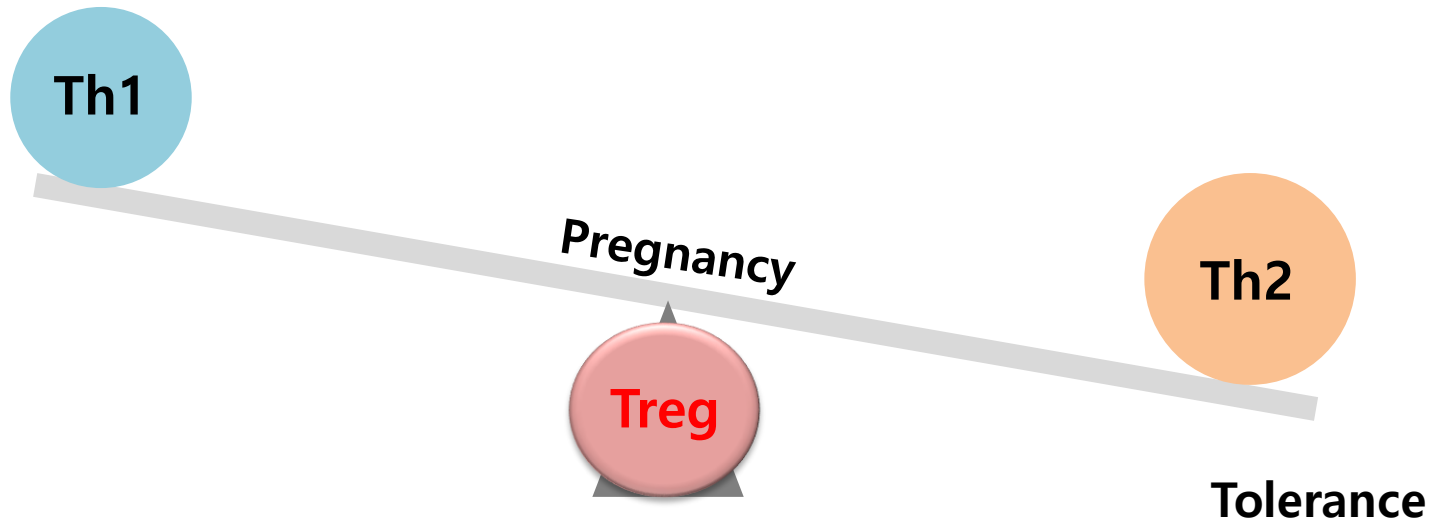
# T helper cell – Th1 and Th2 balance

A balance between Th1 and Th2 cells is important for disease induction and tolerance



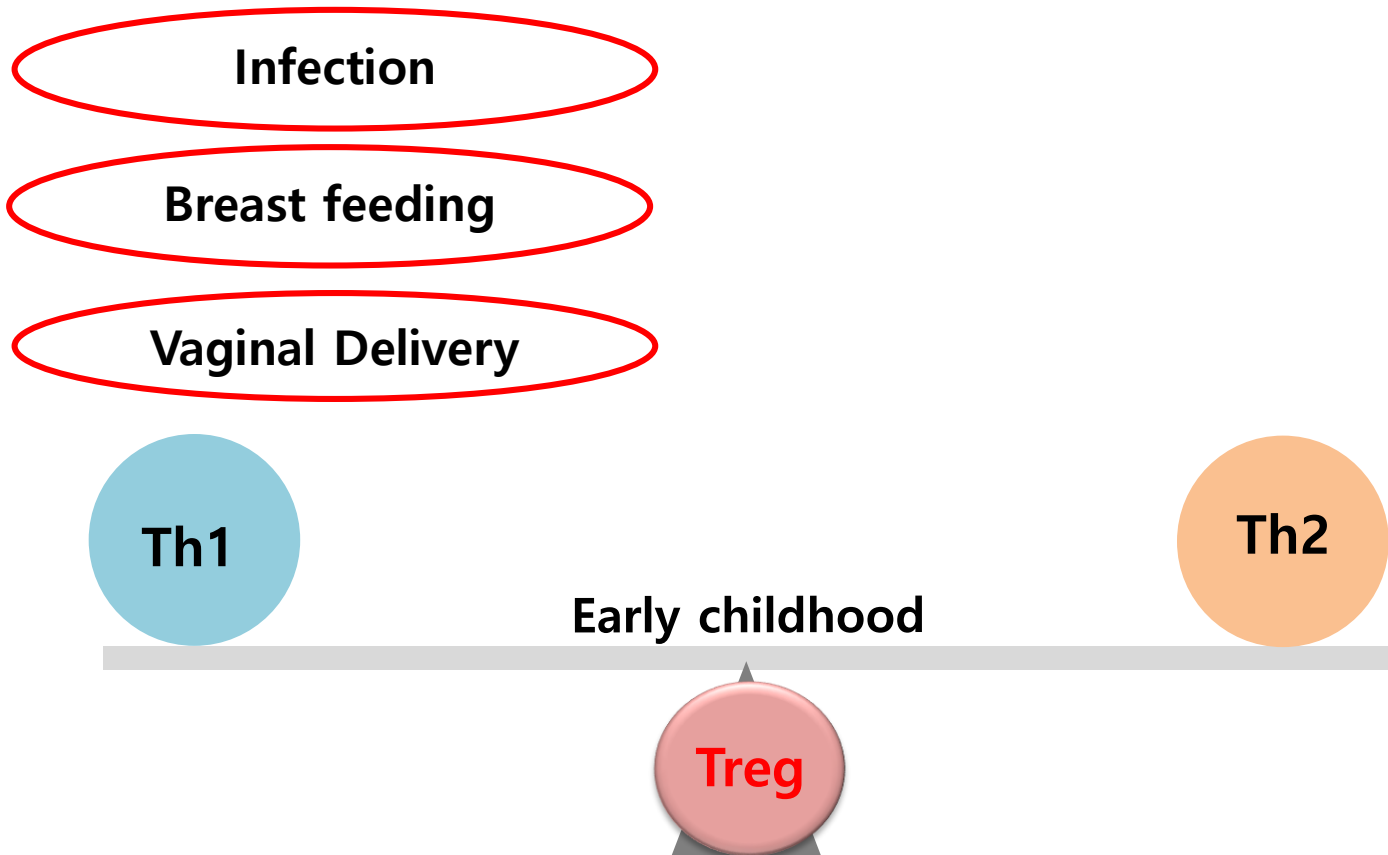
# T helper cell – Th1 and Th2 balance

Throughout human pregnancy,  
'foreign' fetus evade maternal immune responses.  
→ Th2 responses predominant *in utero* and newborn infant.

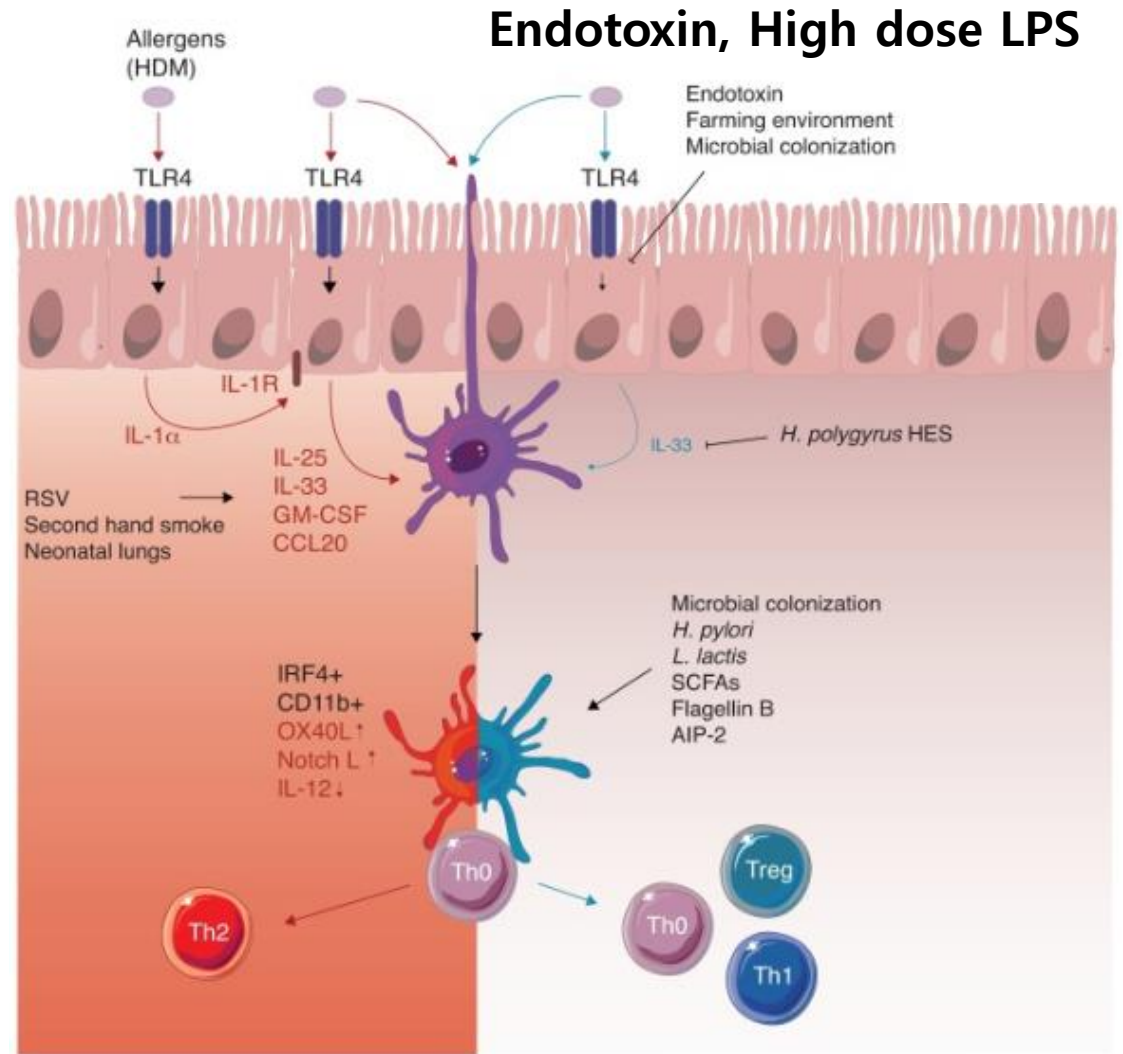
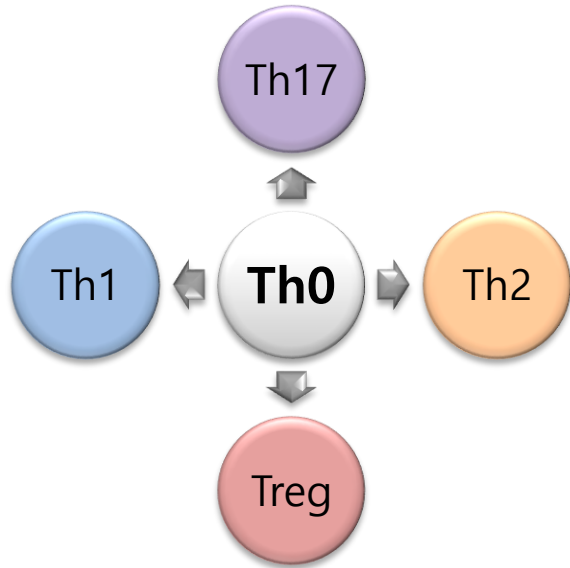


# T helper cell – Th1 and Th2 balance

Exposure to microbial agents that drive the immune system to a Th1/Th17 pattern might counterbalance Th2 responses and asthma development.



# T helper cell – Th1 and Th2 balance



Current Opinion in Immunology



## 4. Evidences of hypothesis



# Hepatitis A infection and Allergic disease

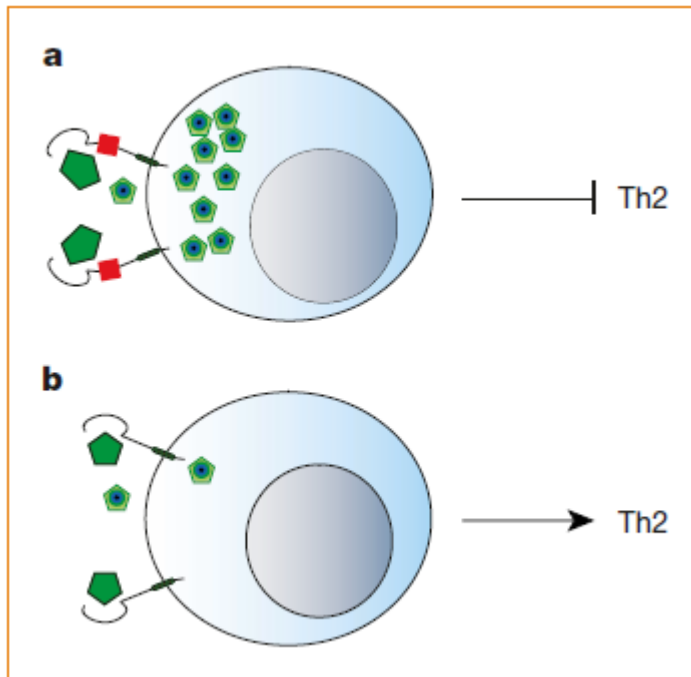
HAV is associated with poor hygiene, large family size  
HAV infection → inversely associated with atopy

human chromosome 5q23-35 → Asthma susceptibility genes

*T cell and Airway Phenotype Regulator (Tapr)*



*T cell membrane proteins (TIMs)*



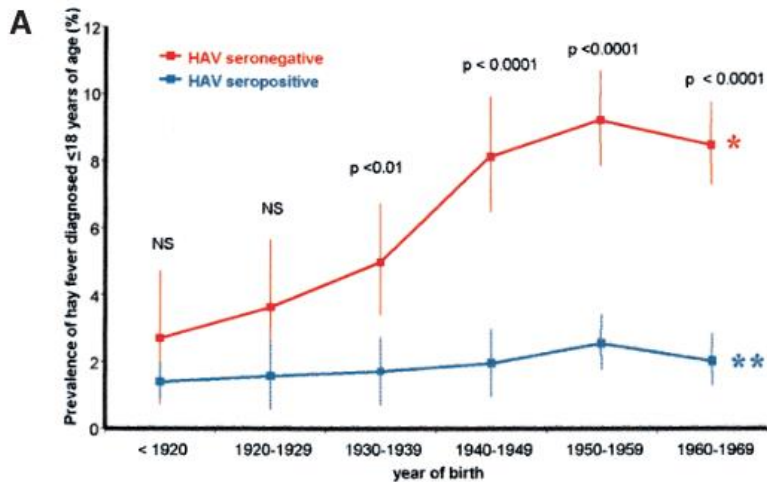
*T cell membrane proteins (TIMs)  
variation → HAV susceptibility*

*Nat Immunol. 2001 Dec;2(12):1109-16.  
Nature. 2003 Oct 9;425(6958):576.*

# Asthma in relation to markers of infection in US

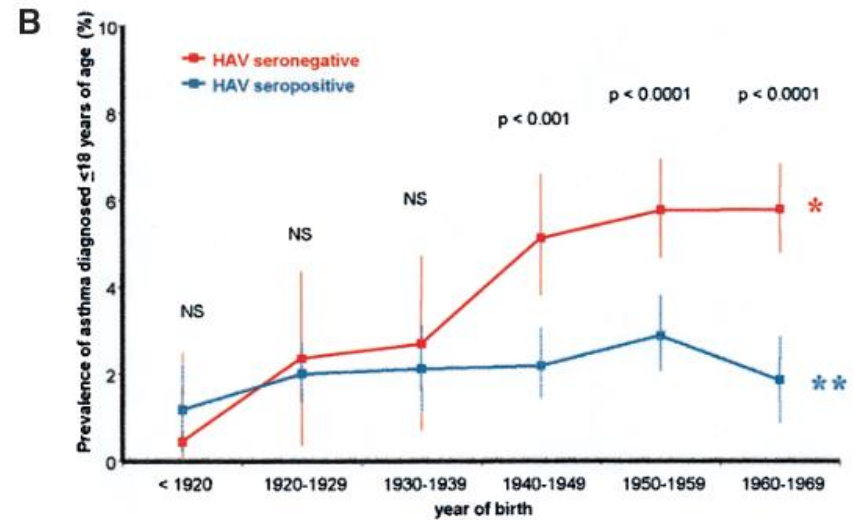
1988-1994 (NHANES III), 33,944 US residents aged 1 to 90 years

*Hay fever, Asthma vs. serology for HAV, T gondii, HSV-1 and 2, HBV, HCV*



HAV-Ab <sup>-</sup>	442	549	663	972	1626	2006
HAV-Ab <sup>+</sup>	1929	1691	1174	1227	1454	1292

\* Test for linear trend  $p < 0.0001$     \*\* Test for linear trend  $p$  NS

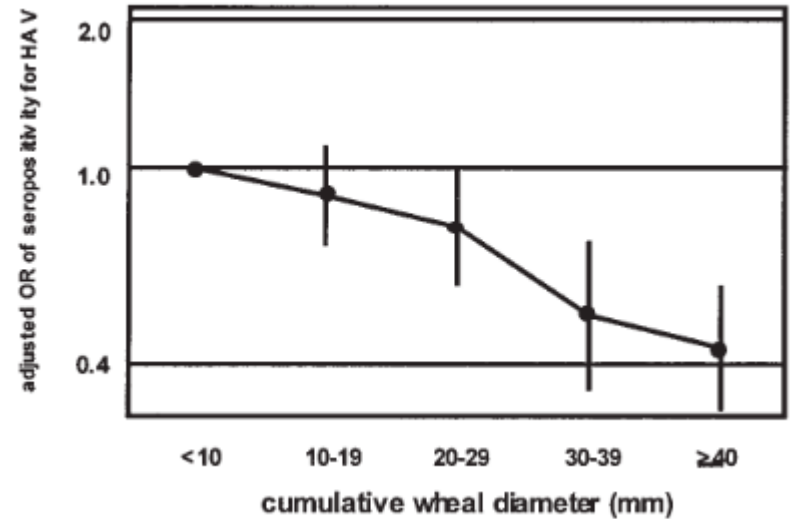
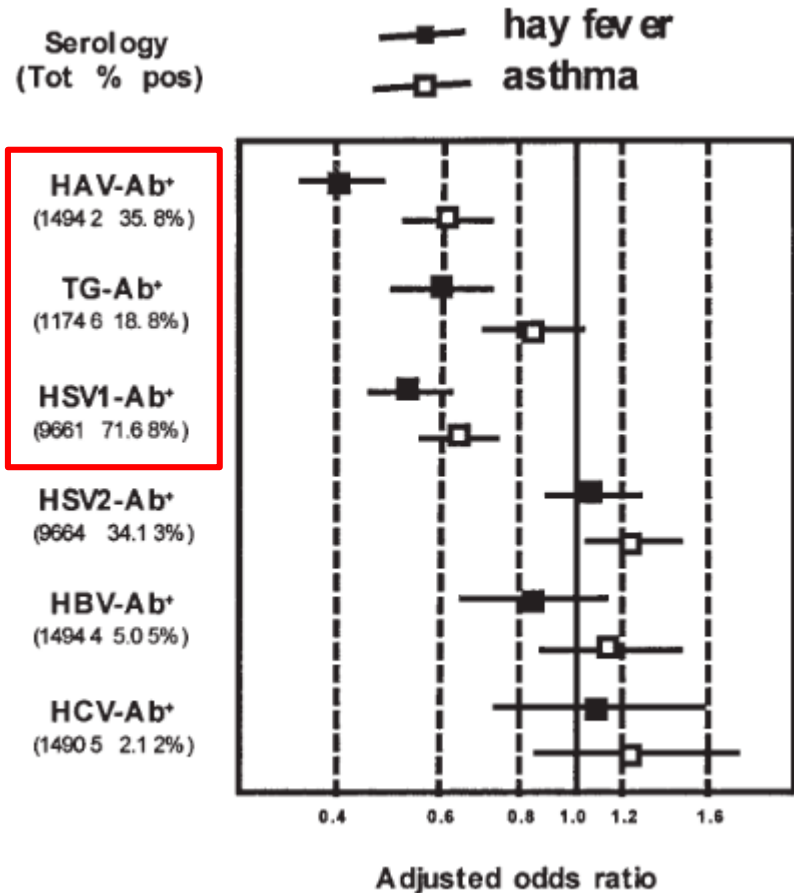


HAV-Ab <sup>-</sup>	443	550	666	974	1630	2005
HAV-Ab <sup>+</sup>	1935	1691	1177	1230	1453	1290

# Asthma in relation to markers of infection in US

1988-1994 (NHANES III), 33,944 US residents aged 1 to 90 years

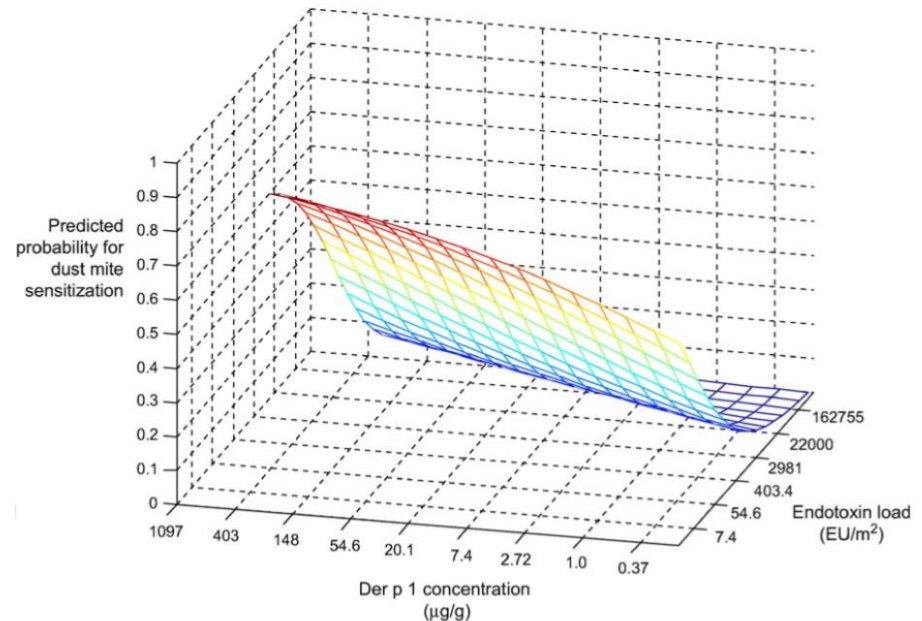
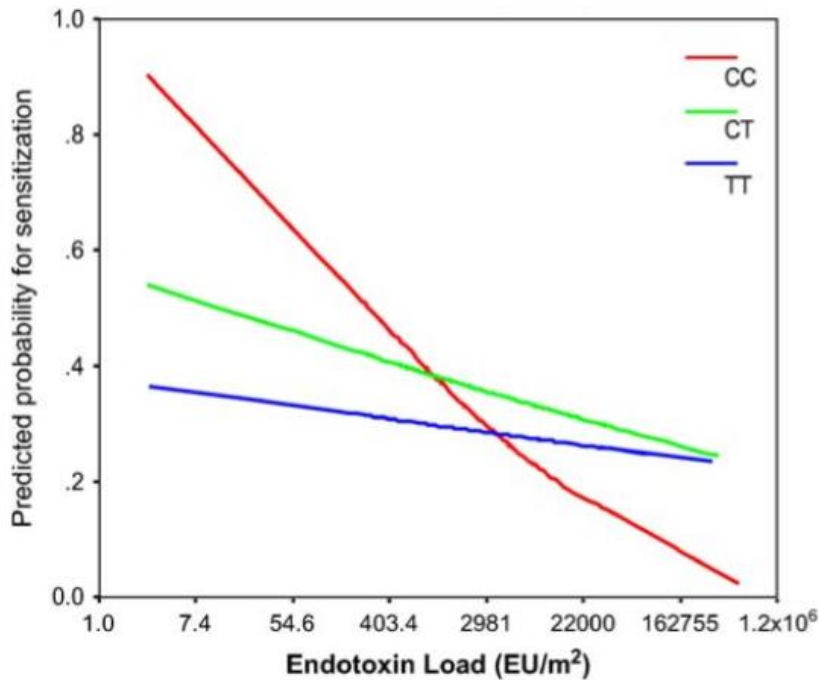
*Hay fever, Asthma vs. serology for HAV, T gondii, HSV-1 and 2, HBV, HCV*



# Endotoxin exposure, CD14, and Allergic disease

Increasing endotoxin exposure is associated with reduced risk of allergic sensitization and eczema with the CC genotype at CD14 gene.

human chromosome 5q31.1 : CD14 gene → receptor complex for LPS  
Activation of pathway → IL-12 expression (Th0 to Th1 favors)



# Early-life antibiotic use and allergic disease

Table 4. Adjusted\* associations between antibiotic orders and other allergies at different ages of diagnosis up to 7 years of age

	Period of antibiotic assessment	Antibiotic order count	Allergy diagnosed up to 1000 days of age (2.74 years)		Allergy diagnosed after 1000 days of age (2.74 years)		All allergy diagnosed at any age up to 7 years	
			Odds Ratio	95% Confidence interval	Odds Ratio	95% Confidence interval	Odds Ratio	95% Confidence interval
Allergy cases with or without a diagnosis of a food allergy <sup>†</sup>	Model 1: 0–12 months of age	1–2 vs. none	1.67	1.48–1.89	1.11	0.99–1.24	1.35	1.24–1.46
		3+ vs. none	2.49	2.17–2.85	1.27	1.11–1.45	1.75	1.59–1.92
	Model 2: 0–24 months of age	1–2 vs. none	1.85	1.60–2.14	1.10	0.95–1.28	1.46	1.31–1.62
		3+ vs. none	3.35	2.89–3.88	1.51	1.31–1.72	2.22	2.01–2.46
	Model 3: Until 60 days prior to diagnosis	1–2 vs. none	1.90	1.64–2.19	1.22	0.97–1.54	1.69	1.50–1.92
		3+ vs. none	3.54	3.04–4.11	2.23	1.82–2.73	3.07	2.72–3.46
Allergy cases excluding cases with a diagnosis of a food allergy <sup>‡</sup>	Model 1: 0–12 months of age	1–2 vs. none	1.68	1.48–1.92	1.08	0.95–1.21	1.32	1.21–1.44
		3+ vs. none	2.54	2.19–2.94	1.29	1.13–1.48	1.76	1.60–1.95
	Model 2: 0–24 months of age	1–2 vs. none	1.91	1.64–2.23	1.09	0.93–1.27	1.46	1.61–1.63
		3+ vs. none	3.50	2.98–4.10	1.49	1.29–1.71	2.22	2.00–2.47
	Model 3: Until 60 days prior to diagnosis	1–2 vs. none	1.96	1.67–2.29	1.19	0.94–1.50	1.71	1.50–2.00
		3+ vs. none	3.72	3.16–4.37	2.17	1.76–2.67	3.12	2.74–3.54

\*Adjusted for Medical Assistance and race/ethnicity.

<sup>†</sup>Includes allergy cases with and without diagnoses of food allergies: < 1001 days includes 1817 cases vs. 9085 controls; > 1000 days includes 1835 cases vs. 9175 controls; diagnosed up to 7 years includes 3652 cases vs. 18 260 controls.

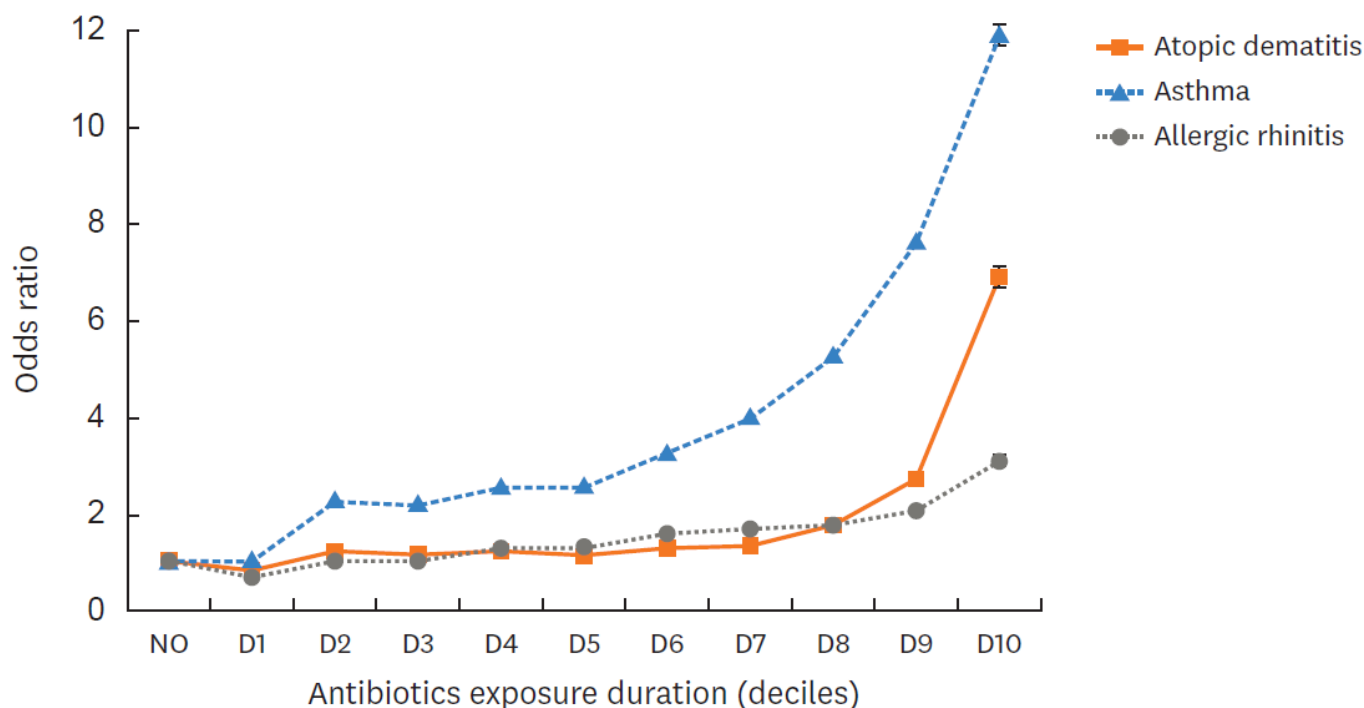
<sup>‡</sup>Excludes cases with a diagnosis of a food allergy: < 1001 days includes 1594 cases vs. 7970 controls; > 1000 days includes 1704 cases vs. 8520 controls; diagnosed up to 7 years includes 3298 cases vs. 16 490 controls.

# Early-life antibiotic use and allergic disease

National Health Insurance Service (2006–2015) database

A total of 5,626,328 children and adolescents

Explored whether exposure to antibiotics over the prior 7 years affects the later development of allergic diseases



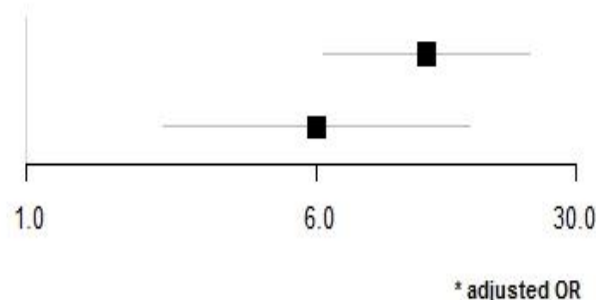
**Figure.** The odds ratios of developing allergic disease by the duration of exposure to antibiotics. The odds ratios reflect the risks in deciles compared with the average risk in the comparison group. The error bars reflect the standard error.

# Early-life antibiotic use and allergic disease

600명 학동 전기 천식 코호트, 3000명 COCOA 자료 짝짓기 분석  
소아 천식 발생의 위험인자 분석

- 출생 후 3일 이상 항생제 사용 빈도는 천식군에서 유의하게 높았다 ( $p < 0.001$ )
- 특히, 생후 12개월 이내 항생제 사용은 천식 발생의 유의한 위험인자로 확인되었고, 알레르기 질환이 있는 경우에 생후 12개월 이내 항생제 사용이 천식의 위험도를 더 증가시키는 결과를 확인하였다.
- 출생 후 1년 이내의 항생제 사용이 부모의 알레르기 질환이 있는 고위험군에서 12배로 부모의 알레르기 질환이 없는 저위험군에 비해 천식 위험도가 2배 증가하였다

Use of Antibiotics	OR	95%CI
Parental allergy (+)	11.87	(6.27-22.45)
Parental allergy (-)	6.02	(2.35-15.44)



# Prenatal delivery mode and allergic disease

Prenatal exposure to antibiotics and cesarean delivery may affect the gut microbiota in early infancy, which is an important period in the development of the immune system

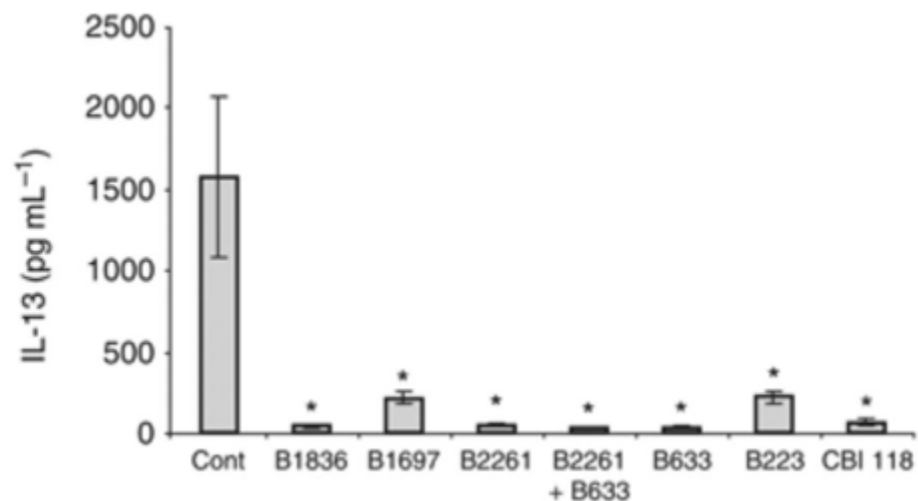
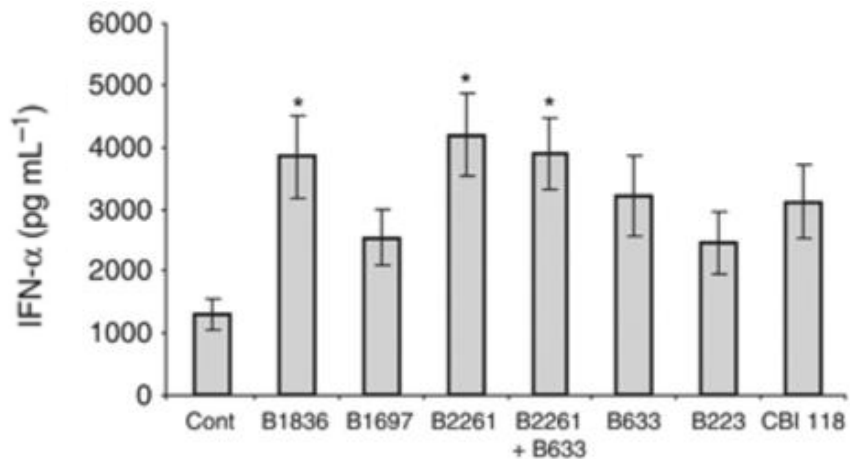
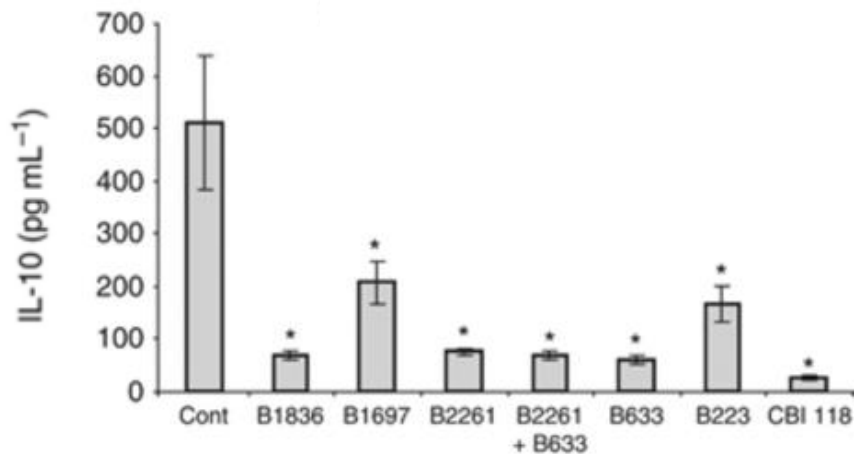
<b>IL-13 rs20541/Delivery mode</b>	<b>Number (%) of AD</b>	<b>OR (95% CI)</b>	<b>p-value</b>	<b>aOR (95% CI)*</b>	<b>p-value</b>
GG/Vaginal delivery	17 (22.7)	1.00		1.00	
GA+AA/Vaginal delivery	27 (26.7)	1.24 (0.61–2.54)	0.55	2.37 (0.96–5.84)	0.06
GG/C-section delivery	15 (45.5)	2.84 (1.19–6.81)	0.02	3.85 (1.25–11.83)	0.02
GA+AA/C-section delivery	13 (43.3)	2.61 (1.06–6.43)	0.04	4.70 (1.43–15.40)	0.01
<b>CD14 rs2569190/Delivery mode</b>					
TT/Vaginal delivery	13 (23.6)	1.00		1.00	
TC+CC/Vaginal delivery	28 (26.7)	1.18 (0.55–2.51)	0.68	1.34 (0.53–3.44)	0.54
TT/C-section delivery	9 (42.9)	2.42 (0.84–7.03)	0.10	3.11 (0.80–12.12)	0.10
TC+CC/C-section delivery	17 (43.6)	2.50 (1.03–6.06)	0.04	3.56 (1.12–11.36)	0.03

\*Adjusted for gestational age at birth, sex, pre-pregnancy maternal body-mass index, maternal age at delivery, maternal education level, prenatal exposure to smoke, prenatal exposure to pets, presence of older sibling(s), and parental history of allergic diseases.

doi:10.1371/journal.pone.0096603.t004

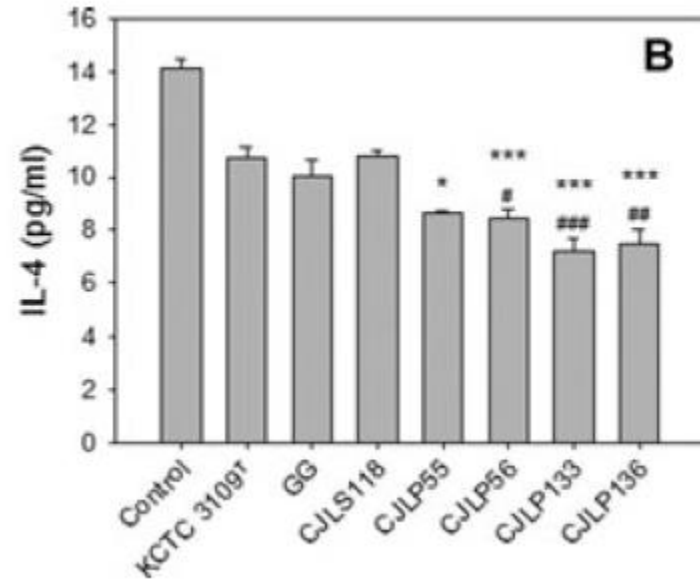
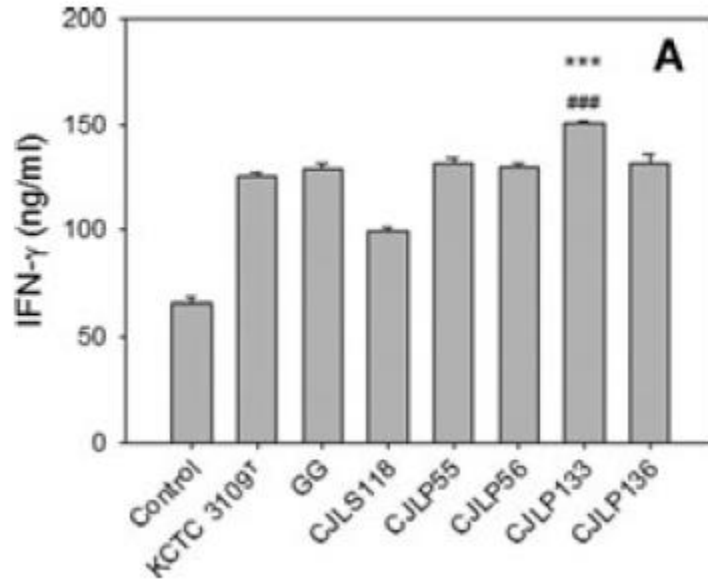
# Modulation of Th1/Th2 balance by lactobacillus

Lactobacillus Strain 자극 후 hPBMC secretion cytokine 의 차이 분석

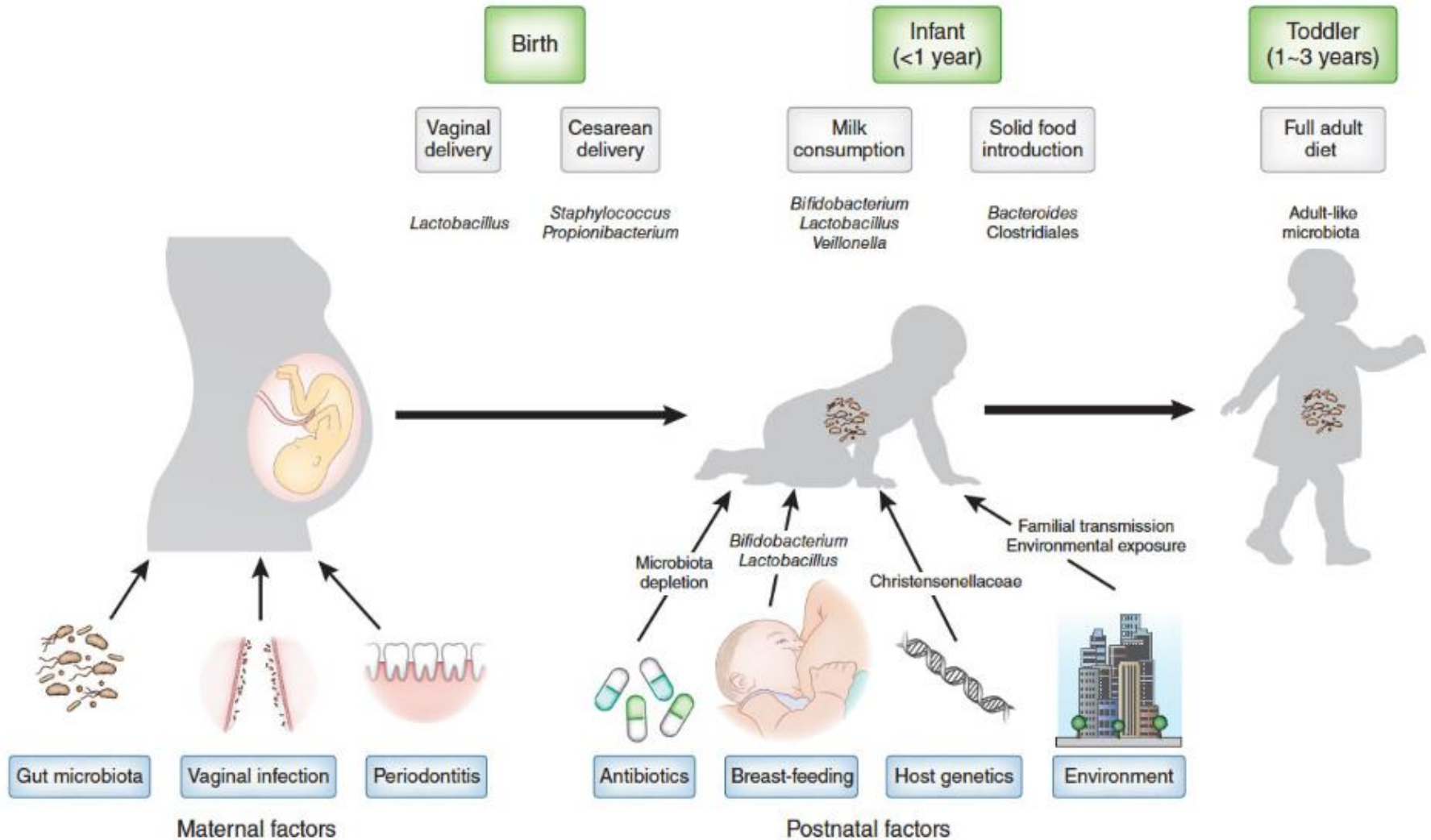


# Modulation of Th1/Th2 balance by lactobacillus

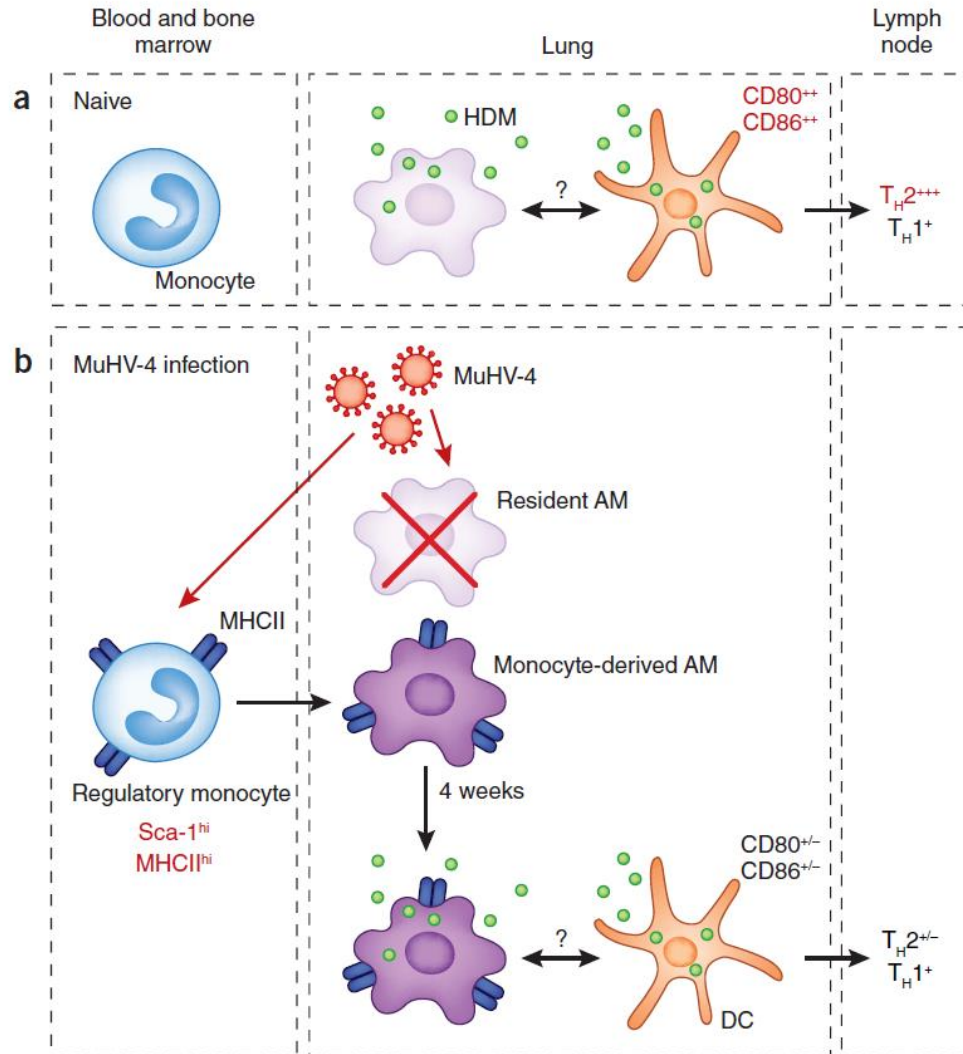
김치 내 유산균으로 연구



# Microbiome, immune balance, allergy



# Infection affects lung immunity – Trained macrophages

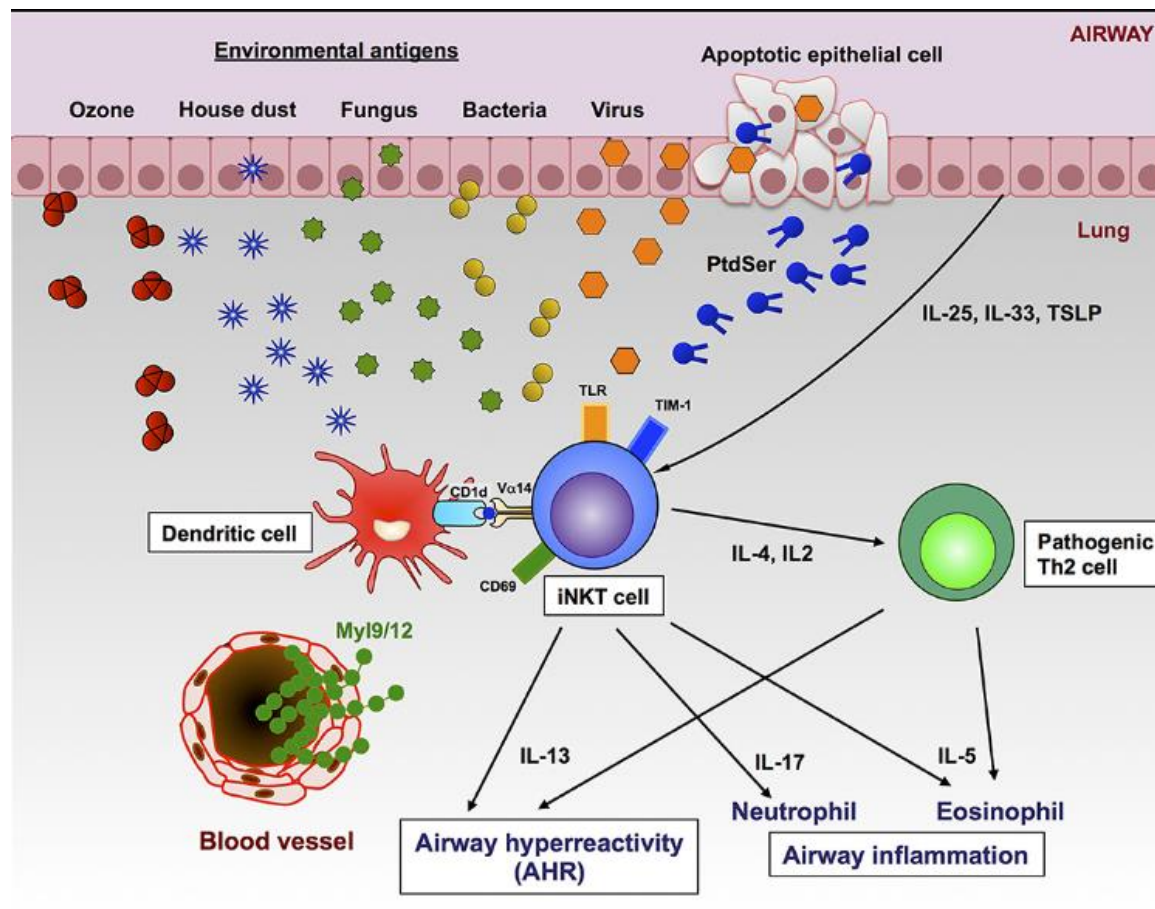


감염에 따라, BM origin의 monocyte 가 lung 으로 유입 되면서 resident AM 로 변환 되고, 이 AM는 감염의 memory로 인해 T2 inflammation을 유발하지 않는다 – Trained macrophage

# NKT cells in allergic disease

NKT cell → immune modulation

Asthma patients BAL fluid iNKT cell increased, development allergen-induced airway hyperreactivity



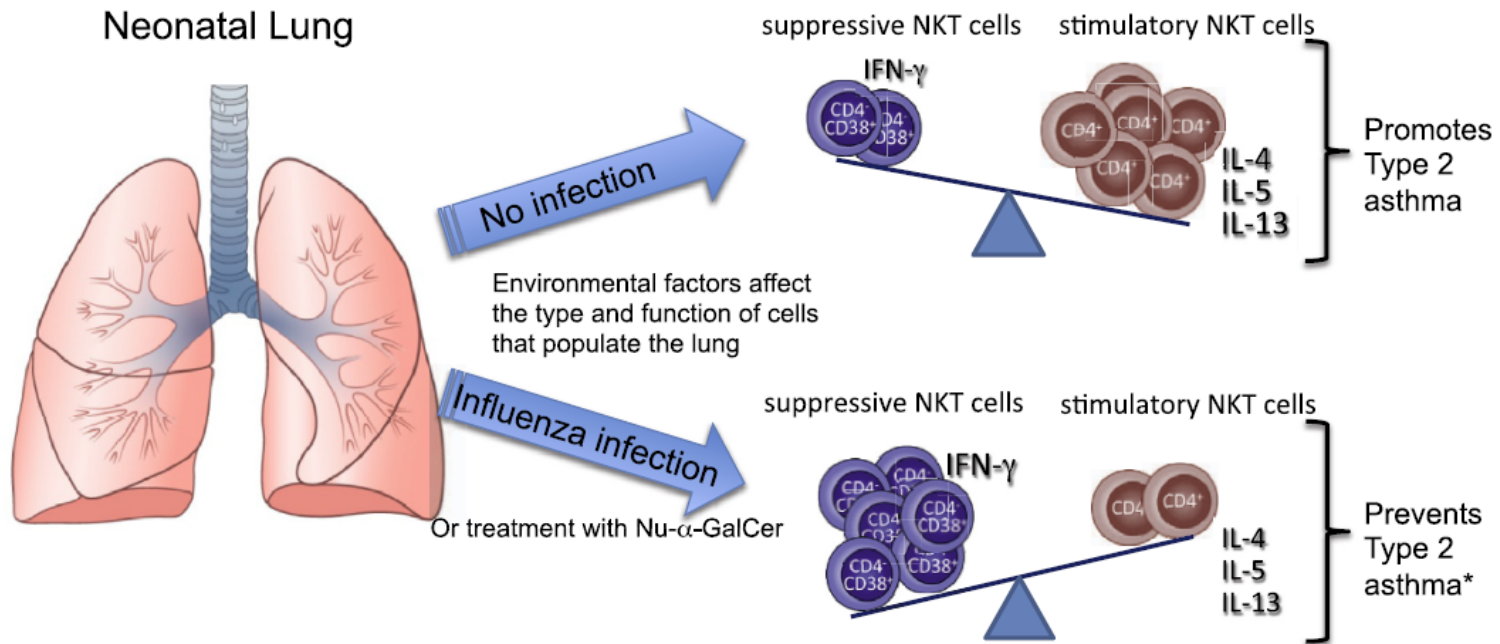
# Early infection affects lung immunity – NKT cells

NKT cell도 유사하게, 감염에 의해 NKT cell을 trained 시켜, T2 inflammation 을 예방한다

## GRAPHICAL ABSTRACT



A Natural Killer T (NKT) cell subset that protects against airway hyperreactivity



\* Inhibits Th2 cell expansion through contact-dependent mechanism



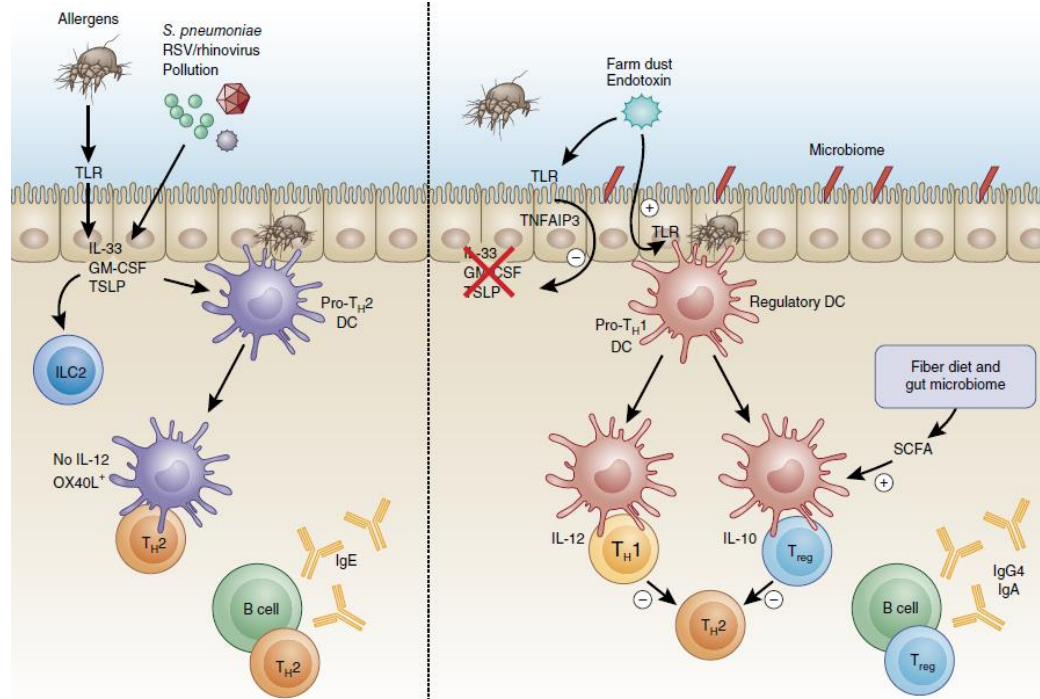
## 5. Conclusions



# Hygiene hypothesis



genetic



# Hygiene hypothesis

- 초기 early lifetime의 immune direct, 방향성과 관련된 이론이다
- hygiene hypothesis는 allergic disease의 pathophysiology, experimental study 등과 관련한 가이드, 청사진을 제시하는 이론이며, 알레르기 질환의 발병과 관련된 근본이 되는 이론이다

# Hygiene hypothesis (위생 가설) 이란

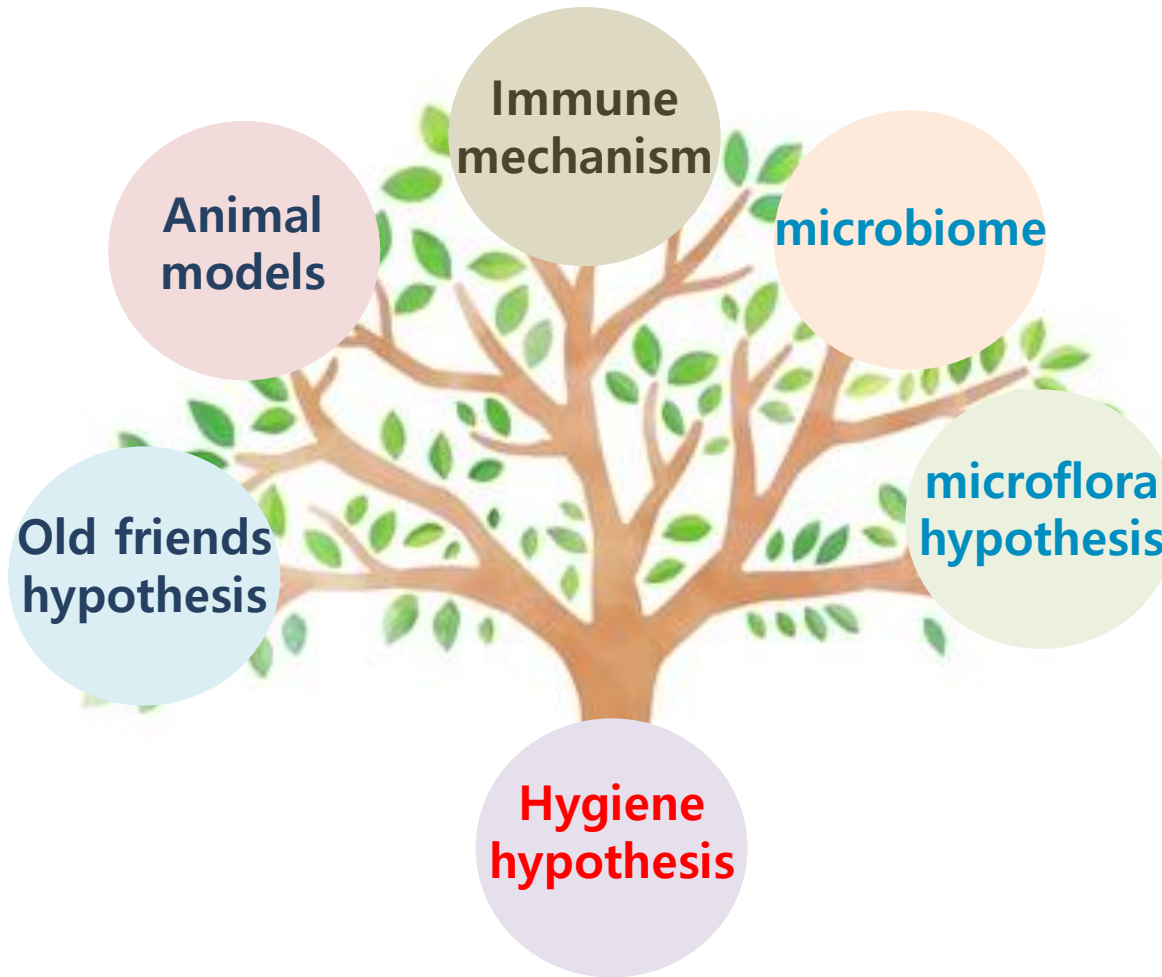
“자연적으로 일어나는 감염(infection)과 미생물에 대한 노출(microbial exposure)이 알레르기 질환의 면역 형성에 관여한다”



“hygiene hypothesis has been described as a misnomer”

Reducing one's personal hygiene, such as not washing hands before eating, is expected to simply increase the risk of infection without having any impact on allergies or immune disorders.

# Hygiene hypothesis



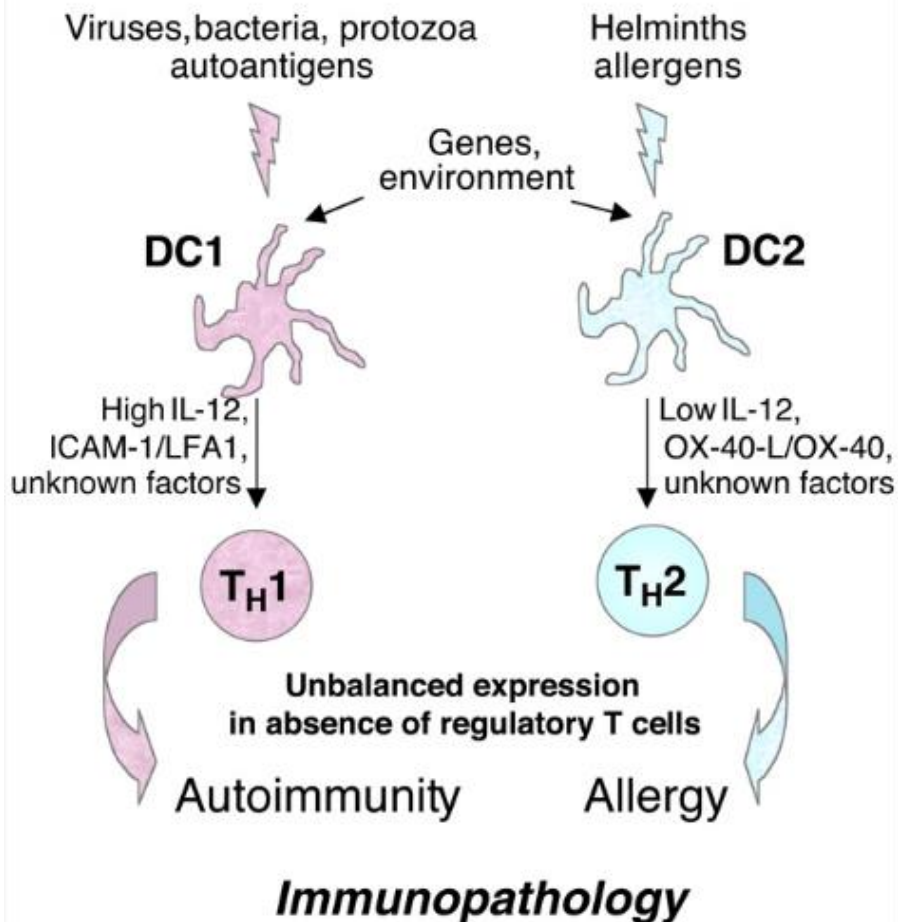
Hygiene hypothesis는 Early childhood asthma 발생 기전에 중요하고 근간이 되는 이론이며 이를 바탕으로 많은 연구가 이루어 졌고 이루어 지고 있다

# 경청해 주셔서 감사합니다

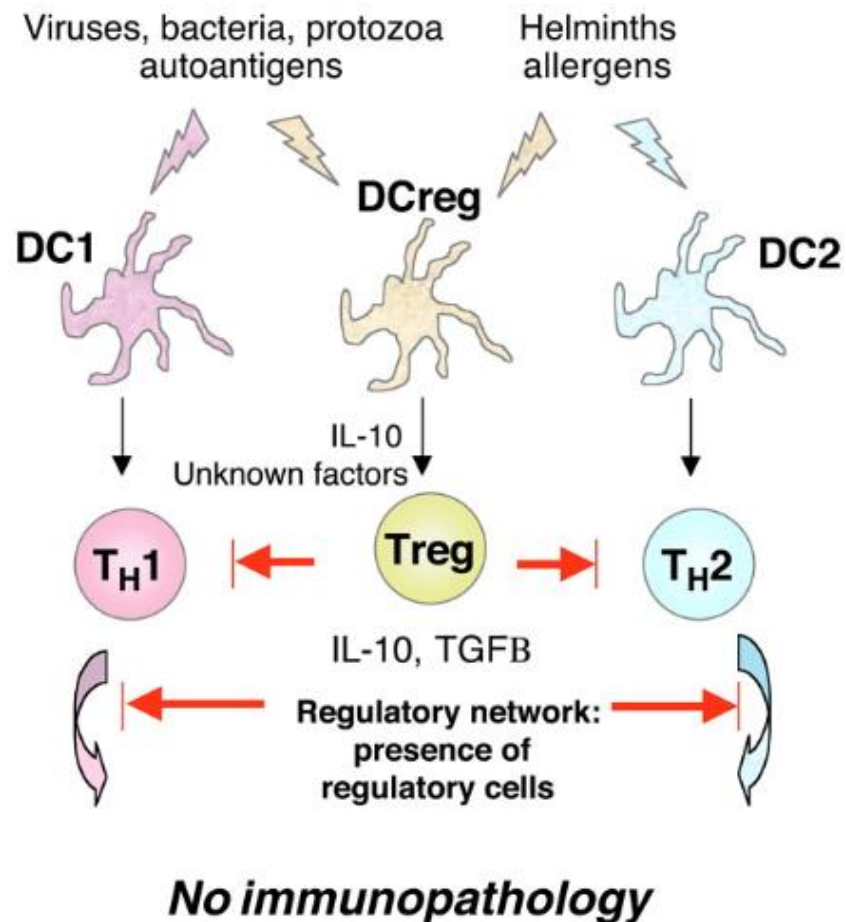


# Counter regulation - homeostatic role of IL-10

High hygiene, low pathogen/adjuvant burden

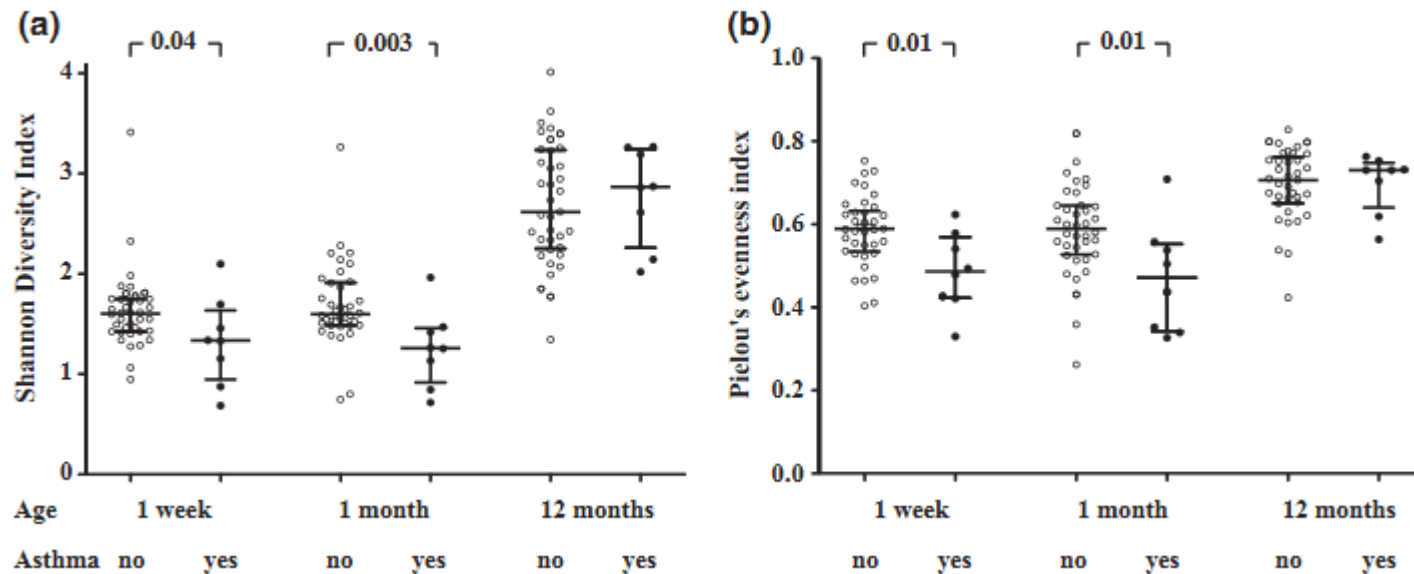


Low hygiene, high pathogen/adjuvant burden



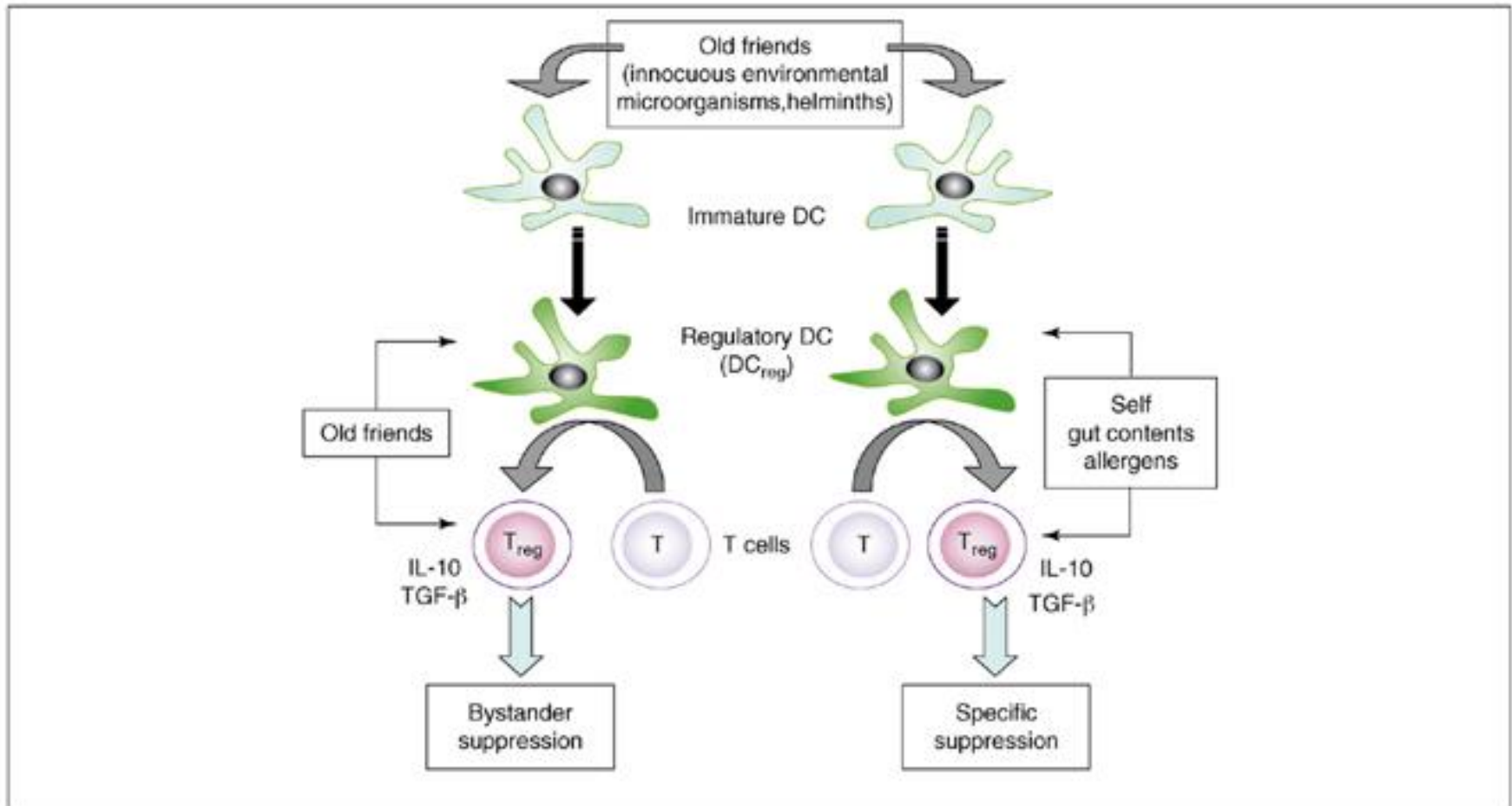
# Low gut microbiota diversity, asthma at school age

Low total diversity of the gut microbiota during the first month of life was associated with asthma



# 2003' Graham Rook - "old friends" hypothesis

Certain types of bacteria (the part of human evolutionary history, "old friends")



# 2005' microorganism diversity-"microflora hypothesis"

