

Hygiene Hypothesis in Asthma, Con

가천대길병원 호흡기알레르기내과
강성윤

Hygiene Hypothesis in Asthma, Con



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Developed vs Developing countries
Urban vs Rural differences



02

Children with siblings



03

Microbe
Friends vs Foes



04

Endotoxin



05

Hygiene habits and conceptions



06

Cleanliness vs Dirtiness



RA

Greenwood BM et al. Lancet 1968



Strachan DP. BMJ. 1989

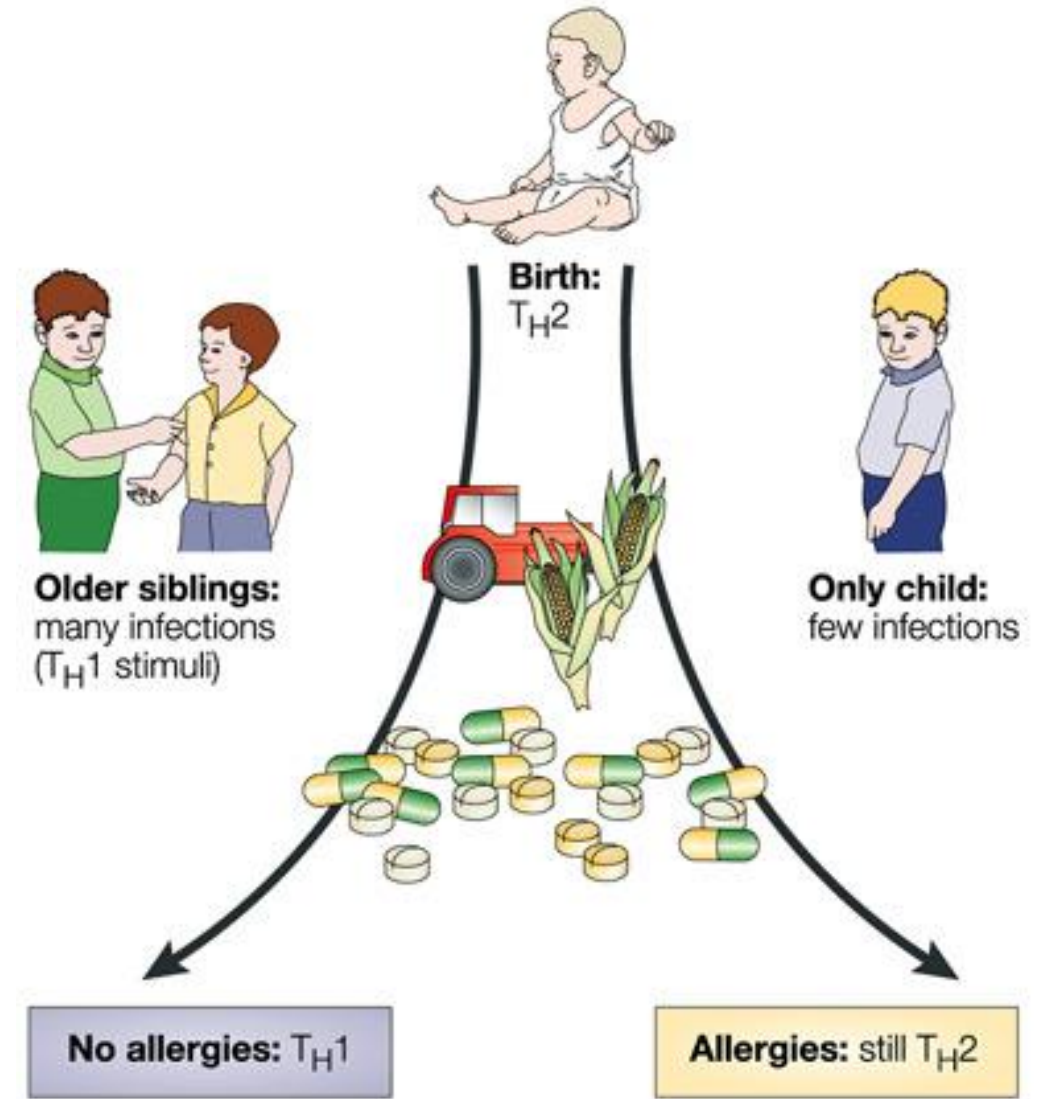
위생가설의 시작

형제 자매가 있는 경우 건초열(hay fever) 발생이 적음을 보고하여 형제 자매가 있는 경우 알레르기 질환 발생에 보호 작용이 될 수 있음을 밝힘

→

어린 시절 손위형제 자매가 있으면 감염성 질환에 노출이 많이 되고 감염 횟수도 증가

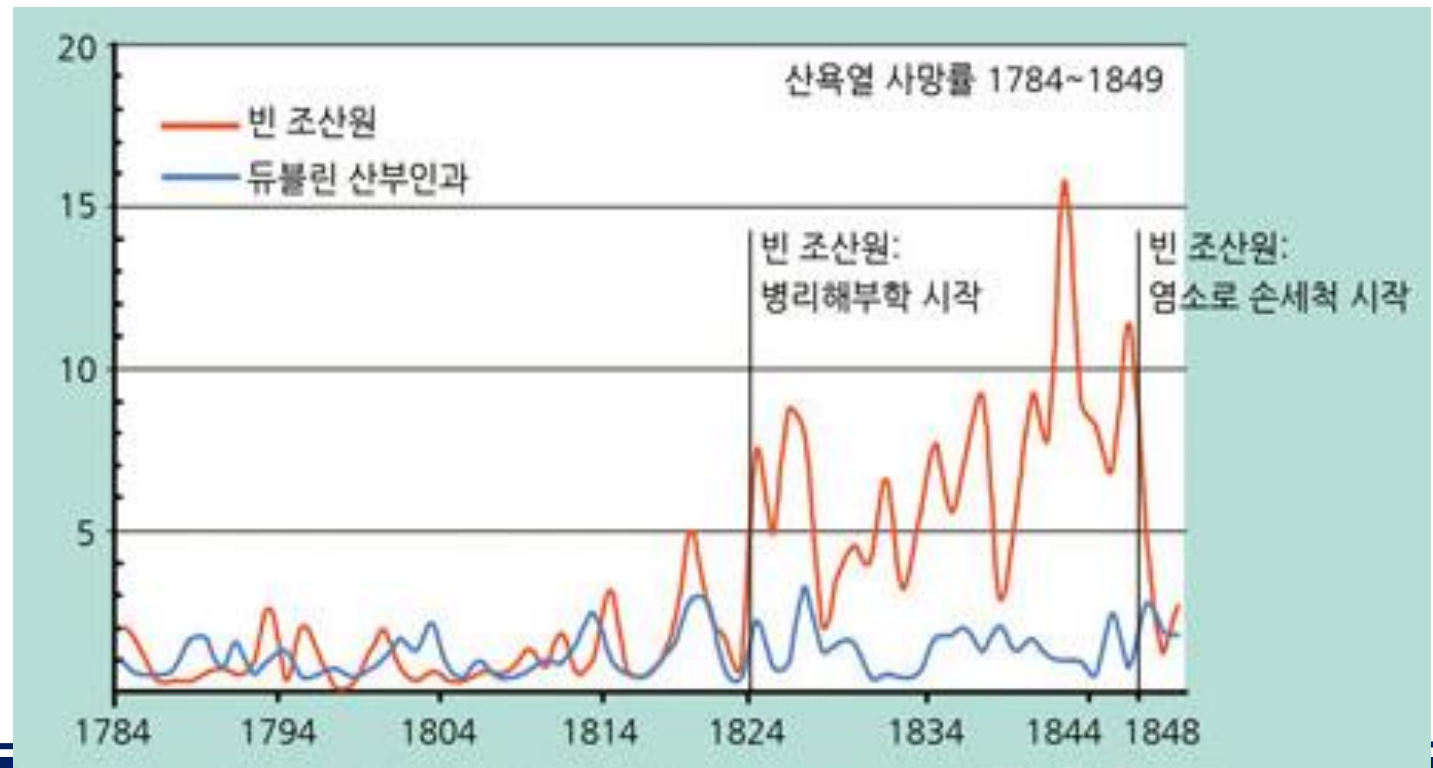
→ Th2cytokine의 생산을 감소시키는 쪽으로 면역 반응



Nature Reviews | Drug Discovery

위생(Hygiene, 衛生)의 개념

- 건강에 유익하도록 조건을 갖추거나 대책을 세우는 일
- **Hygiene**, from the *WHO* refers to conditions and practices that help to maintain health and prevent the spread of diseases



‘시체 입자’라고 불렀던 것은 연쇄구균

감염 (Infection, 感染)의 개념

- 병원체(병의 원인이 되는 본체) 인 미생물이 동물이나 식물의 몸 안에 들어가 증식하는 일
- **Infection**, *from Wikipedia*
 - the invasion of an organism's body tissues by disease-causing agents
 - the reaction of host tissues to the infectious agents and the toxins they produce

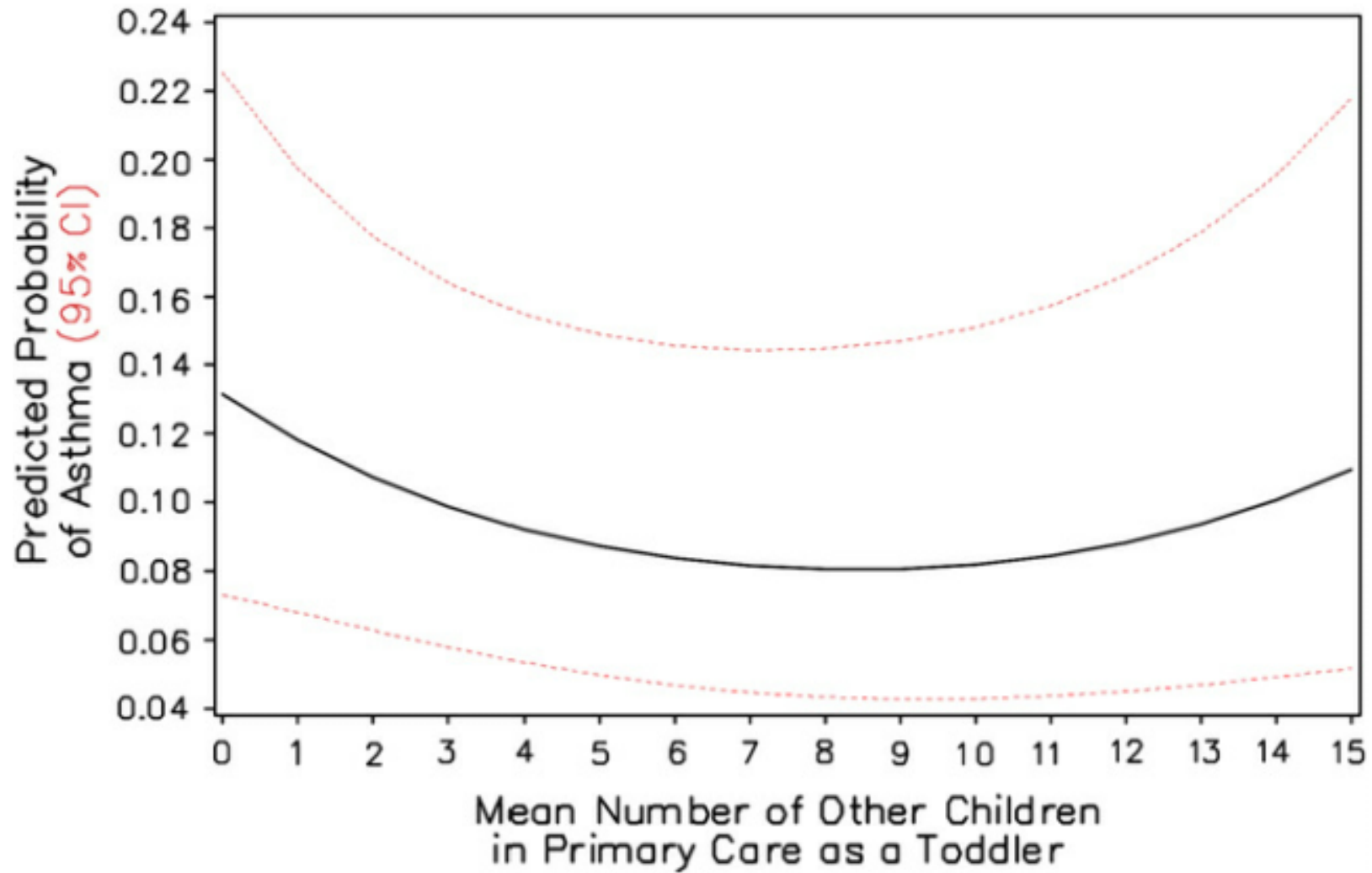
위생 = 감염

Children with siblings

Association of asthma with total and older siblings

Symptom (6 to 7-year-olds)	Total siblings (odds ratio per additional sibling) After adjustment, in children with covariate data		Older siblings (adjusted for younger siblings) After adjustment, in children with covariate data	
	OR (95% CL)	<i>P</i> value	OR (95% CL)	<i>P</i> value
Wheeze ever	0.96 (0.94, 0.98)	< 0.0001	0.98 (0.96, 1.00)	0.04
Wheeze in last 12 months	0.99 (0.96, 1.01)	0.19	1.01 (0.98, 1.04)	0.45
Severe wheeze in last 12 months	1.03 (1.00, 1.06)	0.07	1.05 (1.01, 1.09)	0.02
Asthma ever	0.98 (0.96, 1.01)	0.12	1.00 (0.97, 1.03)	0.82

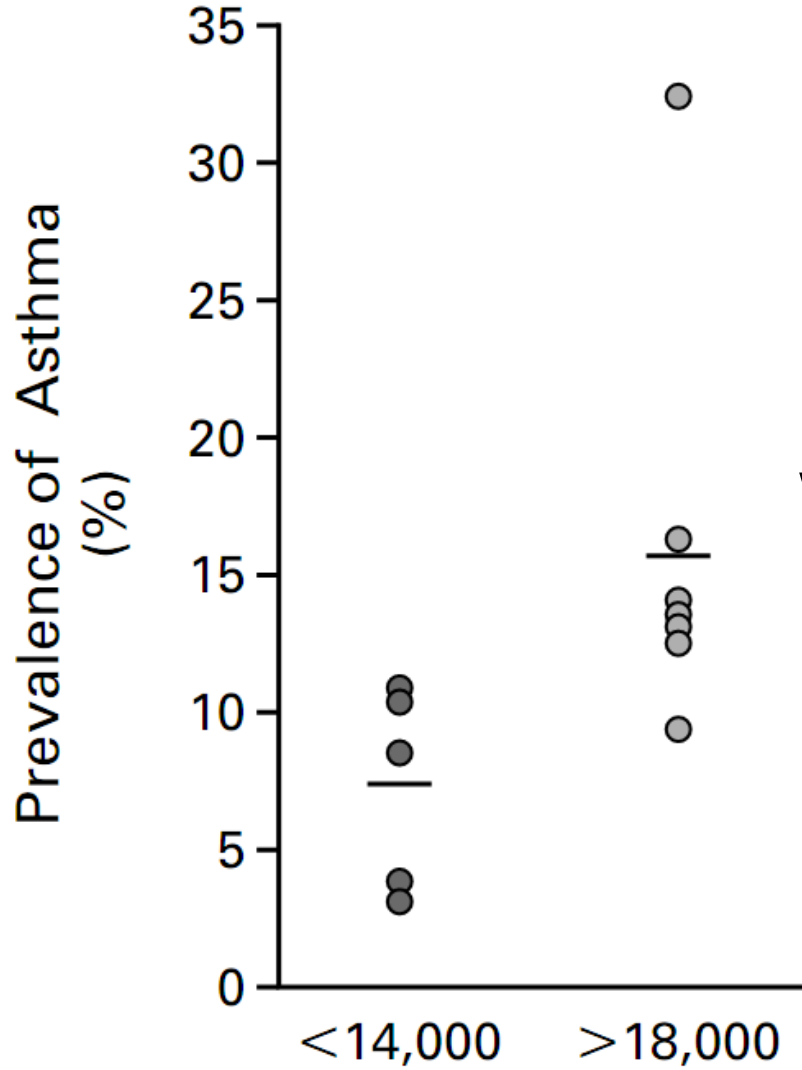
Association of asthma with total and older siblings



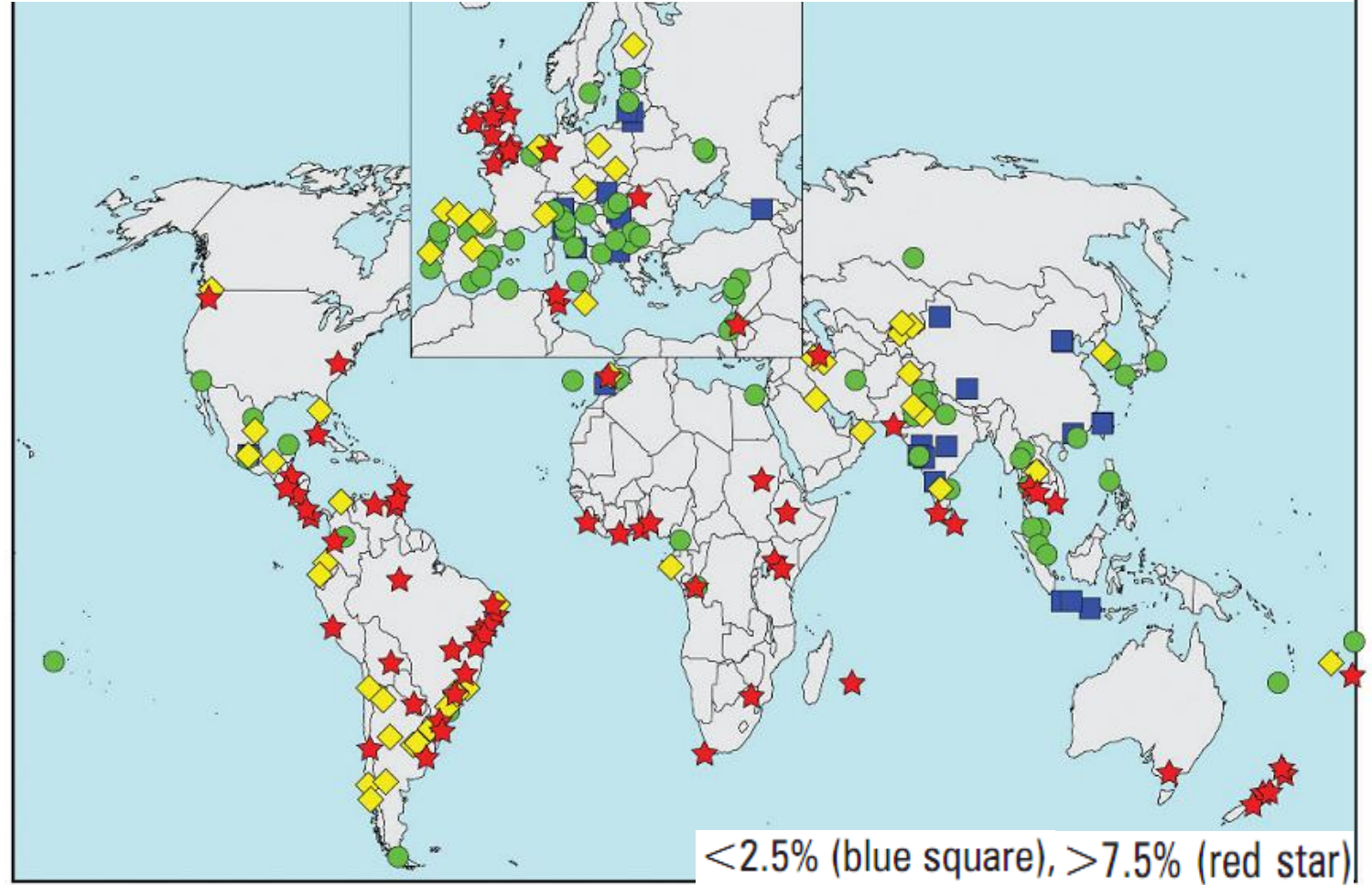
Developed vs Developing countries

Urban vs Rural differences

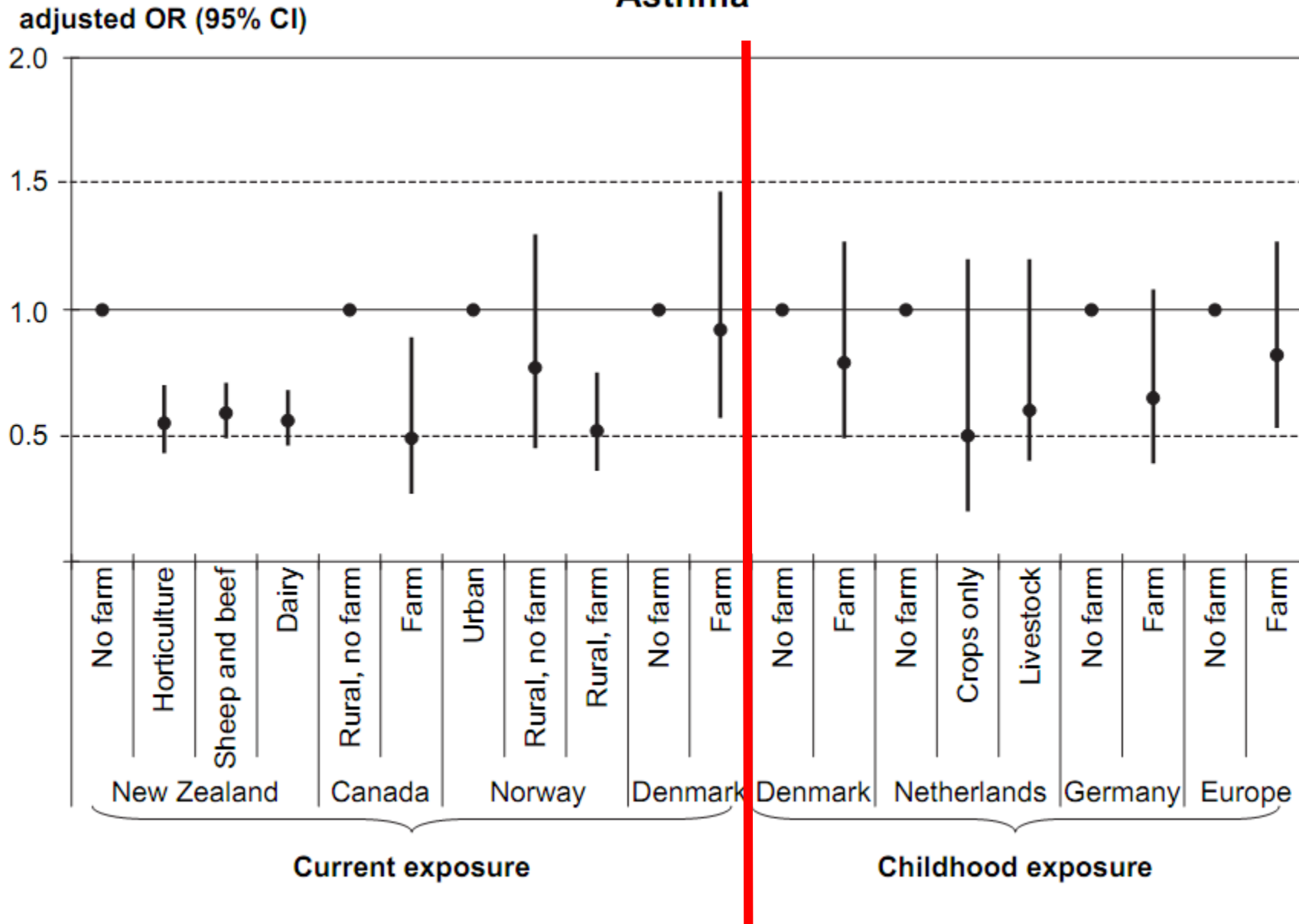
Gross National Product per Capita (\$)



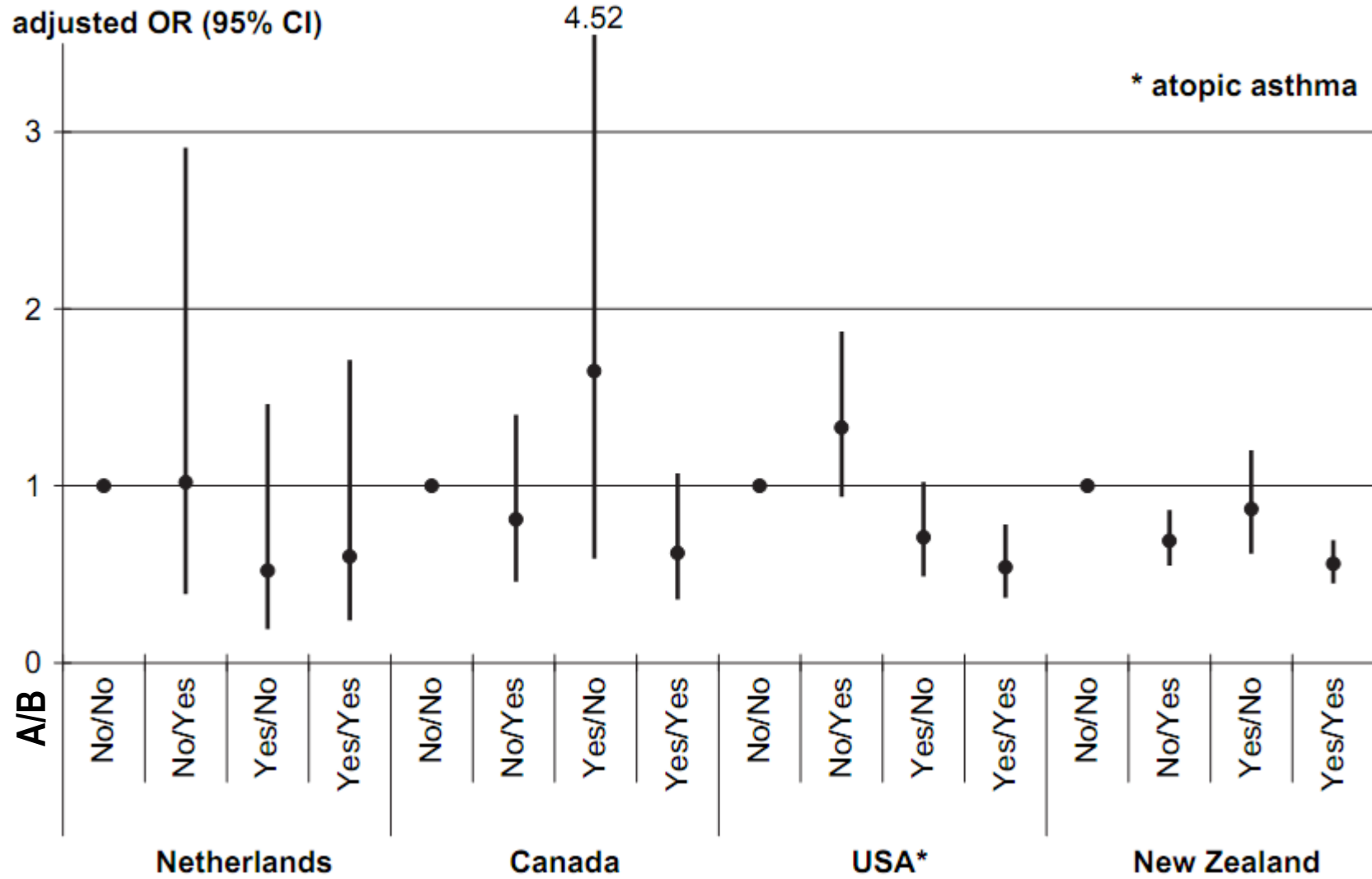
Prevalence of symptoms of severe asthma



Asthma



Asthma



(A) Farm contact during childhood (B) Recent farm contact

Recent Wheeze (Urban vs Rural 9.4% vs 10.1%, p=0.05)

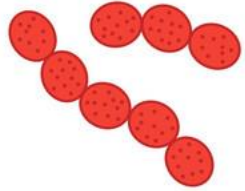
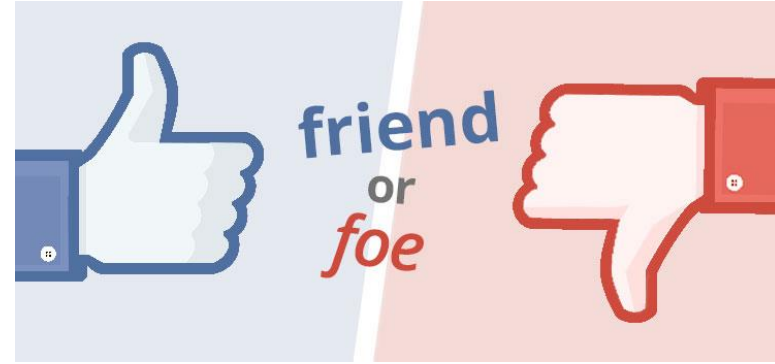
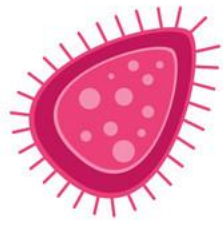
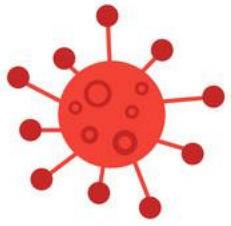


Table 1 Characteristics of schoolchildren in urban and rural areas

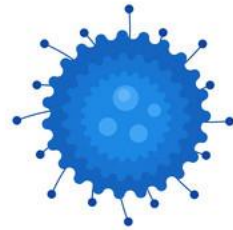
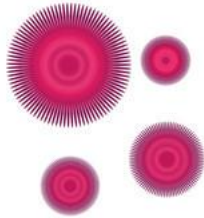
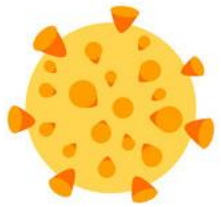
Risk factor	Urban (n=2526)		Rural (n=4295)		p Value for rural vs urban
	n	%	n	%	
Bathroom (%)					
Field	178	7.1	1553	36.1	<0.001
Latrine	595	23.5	2617	61.0	
WC	1752	69.4	123	2.9	
Potable drinking water					
No	199	7.9	4028	93.8	<0.001
Yes	2320	92.1	266	6.2	
Daycare attendance					
No	1431	57.4	2291	54.1	0.008
Yes	1061	42.6	1944	45.9	
Household construction					
Wood/bamboo	218	8.7	2443	57.2	<0.001
Mixed cement/wood	1139	45.2	1151	26.9	
Cement	1163	46.1	678	15.9	
Farming exposures					
Father with agricultural occupation					
No	2306	93.8	2213	52.4	<0.001
Yes	152	6.2	2007	47.5	
Contact with large farm animals*					
No	2306	91.4	2979	69.5	<0.001
Yes	218	8.6	1310	30.5	
Unpasteurised milk†					
No	1594	63.2	2455	57.3	<0.001
Yes	927	36.8	1831	42.7	
Infections					
Geohelminth infections					
Any geohelminth	1036	42.9	2849	69.0	<0.001

Hygiene exposure	Wheeze OR (95% CI) p Value	
	Univariate	Multivariate
Pets inside home Yes vs no	1.09 (0.93 to 1.29) 0.296	
Crowding ≥3 vs <3	0.97 (0.82 to 1.16) 0.733	
Birth order ≥5th vs ≤4th	0.75 (0.62 to 0.91) 0.003	0.75 (0.61 to 0.91) 0.005
Bathroom Field vs others	1.19 (0.99 to 1.43) 0.054	
Potable drinking water No vs yes	1.21 (1.02 to 1.43) 0.028	1.44 (1.16 to 1.78) 0.001
Attended daycare Yes vs no	0.99 (0.84 to 1.16) 0.889	
House construction Wood/bamboo vs others	0.95 (0.81 to 1.12) 0.508	
Father engaged in agriculture Yes vs no	0.89 (0.74 to 1.06) 0.176	0.86 (0.70 to 1.05) 0.144
Contact with farm animals* Yes vs no	1.03 (0.85 to 1.25) 0.781	
Unpasteurised milk† Yes vs no	1.05 (0.89 to 1.24) 0.557	
Any geohelminth Yes vs no	1.12 (0.95 to 1.34) 0.165	

Microbe Friends vs Foes

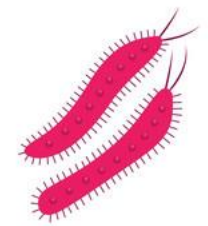
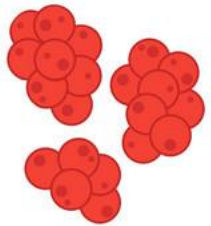


1 Bacteria



2 Virus

3 Parasite



4 Fungus

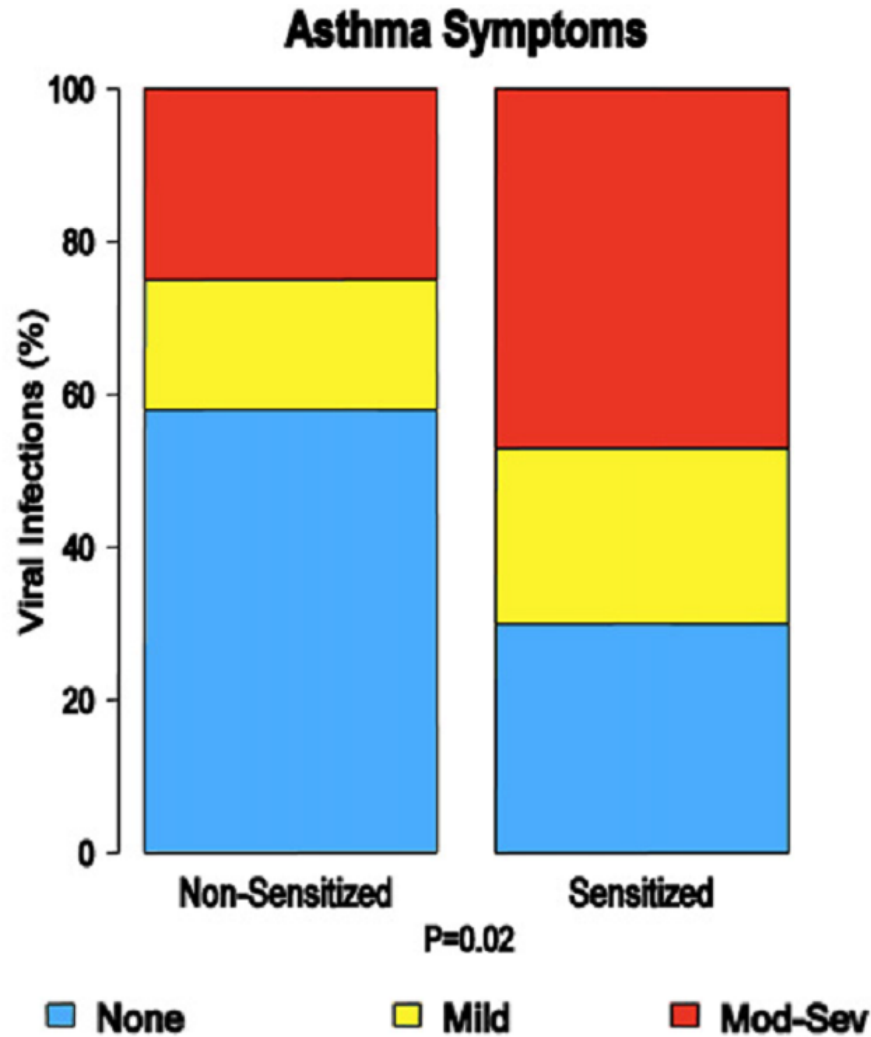
Table 1. Hazard Ratios for the Presence of Bacteria in Cultures from Airways at 1 Month of Age in Relation to Primary End Points.

End Point and Bacterial Species	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)*
First wheezy episode		
At least one of <i>S. pneumoniae</i> , <i>H. influenzae</i> , or <i>M. catarrhalis</i>	1.65 (1.24–2.21)	1.50 (1.08–2.10)
Persistent wheeze		
At least one of <i>S. pneumoniae</i> , <i>H. influenzae</i> , or <i>M. catarrhalis</i>	2.40 (1.45–3.99)	2.01 (1.13–3.57)
Acute severe exacerbation of wheeze		
At least one of <i>S. pneumoniae</i> , <i>H. influenzae</i> , or <i>M. catarrhalis</i>	2.99 (1.66–5.39)	3.14 (1.57–6.30)
Hospitalization for wheeze		
At least one of <i>S. pneumoniae</i> , <i>H. influenzae</i> , or <i>M. catarrhalis</i>	3.85 (1.90–7.79)	3.57 (1.55–8.23)

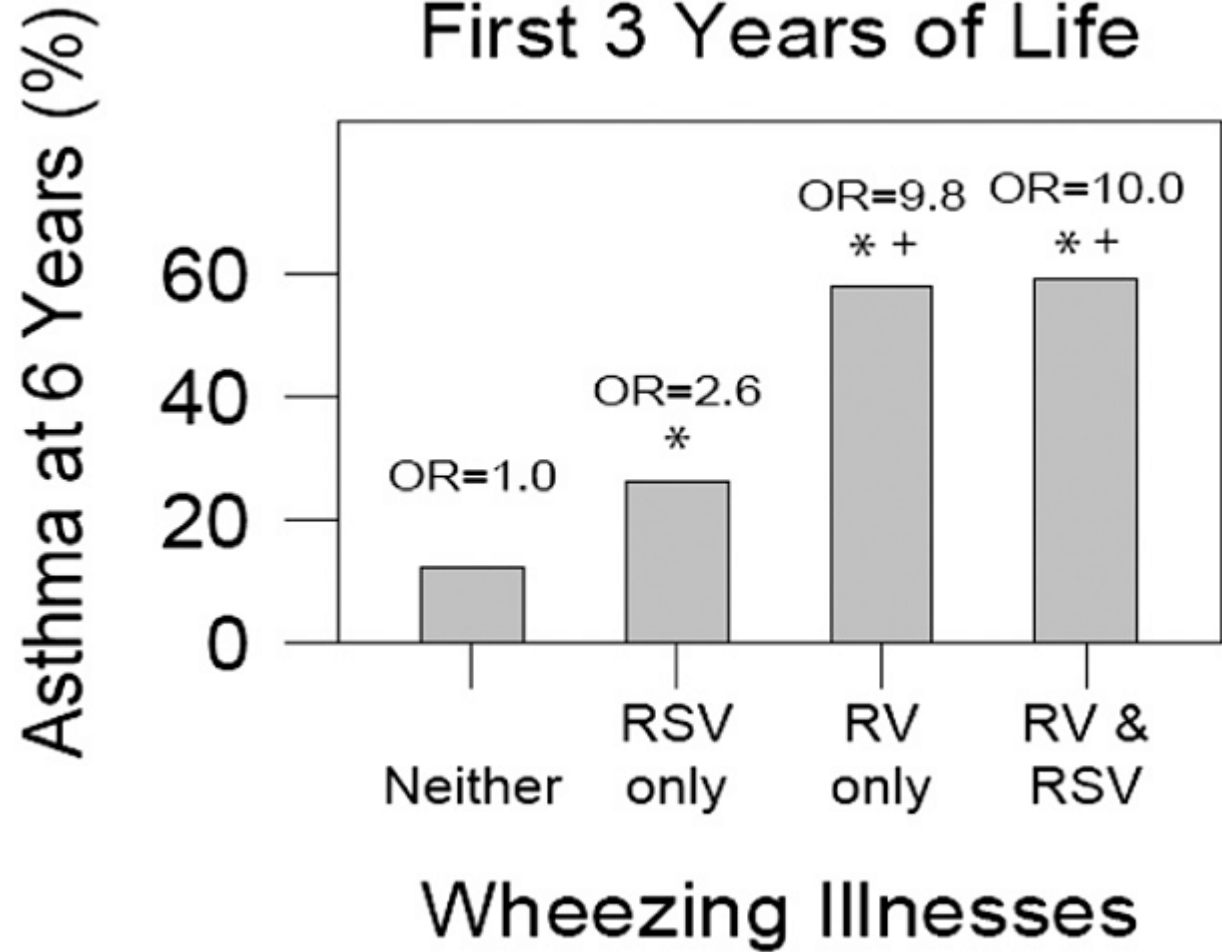
Table 2. Colonization in Relation to Asthma Diagnosis, Lung Function, and Allergy.

Outcome	Colonized	Not Colonized	Odds Ratio (95% CI)	Percent Estimated Difference (95% CI)*
Asthma at 5 yr (no.)				
Yes	17	20	4.57 (2.18 to 9.57)	
No	35	188		

Effect of sensitization on the severity of asthma symptoms associated with rhinovirus infections



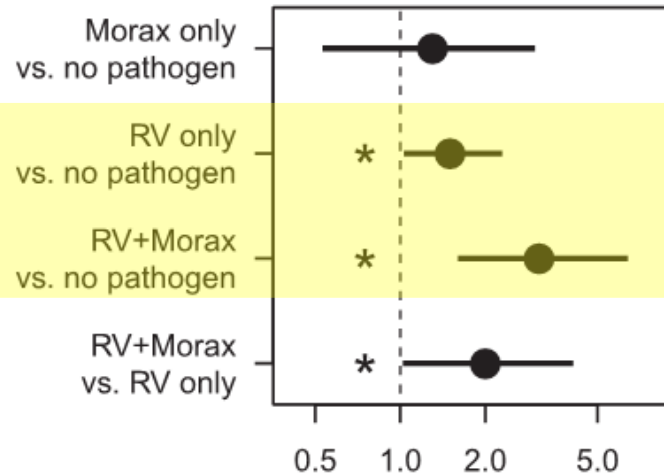
Risk of asthma at age 6 years in children who wheezed during the first 3 years of life with rhinovirus (RV), respiratory syncytial virus (RSV)



Probability of experiencing illness symptoms according to patterns of pathogen

A

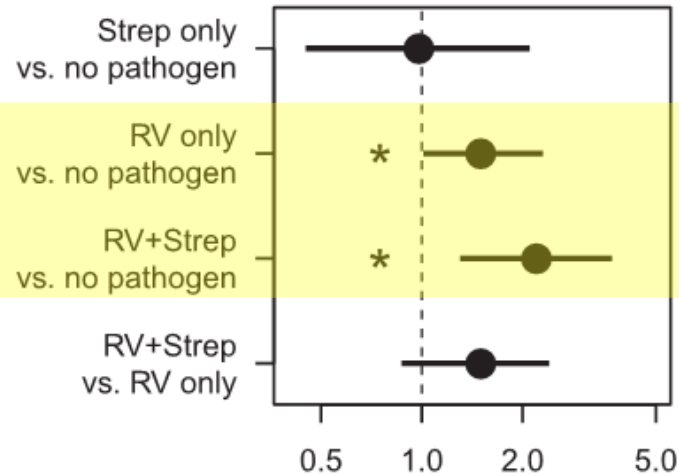
M. Catarrhalis and RV



Odds Ratio for Illness

B

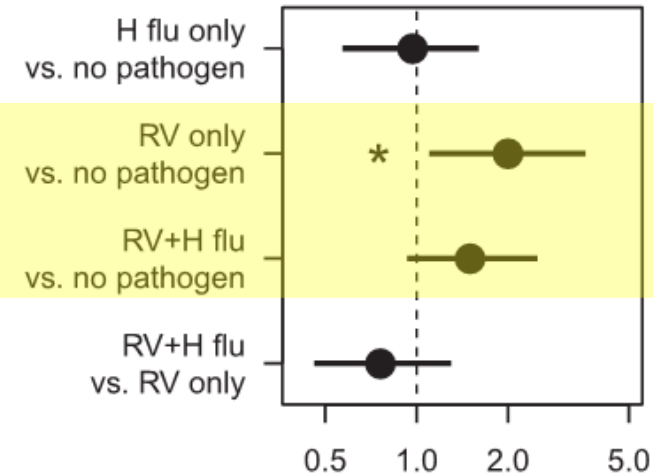
S. Pneumoniae and RV



Odds Ratio for Illness

C

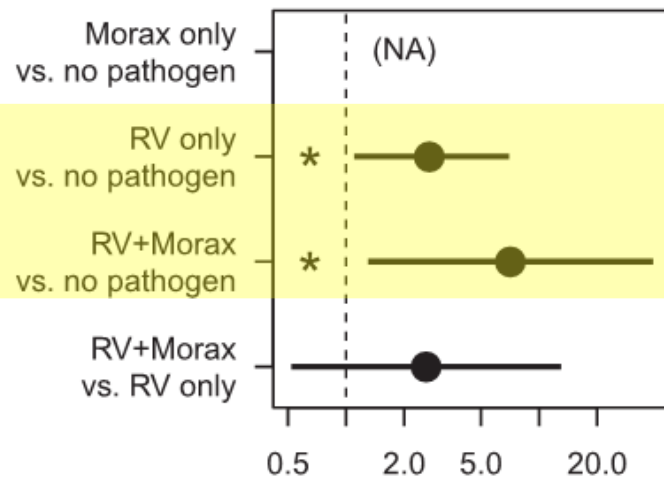
H. Influenzae and RV



Odds Ratio for Illness

D

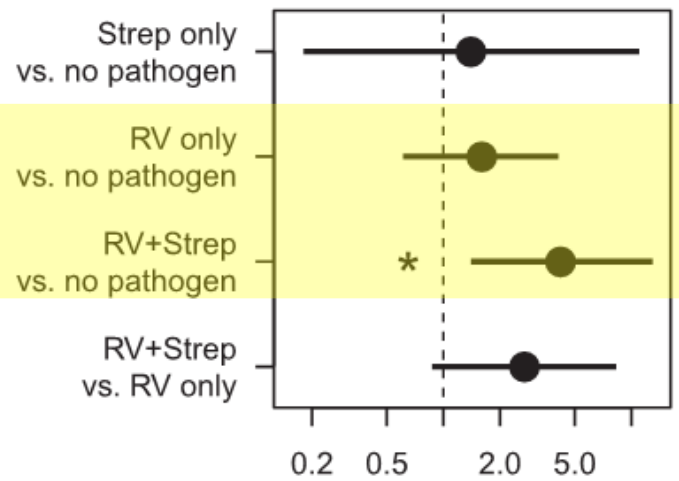
M. Catarrhalis and RV



Odds Ratio for Exacerbation

E

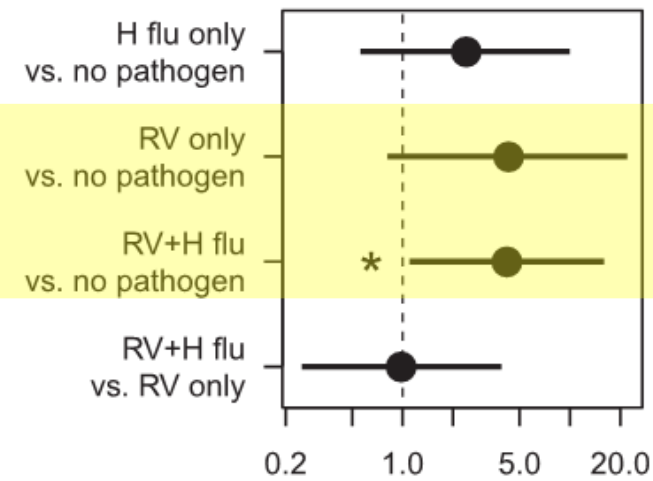
S. Pneumoniae and RV



Odds Ratio for Exacerbation

F

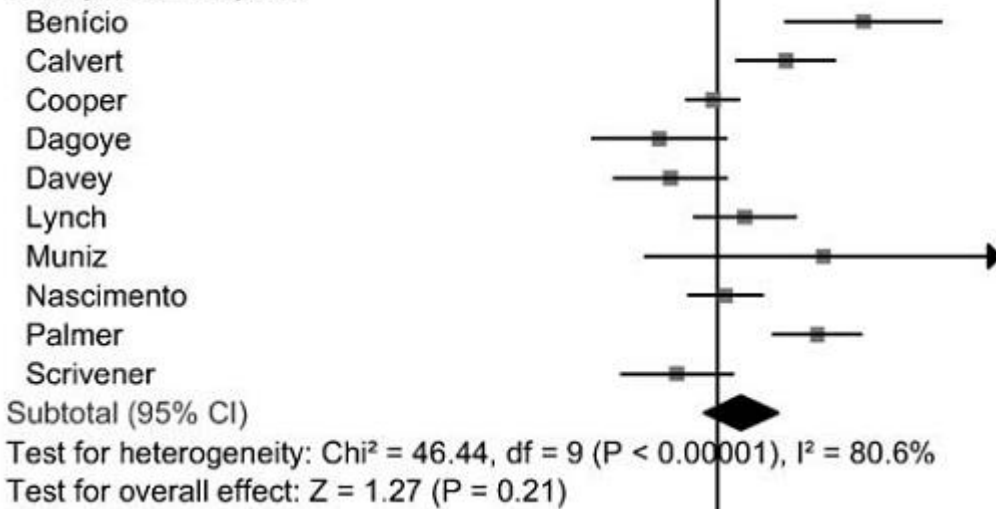
H. Influenzae and RV



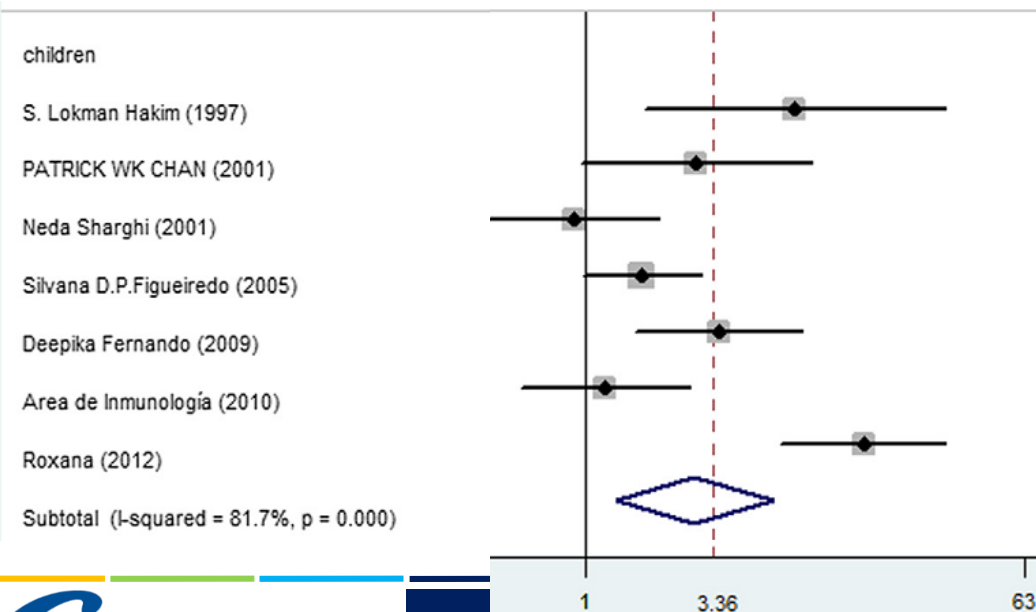
Odds Ratio for Exacerbation

Any current intestinal parasite infection and asthma

02 Adjusted analyses



Toxocariasis seropositivity in asthma

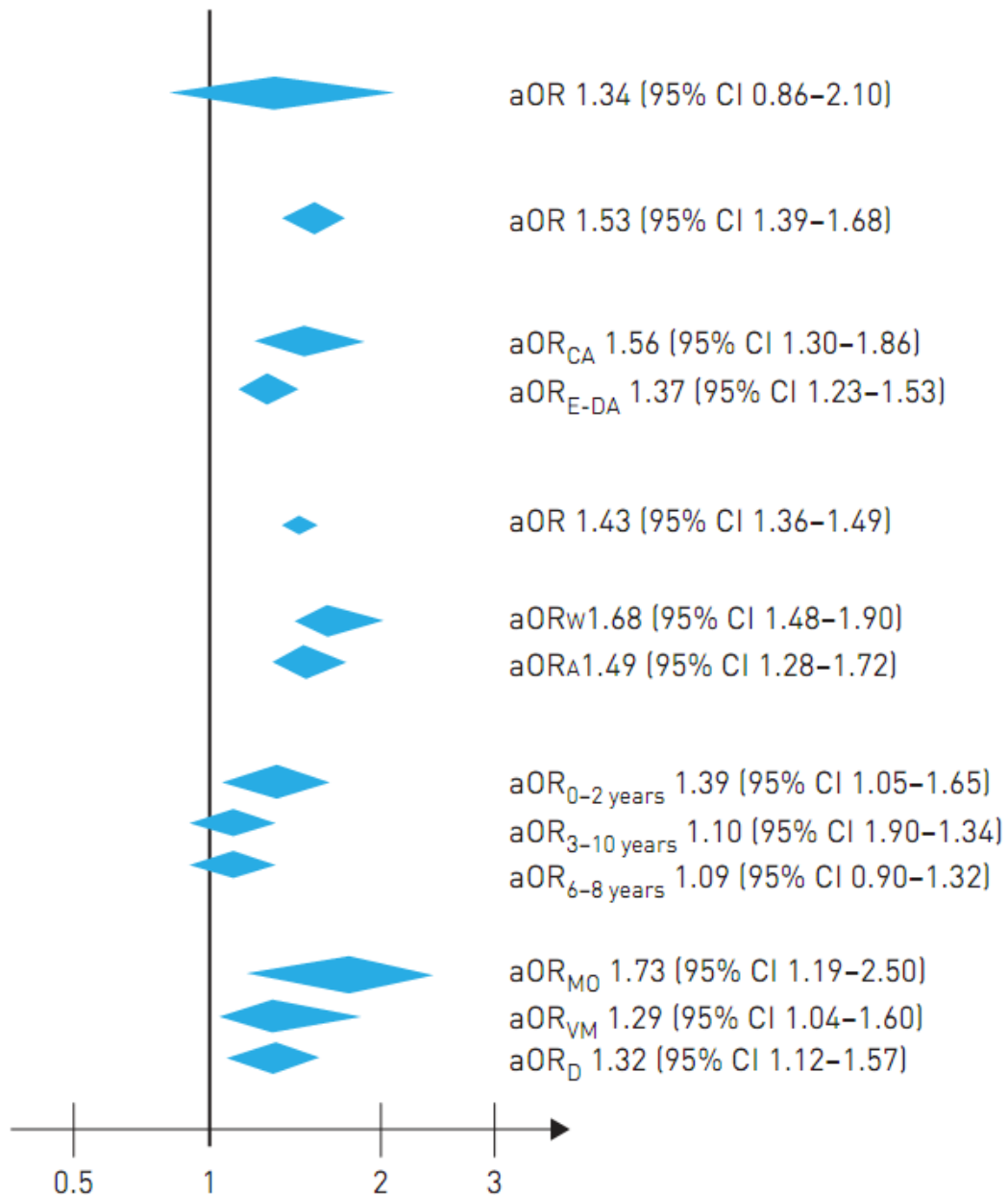


Association of asthma with *Ascaris Lumbricoides* and SPT to aeroallergen

Model	Explanatory Variables	OR (95% CI)	p Value
1*	Positive history or examination for <i>A. lumbricoides</i>	1.71 (1.26 – 2.31)	0.001
2*	Positive history or examination for <i>A. lumbricoides</i>	1.63 (1.19 – 2.22)	0.002
	Number of positive skin tests	1.11 (1.02 – 1.20)	0.01

Prevalence of recent wheezing and asthma according to putative risk factors

Putative risk factor	No. of subjects ^a	Wheezing in the past 12 months and asthma	OR (95% CI)
Exposure to helminths			
Current infection with intestinal helminths			
Yes	24	16.7%	2.42 (0.57–7.75)
No	473	7.6%	1.00
Positive serology for <i>Toxocara</i>			
Yes	104	18.4%	2.39 (1.17–4.85) ^h
No	379	7.1%	1.00



FISK, 2007 [15]
Asthma development (4 studies)
Indoor dampness or mould

FISK, 2007 [15]
Wheeze in children (17 studies)
Indoor dampness or mould

FISK, 2007 [15]
CA (10 studies); E-DA (8 studies)
Indoor dampness or mould

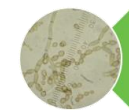
ANTOVA, 2008 [5]
Wheeze in children (12 studies)
Indoor dampness and/or mould

TISCHER, 2011 [7]
Asthma in children (21 studies)
Wheeze in children (19 studies)
Visible mould

TISCHER, 2011 [8]
Asthma development: birth cohorts 0–2 years old (4 studies); 3–10 years old (6 studies); 6–8 years old (6 studies)
Visible mould

QUANSAH, 2012 [9]
Asthma development
MO (8 studies); VM (12 studies); D (9 studies)

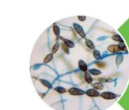
Common Indoor Molds



Cladosporium



Penicillium

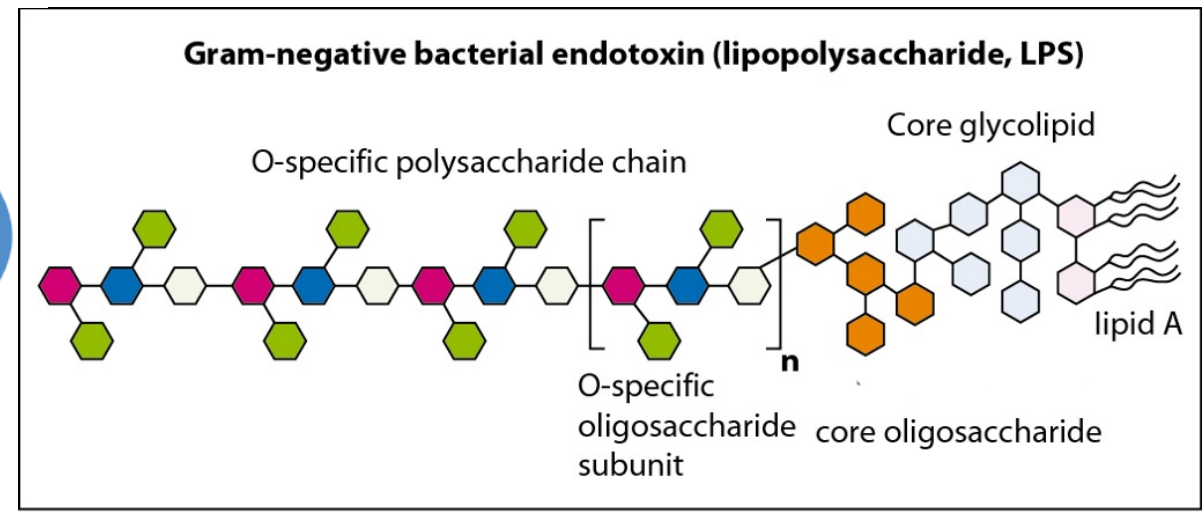
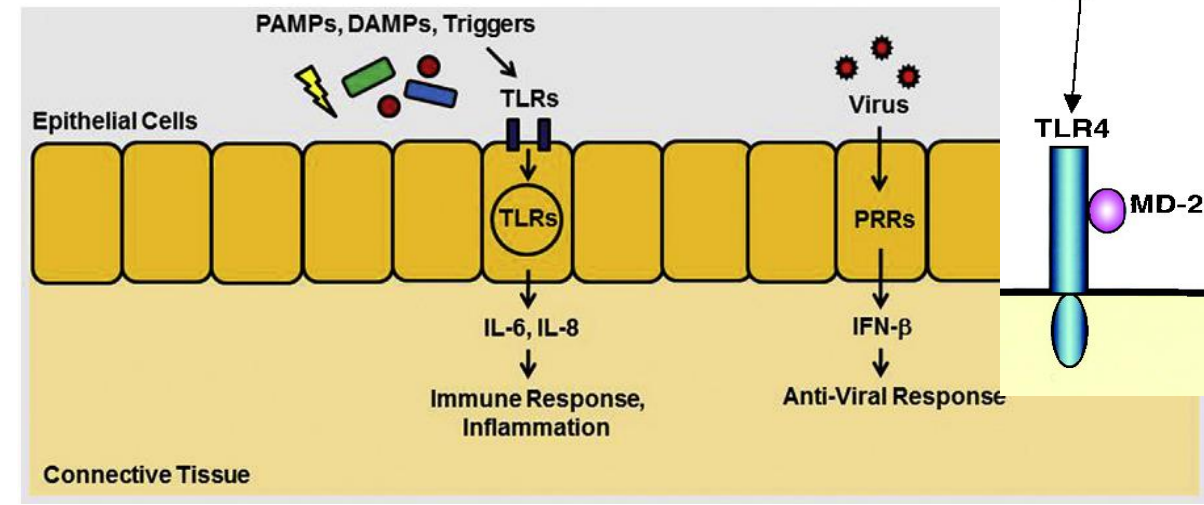
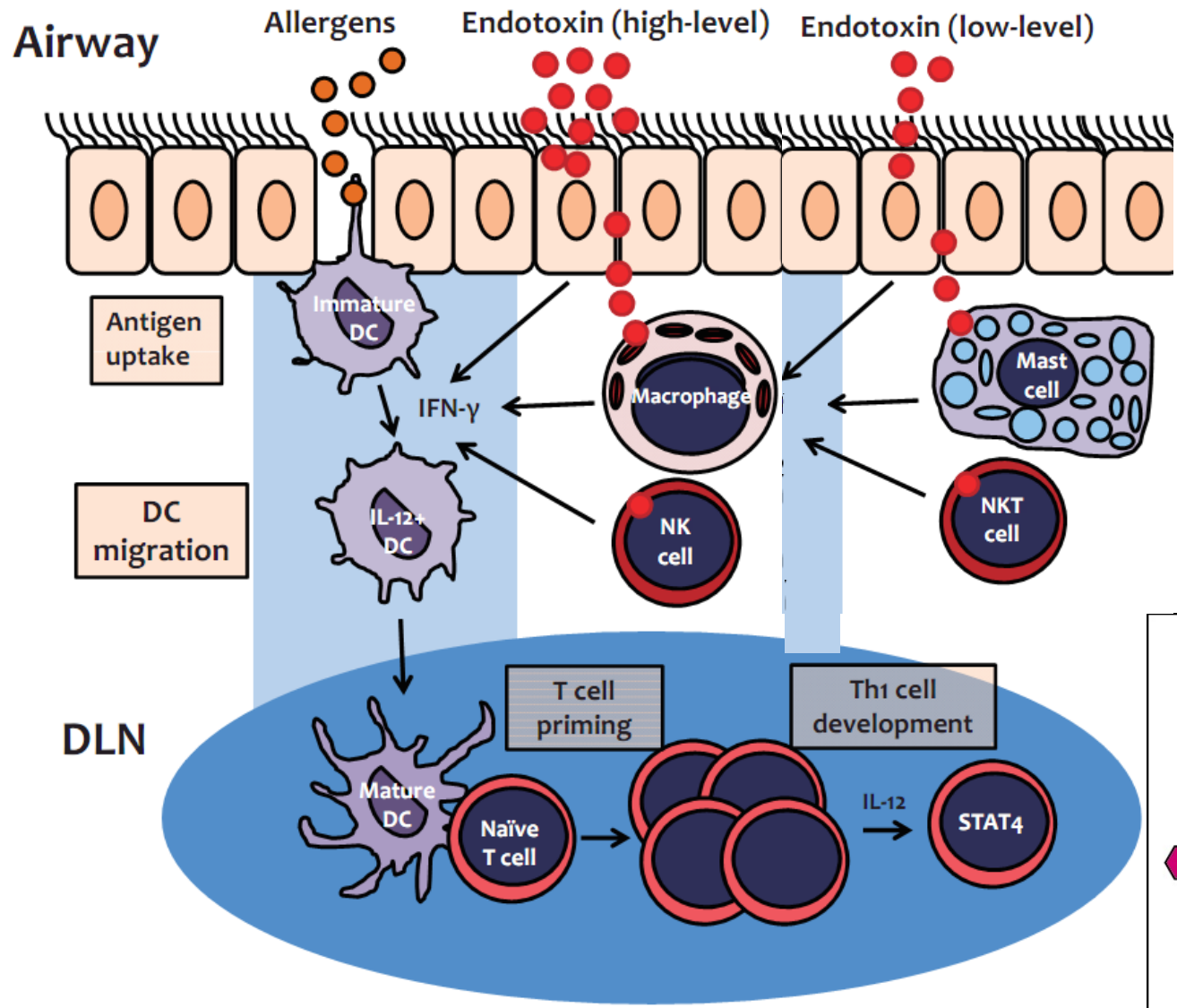


Alternaria



Aspergillus

Endotoxin



Effect of endotoxin level on the risk of asthma

	DD asthma	
	cOR (95% CI)	aOR (95% CI)
Endotoxin	N = 525	N = 477
Medium	0.54 (0.32-0.92)*	0.47 (0.26-0.86)*
High	0.43 (0.24-0.77)†	0.40 (0.21-0.77)†

VS

Endotoxin exposure

	1st quartile (57–1028 EU/g)	4th quartile (7752–1 286 179 EU/g)	P for trend
Infants with parental atopy			
Repeated wheeze*	17% (50)	27% (73)	0.008
	1.00	1.77 (1.14–2.73)	0.025
Repeated wheeze†	16% (80)	22% (108)	0.040
	1.00	1.52 (1.08–2.14)	0.031

Effect of endotoxin level on the risk of asthma

HEALTH OUTCOME	EXPOSURE TO FARMING DURING THE FIRST YEAR†	CURRENT ENDOTOXIN EXPOSURE‡
	odds ratio (95% CI)	
Hay fever	0.26 (0.13–0.52)§	0.61 (0.40–0.95)§
Sneezing and itchy eyes after 1 yr of age	0.55 (0.31–0.97)§	0.53 (0.36–0.77)§
Atopic sensitization¶	0.45 (0.30–0.68)§	0.83 (0.63–1.09)
Atopic asthma	0.42 (0.18–0.96)§	0.52 (0.30–0.90)§

VS

TABLE IV. Endotoxin exposure at age 2 to 3 months and wheezing between ages 1 and 7 years

	Wheezing between ages 1 and 7 years Hazard ratio, 95% CI, P value		
	All children†‡	Atopy or atopic diseases at age 7 years*	
		Yes†§	No†
Each quartile increment in endotoxin levels (EU/mg)	1.23 (1.07-1.43), .004	1.23 (1.02-1.49), .03	1.23 (1.0-1.51), .05

Hygiene habits and conceptions

이재열 경북대학교 미생물학과 교수

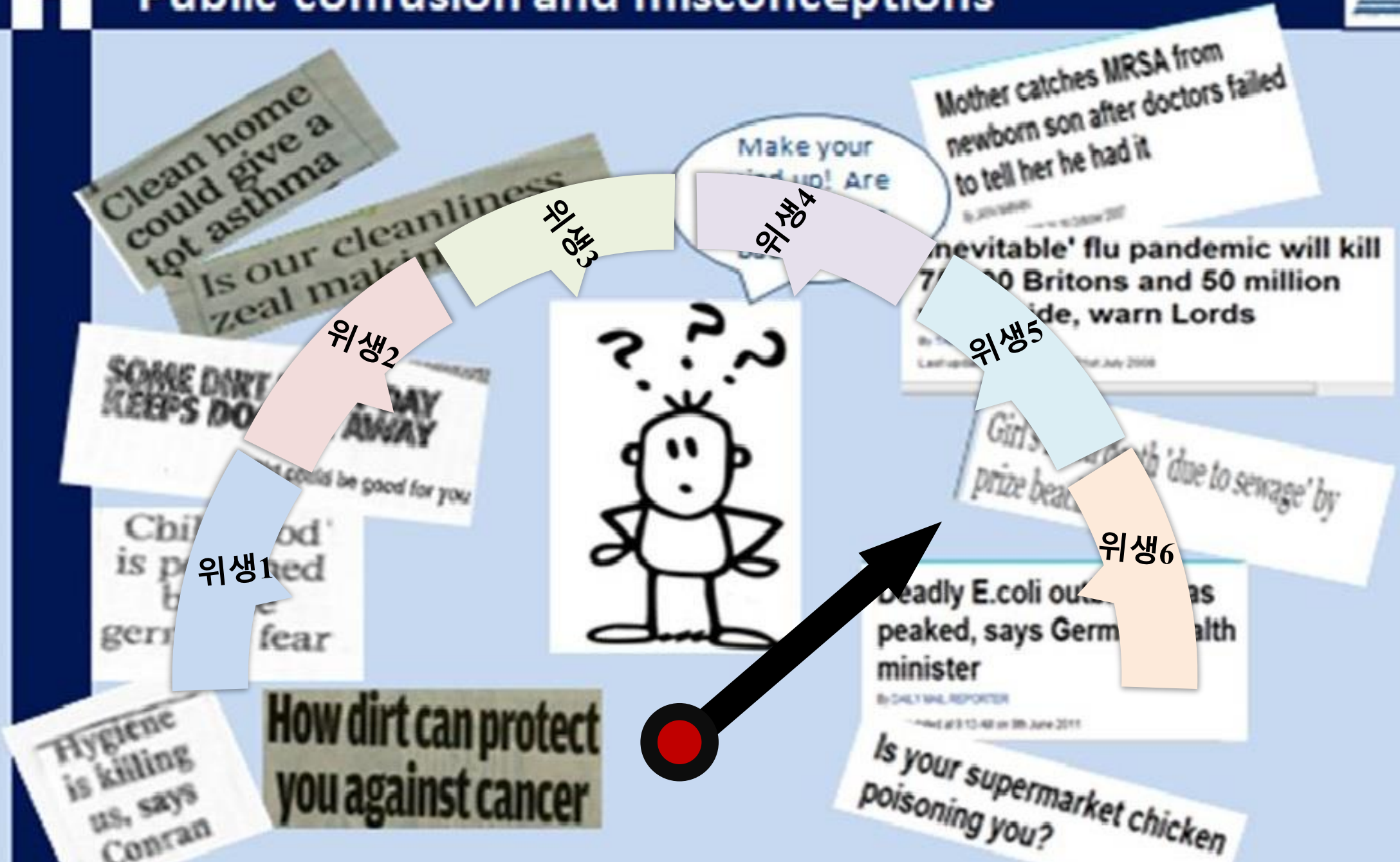
모든 부모는 아이를 깨끗하고 청결한 환경,
무균적인 상태에서 기르고 싶어 합니다



이현주 주부

사람들이 청결하게 지내는 것과 무균 상태로
지내는 것이 같다고 혼동해요

Public confusion and misconceptions



Cleanliness vs Dirtiness

Asthma and the Hygiene Hypothesis Does Cleanliness Matter?

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¹Dr von Hauner Children's Hospital, Ludwig Maximilians University of Munich, Munich, Germany; ²Institute and Outpatient Clinic for Occupational, Social, and Environmental Medicine, University Hospital of Munich, Munich, Germany; ³Member of the German Center for Lung Research (DZL), Germany; and ⁴Division of Structural Biochemistry, Research Center Borstel, Leibniz-Center for Medicine and Biological Sciences, Airway Research Center North, Borstel, Germany

Rationale: The early hygiene hypothesis explained the development of allergies by a lack of infections; nowadays, the aspect of excessive cleanliness in affluent populations seems to have replaced this concept. Yet, no investigation has shown that home or personal cleanliness relate to allergic diseases.

Objectives: To relate personal and home cleanliness to risk of asthma and allergies.

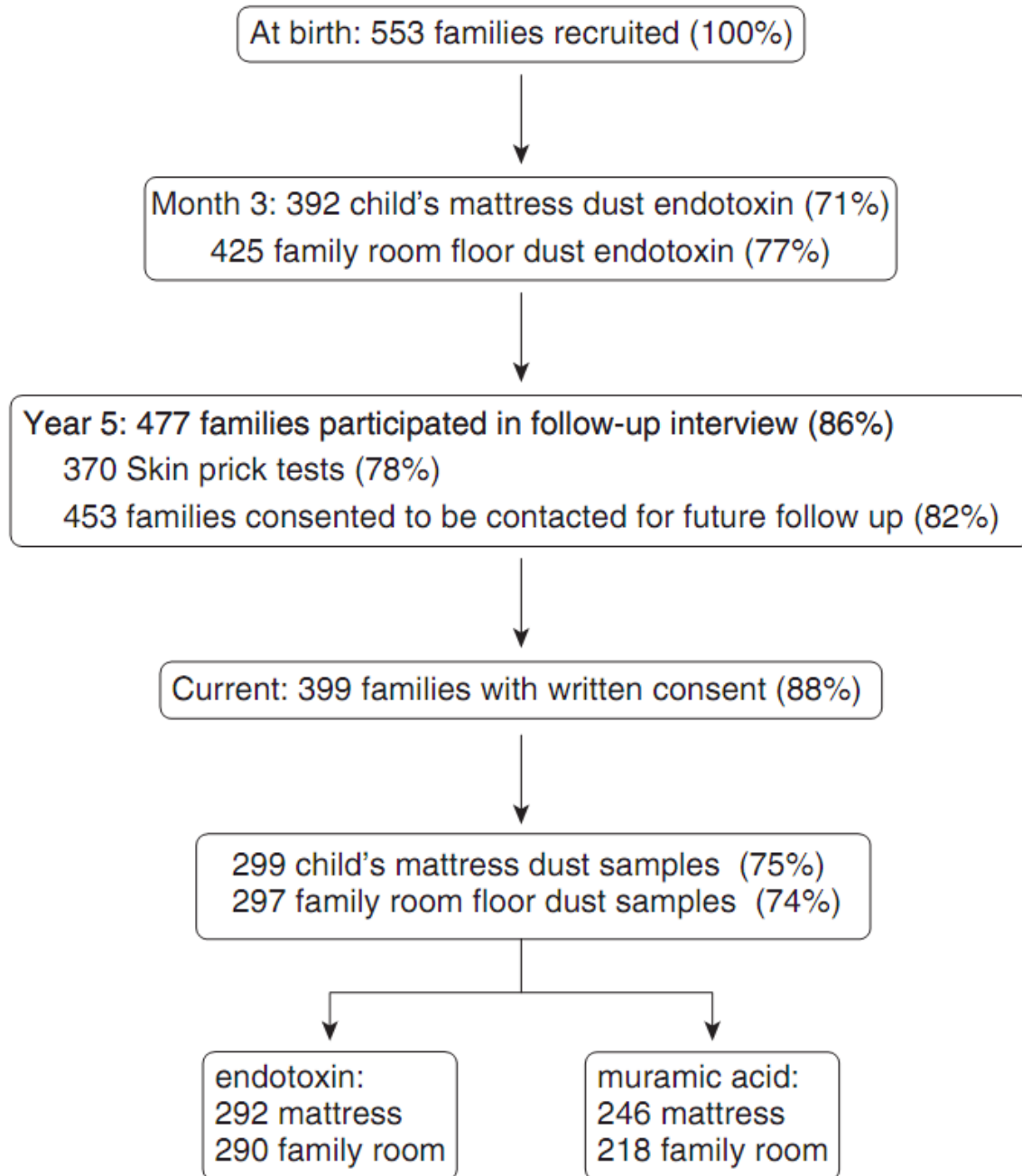


Table 1. List of Variables Related to Personal and Home Cleanliness and Home Characteristics

Home cleanliness
Frequency of
... cleaning the soother by boiling in the child's first year*
... sweeping, vacuuming, or wiping floors*
... wiping dust [†]
... dry cleaning or shampooing rugs [†]
... vacuuming mattresses [†]
... cleaning the toilet/kitchen/bathroom*
... cleaning windows*
... changing towels in kitchen, toilet, and bathroom*
... use of washing powder, liquid detergents for floors, liquid detergents for smooth surfaces, bleach, ammoniac, decalcifier, organic solvents, toilet cleaner [†]
Habit of
... taking off shoes before entering the home*
... sharing towels in kitchen, toilet, and bathroom [†]
Child's personal cleanliness
Frequency of
... washing hands after playing outdoors/before meals/after using the toilet/with soap*
... cutting fingernails/toenails [†]
... taking a bath, taking a shower [†]
... washing hair with shampoo*
... changing toothbrush [†]
... changing bed sheets*
... changing underwear*
... swimming in an indoor/outdoor or natural pool [†]
Habit of
... sleeping in clothes from the day*
... chewing finger nails (yes, no)
... washing feet before bedtime after walking with bare feet [†]
Home characteristics and lifestyle
Number of family members, children, visitors, smokers in the home
Level of child's room (first floor or lower, above first floor)
Level of family room (ground floor or lower, above ground floor)
Pets (which, how many, where, in bed?)
Guest animals [§] (yes/no)
Ventilation (five questions)
Indoor plants (yes/no)
Moisture damage, mold and damp spots, humidifier, fish tank (yes/no)
Garden, front yard (yes/no)
Compost container indoors/outdoors (yes/no)

Associations of floor dust (Lt) and mattress dust (Rt) parameters with lifestyle and home characteristics

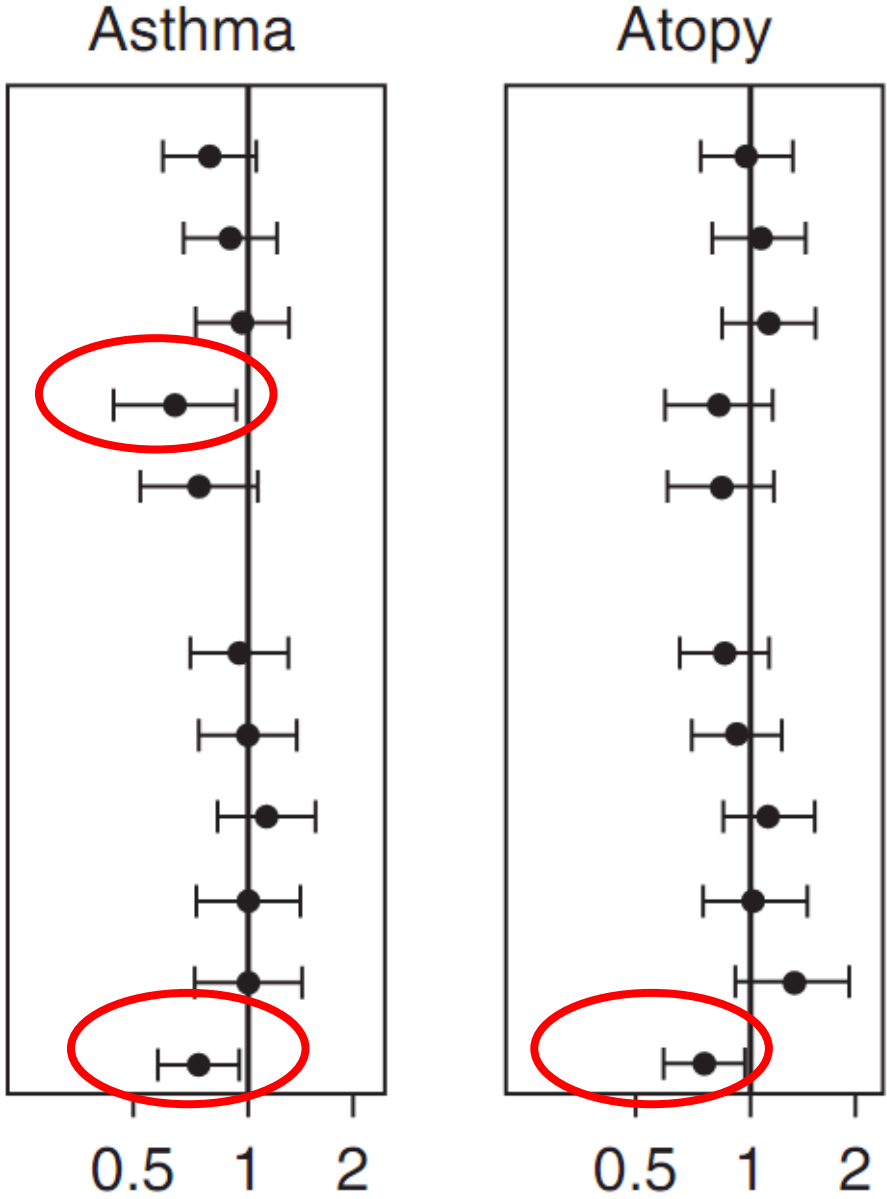
Variable	Endotoxin Load	
	β [95% CI]	<i>P</i> Value
Female sex	-0.180 [-0.409; 0.049]	0.12
Mother has university degree	0.191 [-0.038; 0.420]	0.10
More than two children in home	0.295 [0.012; 0.577]	0.04
More than four visitors/wk	0.282 [0.047; 0.518]	0.02
Pets	0.222 [-0.010; 0.455]	0.06
Guest animals*	0.274 [-0.015; 0.563]	0.06
House with garden [†]	0.292 [-0.064; 0.647]	0.11
Level of family room on ground floor or lower [†]	0.266 [0.001; 0.531]	0.05
Level of child's room on first floor or lower [†]	0.185 [-0.107; 0.476]	0.22

Variable	Endotoxin Load	
	β [95% CI]	<i>P</i> Value
Female sex	-0.074 [-0.303; 0.155]	0.53
Pets	0.299 [0.070; 0.527]	0.01
Guest animals*	0.044 [-0.244; 0.332]	0.76
Dust sampling in cold season [†]	-0.244 [-0.506; 0.017]	0.07
Using dryer to dry laundry [†]	-0.317 [-0.548; -0.086]	0.007
Mold spots in the home in the last 12 mo [†]	0.122 [-0.159; 0.404]	0.39

Associations of dust parameters with asthma and sensitization

Floor:
 Dust Weight
 Endotoxin Load
 Endotoxin Concentration
 Muramic Acid Load
 Muramic Acid Concentration

Mattress:
 Dust Weight
 Endotoxin Load
 Endotoxin Concentration
 Muramic Acid Load
 Muramic Acid Concentration
 Endotoxin concentration mo 3*



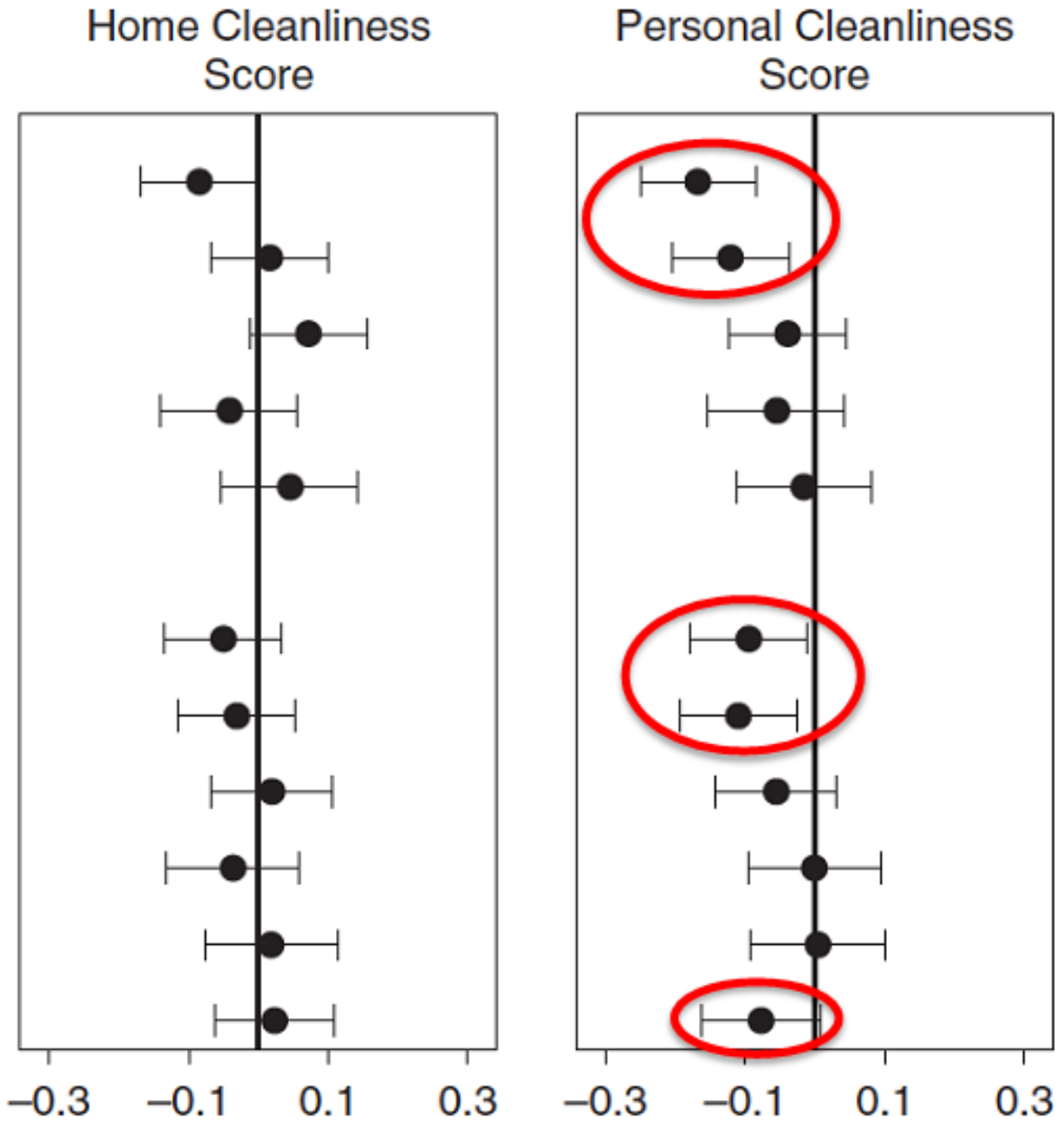
Associations of cleanliness scores with dust parameters

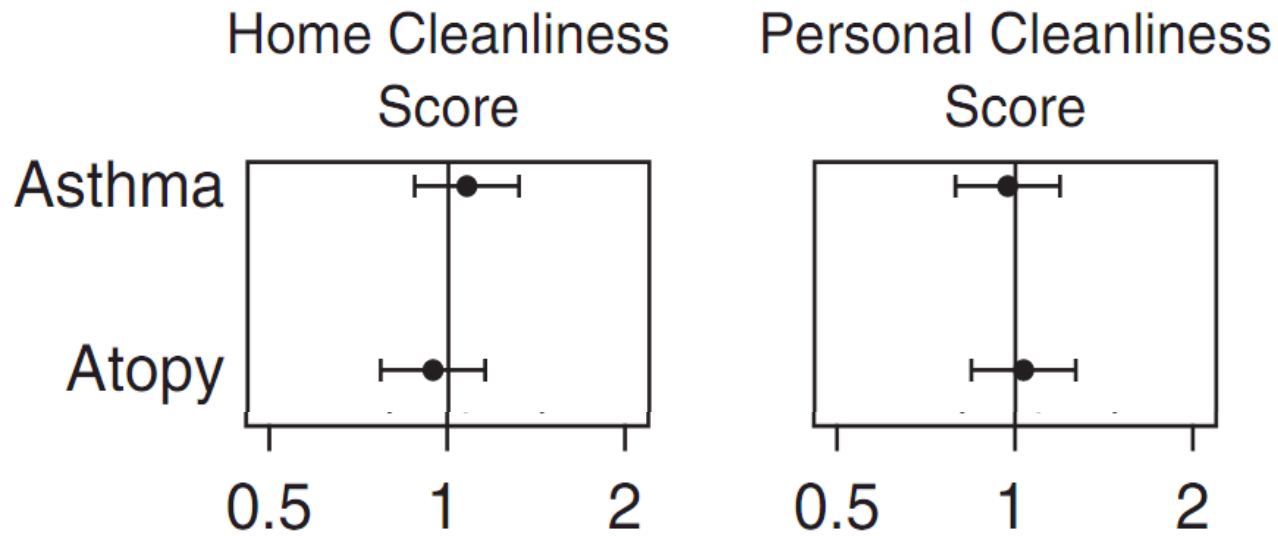
Floor:

- Dust Weight
- Endotoxin Load
- Endotoxin Concentration
- Muramic Acid Load
- Muramic Acid Concentration

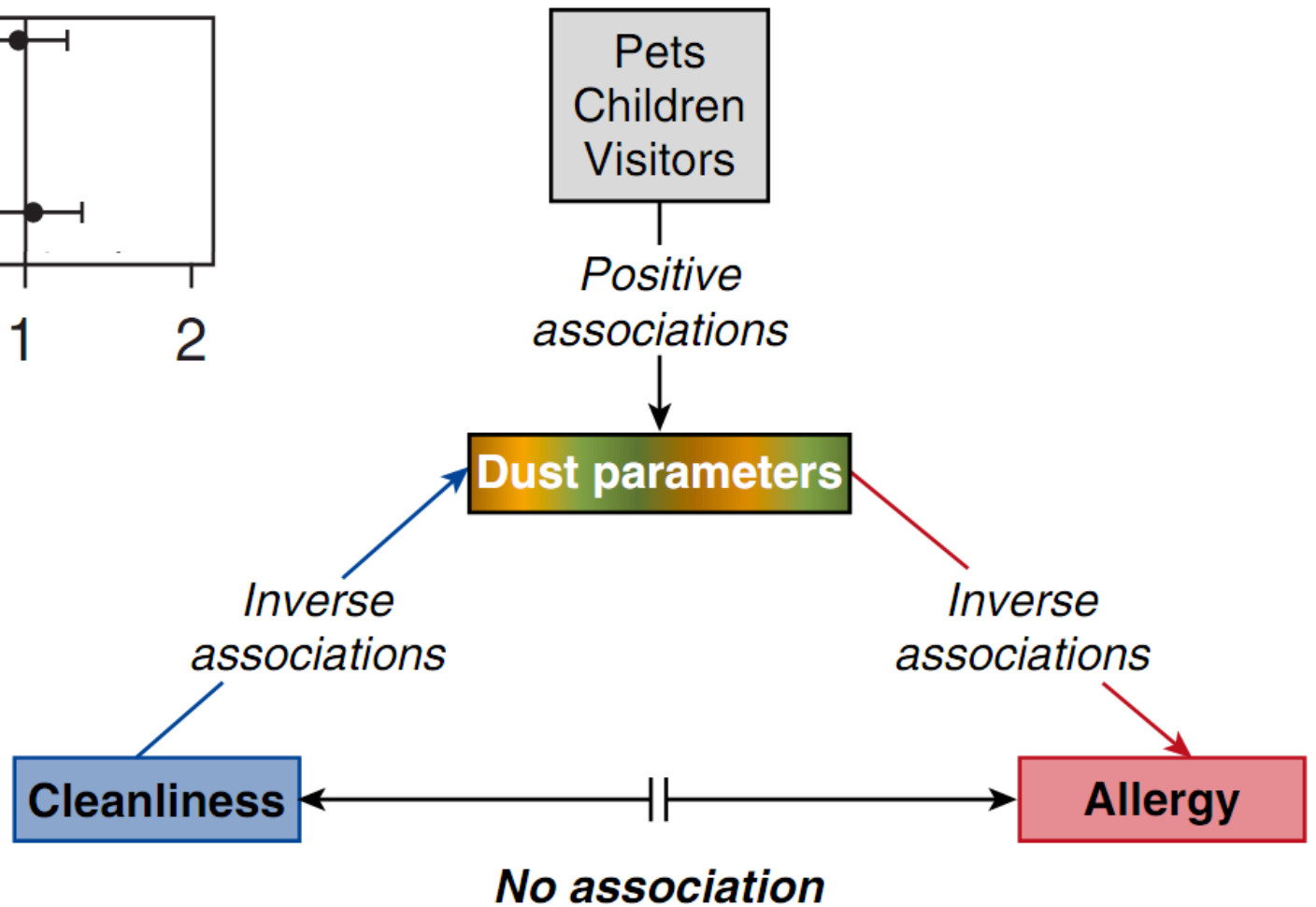
Mattress:

- Dust Weight
- Endotoxin Load
- Endotoxin Concentration
- Muramic Acid Load
- Muramic Acid Concentration
- Endotoxin concentration mo 3*



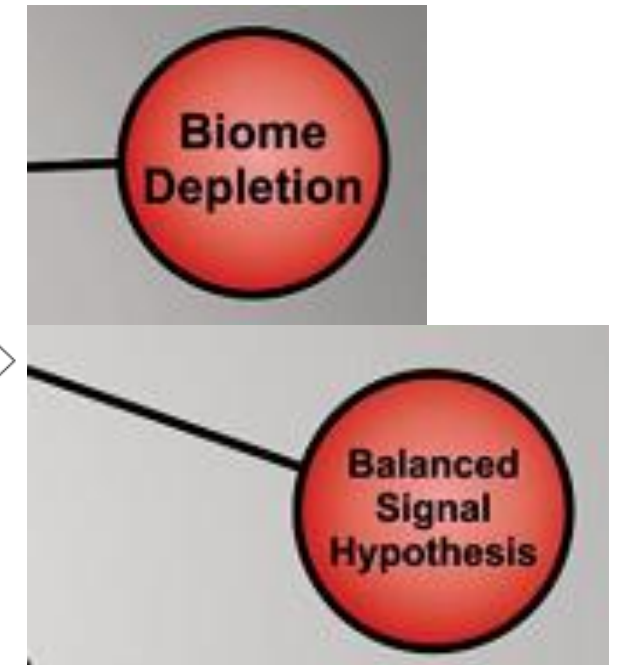
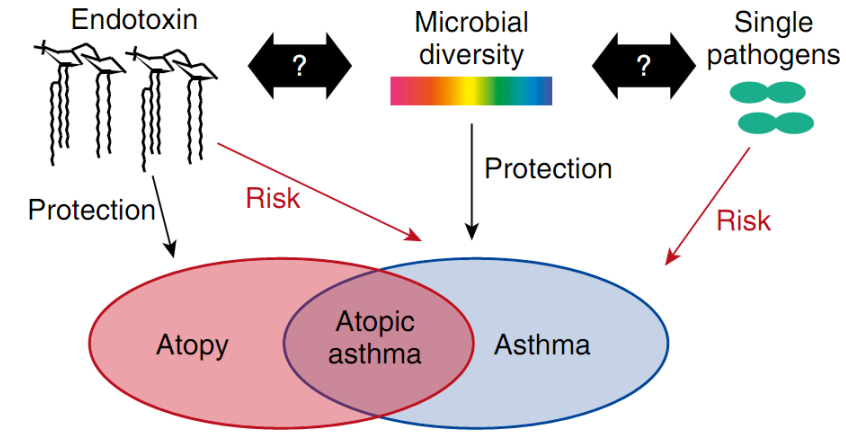
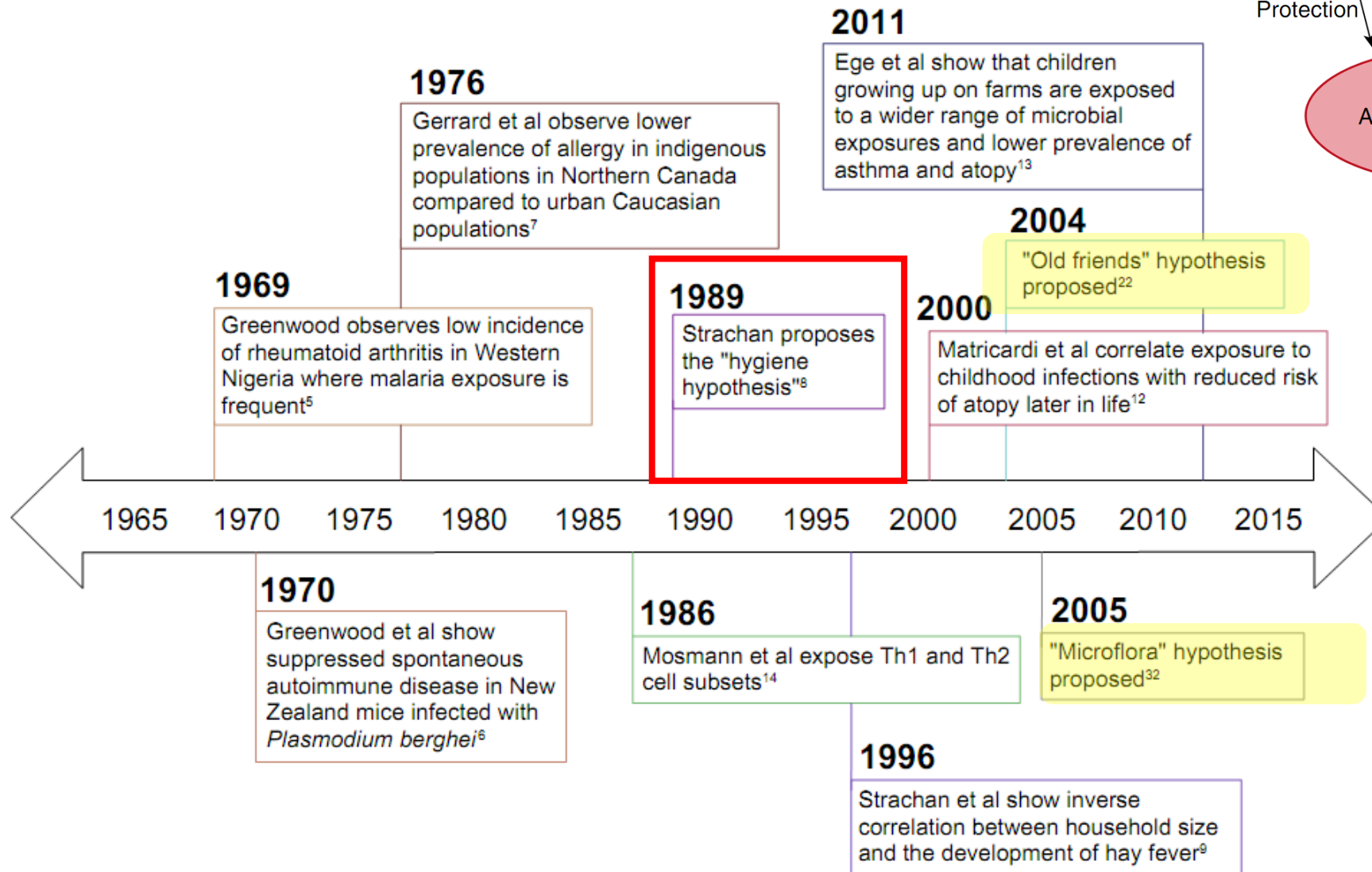


Taken together, the current results suggest that neither home nor personal cleanliness impact on the development of asthma and allergies, although cleanliness was substantiated by objective, but rather unspecific



Others

Beyond Hygiene Hypothesis



Children are not miniature adults, how about the adults?



Hygiene Hypothesis in Asthma, Con



01

Some evidences shows that the hygiene hypothesis can not be applied to all these geographic-distinct populations



02

Specific microorganisms have been considerably associated with asthma



03

Obsessive hygiene and cleanliness is root cause of the rise in asthma is no longer supported



04

Beyond hygiene hypothesis, different microbial exposure and diversity can prove to be an instructive concept for understanding asthma

Thank you for your attention

