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INFECTIOUS AGENTS AND NON-COMMUNICABLE DISEASES

Jeroen Douwes

CENTRE FOR PUBLIC HEALTH RESEARCH

INFECTIOUS AGENTS AND NON-COMMUNICABLE DISEASES

Infectious agents and Cancer – Risk factor?

Microbial agents and asthma – Protective?

PATHOGENS AND CANCER

IARC Group 1 carcinogens

- Aflatoxin
- Epstein-Barr virus
- Helicobacter pylori
- Hepatitis B virus
- Hepatitis C virus
- Human immunodeficiency virus type 1
- Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66
- Human T-cell lymphotropic virus type I
- Opisthorchis viverrini
- Schistosoma haematobium

IARC Group 2A carcinogens

- Clonorchis sinensis
- Kaposi's sarcoma herpesvirus/human herpesvirus 8

IARC Group 2B carcinogens

- Ochratoxin B

PATHOGENS AND CANCER

Cervical cancer – HPV

Stomach cancer – Helicobacter Pylori

Liver cancer - Aflatoxins

SITE SPECIFIC CANCERS IN AGRICULTURAL WORKERS

Decreased risk

- Lung
- Bladder
- Nasal
- Colon
- Rectum
- Liver

Increased risk

- Hodgkin's Disease
- Non-Hodgkin's lymphoma
- Multiple myeloma
- Leukemia
- Stomach
- Lip
- Brain
- Prostate
- Connective tissue

POSSIBLE EXPLANATIONS FOR INCREASED CANCER RISKS IN AGRICULTURAL WORKERS

- Herbicides
- Phenoxy herbicides (2,4,5-T; 2,4-D)
- Insecticides
- Organochlorines
- Organophosphates
- Other agricultural chemicals
- Arsenic
- Zoonotic viruses/bacteria

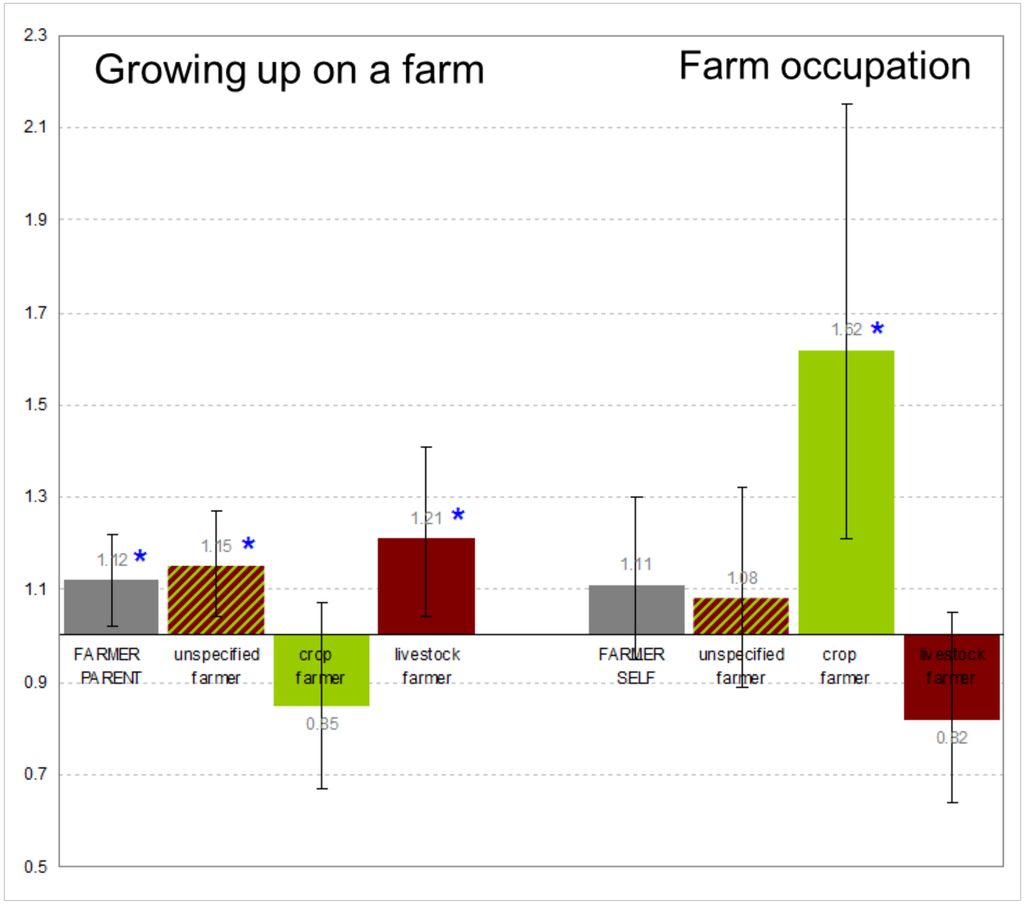
FARMING AND HAEMATOLOGICAL CANCER

Original article

PRESS RELEASE

Farming, growing up on a farm, and haematological cancer mortality

Andrea 't Mannetje,[1] Amanda Eng,[1] Neil Pearce[1,2]



- In New Zealand, working as a crop farmer is a risk factor for hematologic cancer
- Growing up on a farm may be an independent risk factor for hematologic cancer, with the strongest effect observed for growing up on an animal farm
- Zoonotic diseases?

MEAT WORKERS AND LUNG CANCER

Dave McLean

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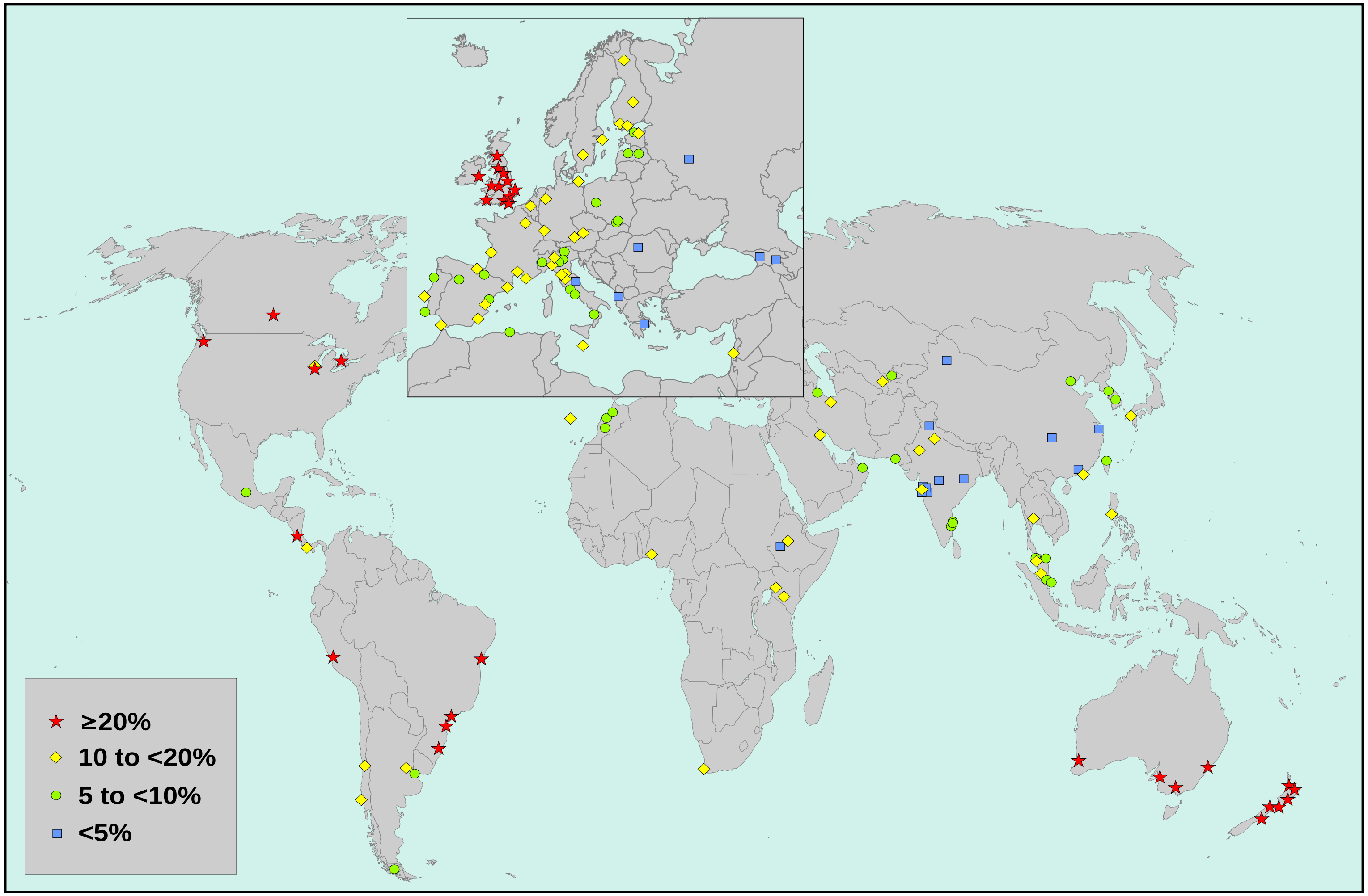
INFECTIOUS AGENTS AND NON-COMMUNICABLE DISEASES

Infectious agents and Cancer – Risk factor?

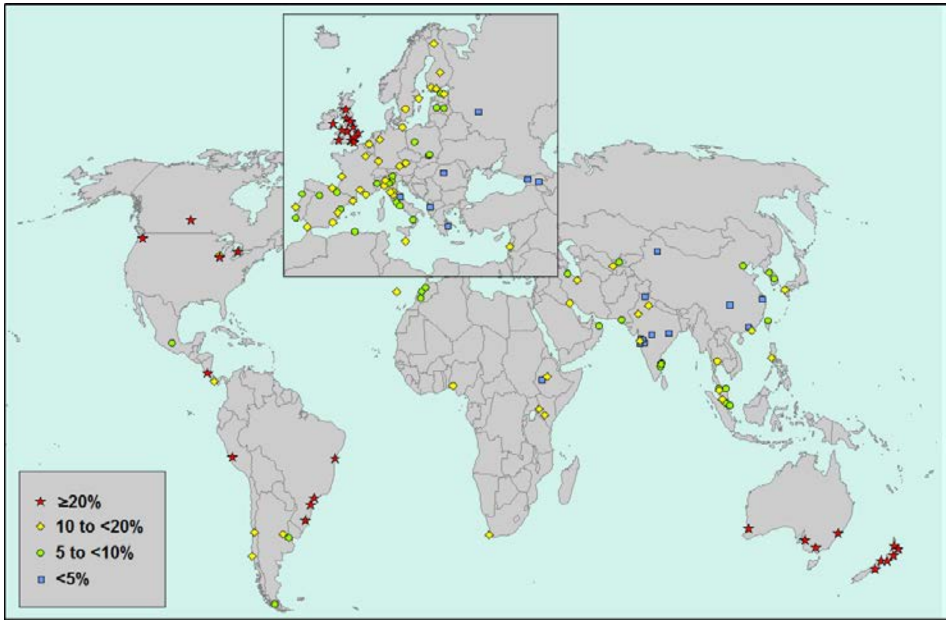
Microbial agents and asthma – Protective?

ASTHMA PREVALENCE – A GLOBAL PICTURE



WHAT IS "WESTERN LIFESTYLE"?

- Greater allergen exposure?
- More Air pollution?
- "Cleaner" environment?
- Move from rural to urban living?



"ESTABLISHED" ASTHMA RISK FACTORS DO NOT EXPLAIN THE INTERNATIONAL PATTERNS

- House dust mite allergen
- Other indoor allergens
- Parental smoking
- Diet
- Air pollution
- Occupational exposures
- Genetic factors

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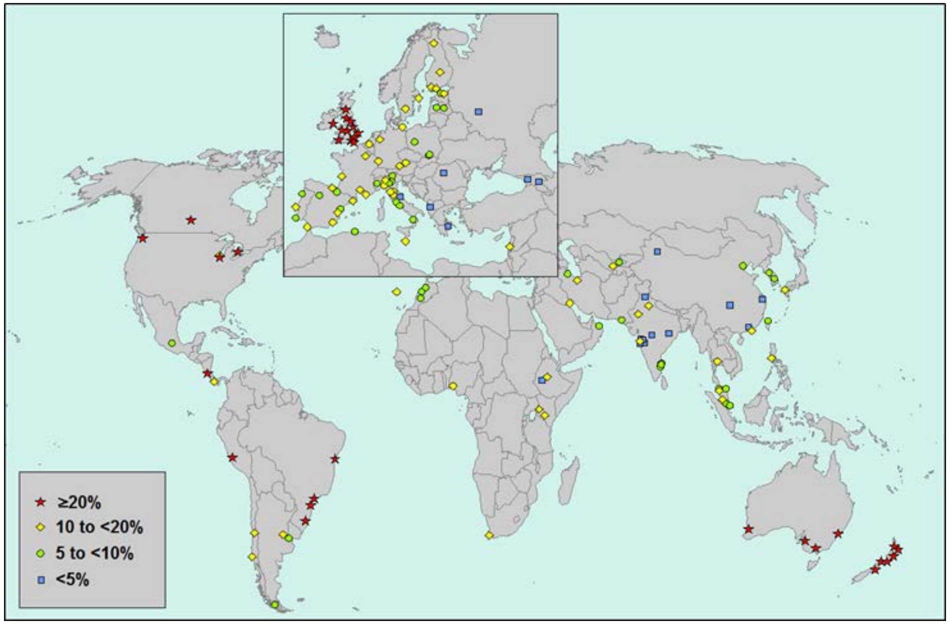
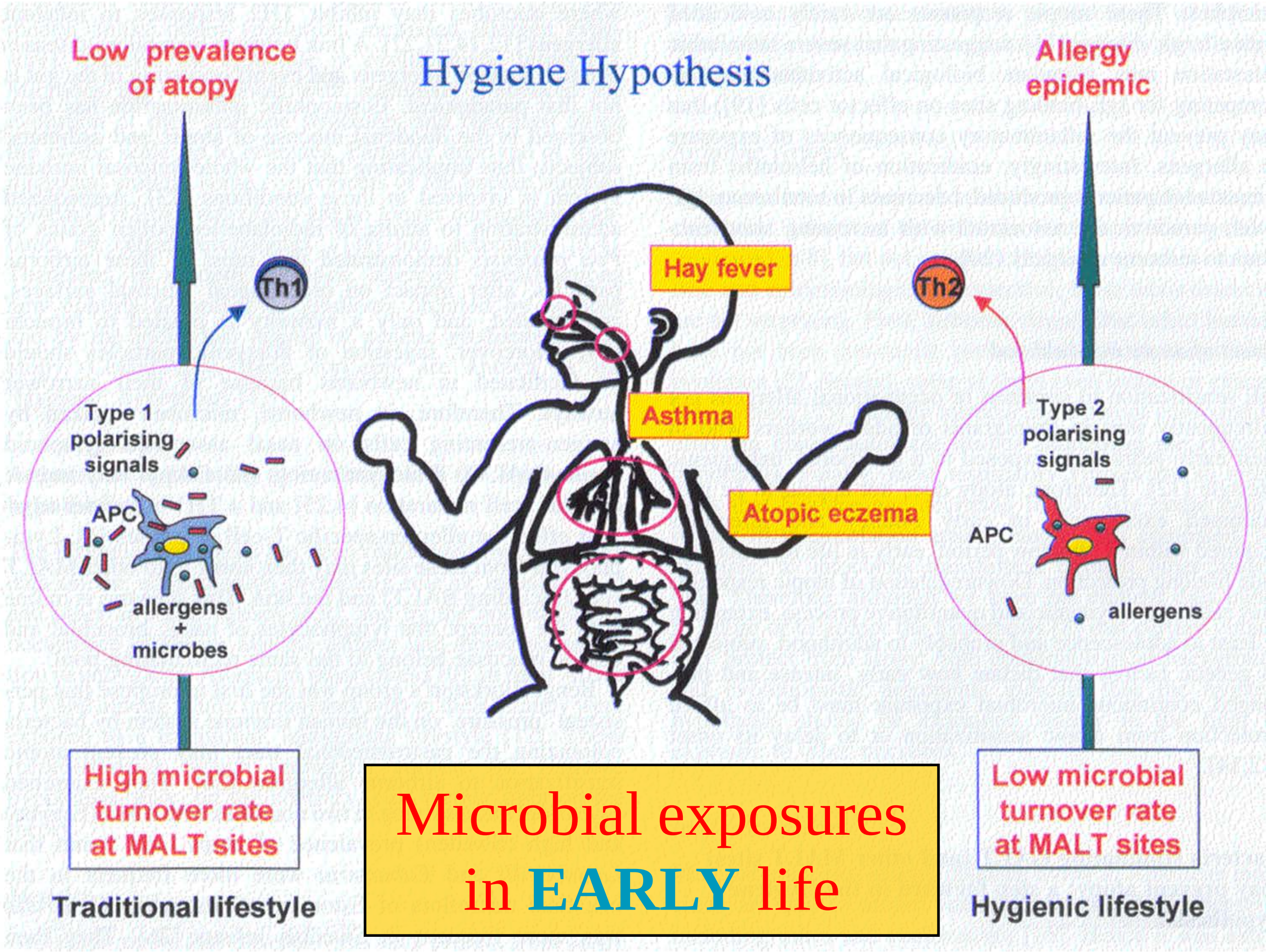


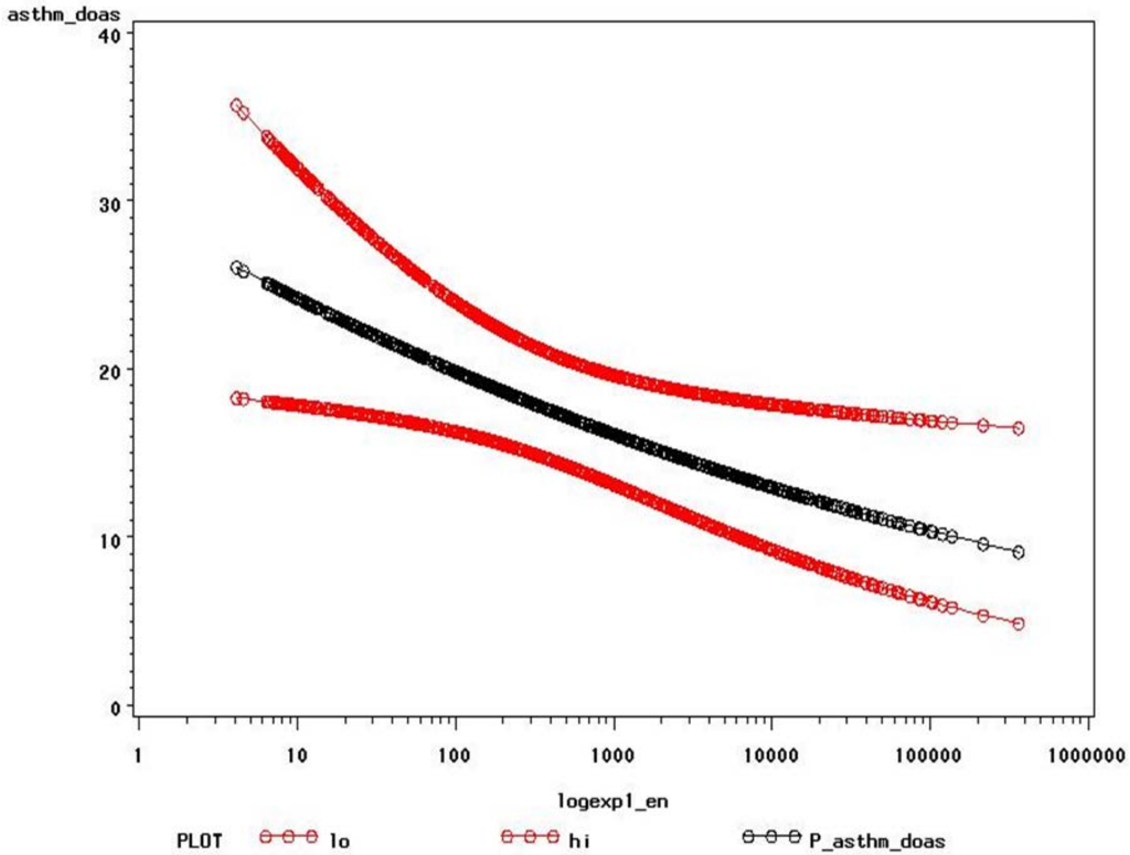
THE HYGIENE HYPOTHESIS

- Western populations may have lost the previous protective effect of infant infections
- Decreased family size increases risk of atopy and asthma
- Some evidence that infections in infancy reduce the risk of asthma and atopy
- Some evidence that non-infectious agents may also be protective



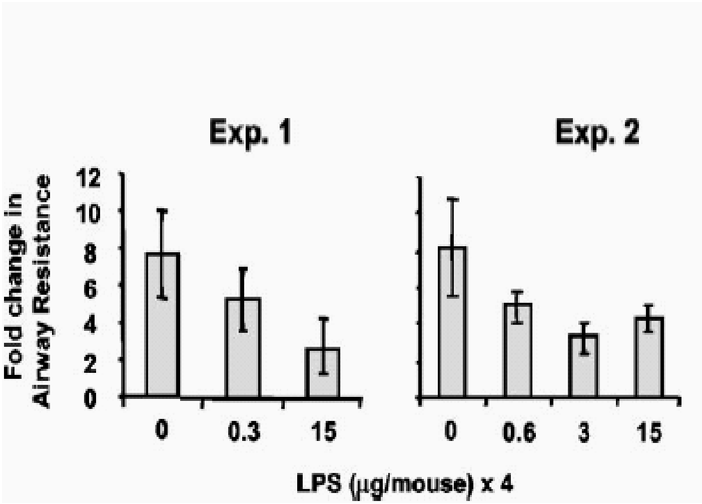
ENDOTOXIN EXPOSURE AT 12 MONTHS AND DOCTOR'S DIAGNOSED ASTHMA AT 48 MONTHS

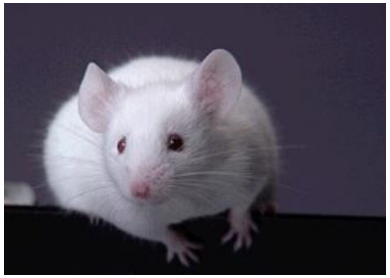
- Douwes et al., JACI 2006

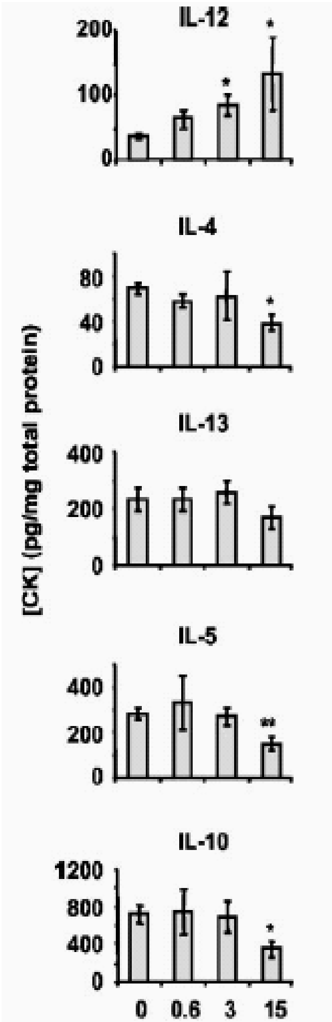


Log endotoxin concentration

ENDOTOXIN IN PRE-SENSITISED PRE-CHALLENDED MICE SUPRESSES AHR AND AIRWAY EOSINOPHILIA AND TH2 CYTOKINES (LUNDY ET AL., 2003)







	Bronchoalveolar lavage			
Group	Total leukocytes (cells/HPF)	PMN (%)	Eosinophils (%)	Lymphs (%)
Exp. 1				
No LPS	15.5 ± 2.5	48.8 ± 4.8	4.3 ± 1.5	2.4 ± 0.4
LPS, 0.3 µg	21.1 ± 2.0§	70.2 ± 6.0§	6.3 ± 2.4	1.4 ± 0.6
LPS, 15 µg	47.1 ± 3.1§	81.2 ± 0.4§	0.0 ± 0.0§	0.9 ± 0.1§

Exposure to Environmental Microorganisms and Childhood Asthma

Markus J. Ege, M.D., Melanie Mayer, Ph.D., Anne-Cécile Normand, Ph.D., Jon Genuneit, M.D., William O.C.M. Cookson, M.D., D.Phil., Charlotte Braun-Fahrländer, M.D., Dick Heederik, Ph.D., Renaud Piarroux, M.D., Ph.D., and Erika von Mutius, M.D., for the GABRIELA Transregio 22 Study Group

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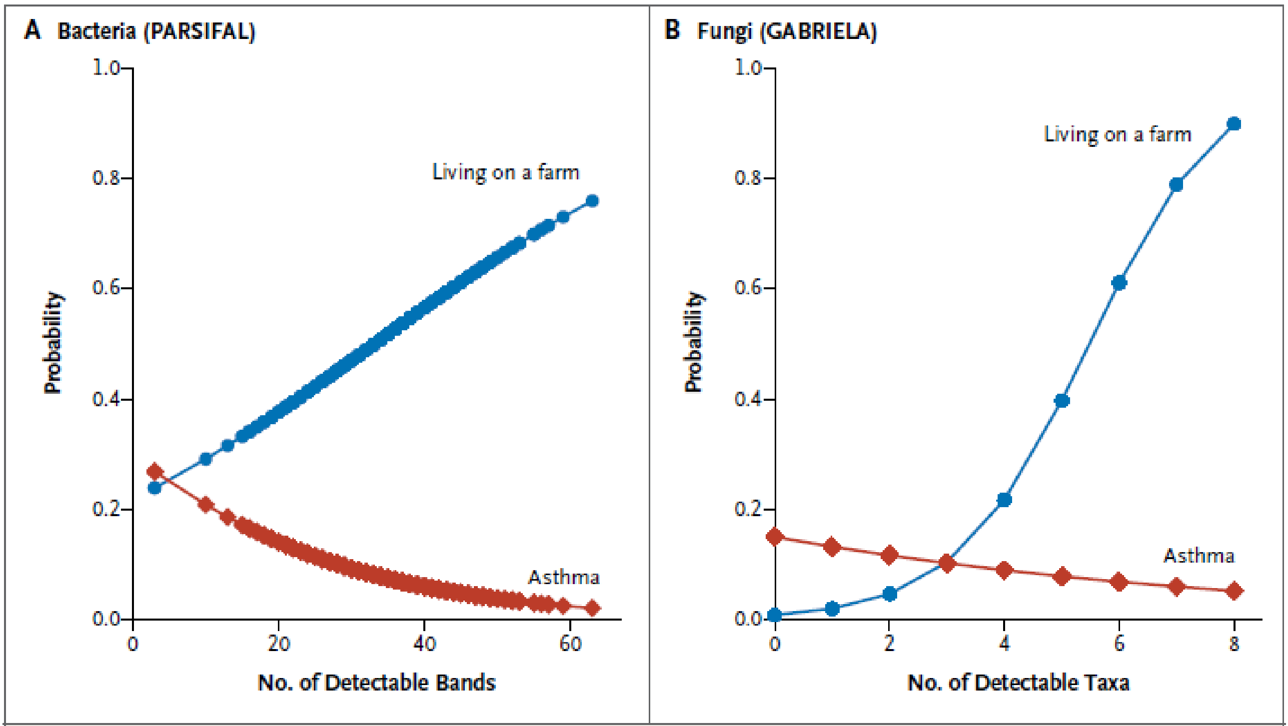


Figure 3. Relationship between Microbial Exposure and the Probability of Asthma.
In both the PARSIFAL study and GABRIELA, the range of microbial exposure was inversely associated with the probability of asthma.

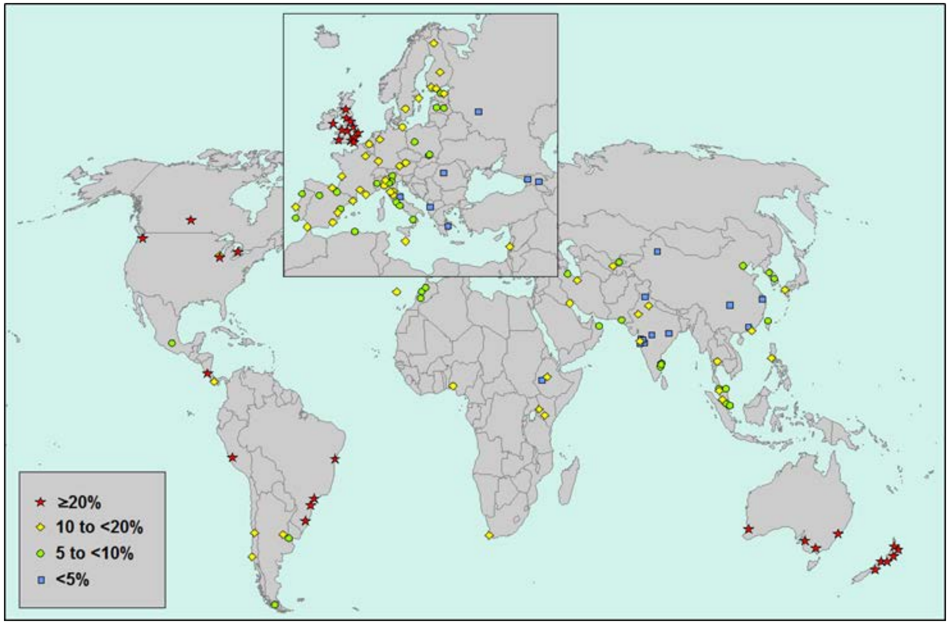
Table 2. Associations of Asthma and Atopy with Measures of Microbial Diversity and with Specific Microbial Exposures.

Microbial Exposure	Unadjusted Odds Ratio (95% CI)	P Value	Odds Ratio Adjusted for Living on a Farm (95% CI)	P Value	Mutually Adjusted Odds Ratio (95% CI)*	P Value
Asthma						
PARSIFAL						
Diversity score†	0.62 (0.44–0.89)	0.01	0.65 (0.45–0.94)	0.02	0.83 (0.55–1.24)	0.36
Factor 4‡	—		0.62 (0.42–0.91)	0.01	0.67 (0.44–1.01)	0.06
Factor 5‡	—		0.53 (0.35–0.81)	0.003§	0.57 (0.38–0.86)	0.007
GABRIELA						
Diversity score¶	0.86 (0.75–0.99)	0.04	0.87 (0.73–1.03)	0.09	1.01 (0.86–1.19)	0.93
Eurotium species	—		0.37 (0.19–0.71)	0.003§	0.37 (0.18–0.76)	0.007
Penicillium species	—		0.56 (0.32–0.99)	0.04	0.57 (0.31–1.05)	0.07
Atopy						
PARSIFAL						
Diversity score†	0.79 (0.60–1.04)	0.09	0.86 (0.65–1.15)	0.309	—	
GABRIELA						
Diversity score¶	0.88 (0.77–1.01)	0.07	0.93 (0.79–1.11)	0.435	0.97 (0.81–1.15)	0.723
Gram-negative rods	—	—	0.45 (0.27–0.76)	0.003§	0.46 (0.27–0.78)	0.004

* Mutual adjustment means that all the exposure variables were entered into the same model for the analysis of asthma (the diversity score and factors 4 and 5 in the PARSIFAL study and the diversity score and eurotium and penicillium species in GABRIELA) and the analysis of atopy (the diversity score and gram-negative rods in GABRIELA).
† The odds ratios are for each increase of 10 bands.
‡ Factors 4 and 5 are from a factor analysis of band densities.
§ P<0.05 if Bonferroni's correction was applied. In the PARSIFAL study, 10 factors were tested simultaneously; in GABRIELA, 15 independent taxa were tested simultaneously.
¶ The odds ratios are for each increase of one taxon.

WHAT IS "WESTERN LIFESTYLE"?

- Greater allergen exposure? - No
- More Air pollution? - No
- "Cleaner" environment? Maybe
- Move from rural to urban living?



Nature Reviews Immunology | AOP, published online 9 November 2010; doi:10.1038/nri2871

Table 1 | **Studies primarily investigating the effect of childhood farm exposures**

Country	Age	Asthma	Wheeze	Hay fever diagnosis	Hay fever symptoms	Atopic dermatitis	Atopic sensitization	AHR	Refs
Europe									
Switzerland	6–15	↓	⇓	↓	⇓	↓	⇓	–	5
Finland	18–24	↓	–	⇓	–	–	–	–	59
Austria, Germany, the Netherlands, Sweden and Switzerland	5–13	⇓	⇓	⇓	⇓	↓	⇓	–	60
Southern Germany	5–7	↓	⇓	⇓	↓	↓	–	–	8
Sweden	7–8	⇓	–	–	⇓	↓	–	–	61
Austria	8–11	–	–	–	–	–	⇓	–	62
Austria	8–10	⇓	⇓	⇓	⇓	↔	⇓	–	6
Denmark	17–26	↓	↓	↓	–	–	⇓	⇓	63
The Netherlands	20–70	↓	–	⇓	–	–	–	–	64
Germany	18–44	↓	↓	⇓	–	–	⇓	↓	65
Finland	20–44	–	–	–	–	–	↓	–	66
UK	4–11	⇓	–	⇓	–	↓	↓	–	14
Northern Germany	18–44	⇓	–	⇓	–	↓	–	–	67
Eastern Finland	6–13	–	–	–	–	–	⇓	–	68
Sweden	17–20	⇓	–	⇓	–	↓	–	–	69
Austria, Germany and Switzerland	6–13	⇓	–	–	⇓	–	⇓	–	3
Tyrol, Austria	6–10	⇓	–	–	–	–	–	–	70
Gothenburg, Sweden	16–20	⇓	↑	–	–	–	–	–	71
West Gothia, Sweden	16–75	–	–	–	↓	–	–	–	72
Turku, Finland	18–25	⇓	–	–	–	–	–	↓	73
Belgium, France, the Netherlands, Sweden and New Zealand	20–44	↓	↓	–	⇓	–	⇓	–	74

PERSPECTIVES

Australasia									
Australia	7–12	↓ or ⇓	↓ or ⇓	↓	–	↓	–	–	75
New Zealand	7–10	↓	↓	↓	–	↓	↓	–	15
New Zealand	5–17	⇓	⇓	⇓	–	⇓	–	–	9
New Zealand	25–49	⇓	⇓	–	⇓	↓	–	–	24
North America									
Canada	0–11	⇓	–	–	–	–	–	–	76
British Columbia, Canada	8–20	⇓	↓	⇓	–	⇓	–	–	77
USA	20–88	⇓	–	–	–	–	–	–	78
Quebec, Canada	12–19	⇓	⇓	–	–	–	⇓	⇓	79
Wisconsin, USA	4–17	⇓	⇓	⇓	–	–	–	–	80
Iowa, USA	0–17	↓	↓	–	–	–	↓	↓	81
Iowa, USA	6–14	↓	↓	–	–	–	–	–	82

See Supplementary information S1 (table) for an extended version of this table. ↓, reduction in risk not reaching statistical significance; ⇓, reduction in risk reaching statistical significance; ↑, increase in risk not reaching statistical significance; ↔, no farm effect; –, not determined; AHR, airway hyperresponsiveness.

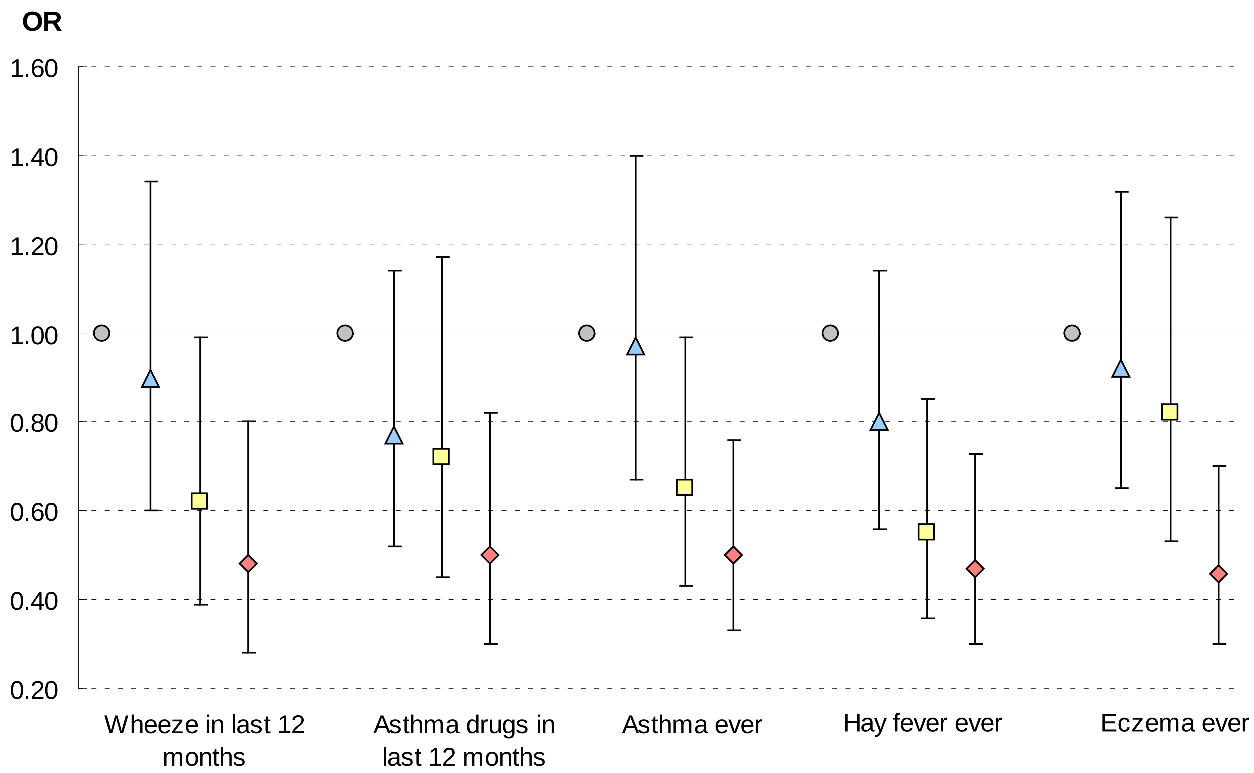
HAY-FEVER AN ARISTOCRATIC DISEASE?

- Blackley CH. Experimental researches on the causes and nature of Catarrhus aestivus.Ballière-Tindall & Cox, London, 1873.

- *“One very curious circumstance in connection with hay-fever is that the persons who are most subjected to the action of pollen belong to a class which furnishes the fewest cases of the disorder, namely, the farming class”*
- *“As civilisation and education advance, the disorder will become more common than it is at the present time”*

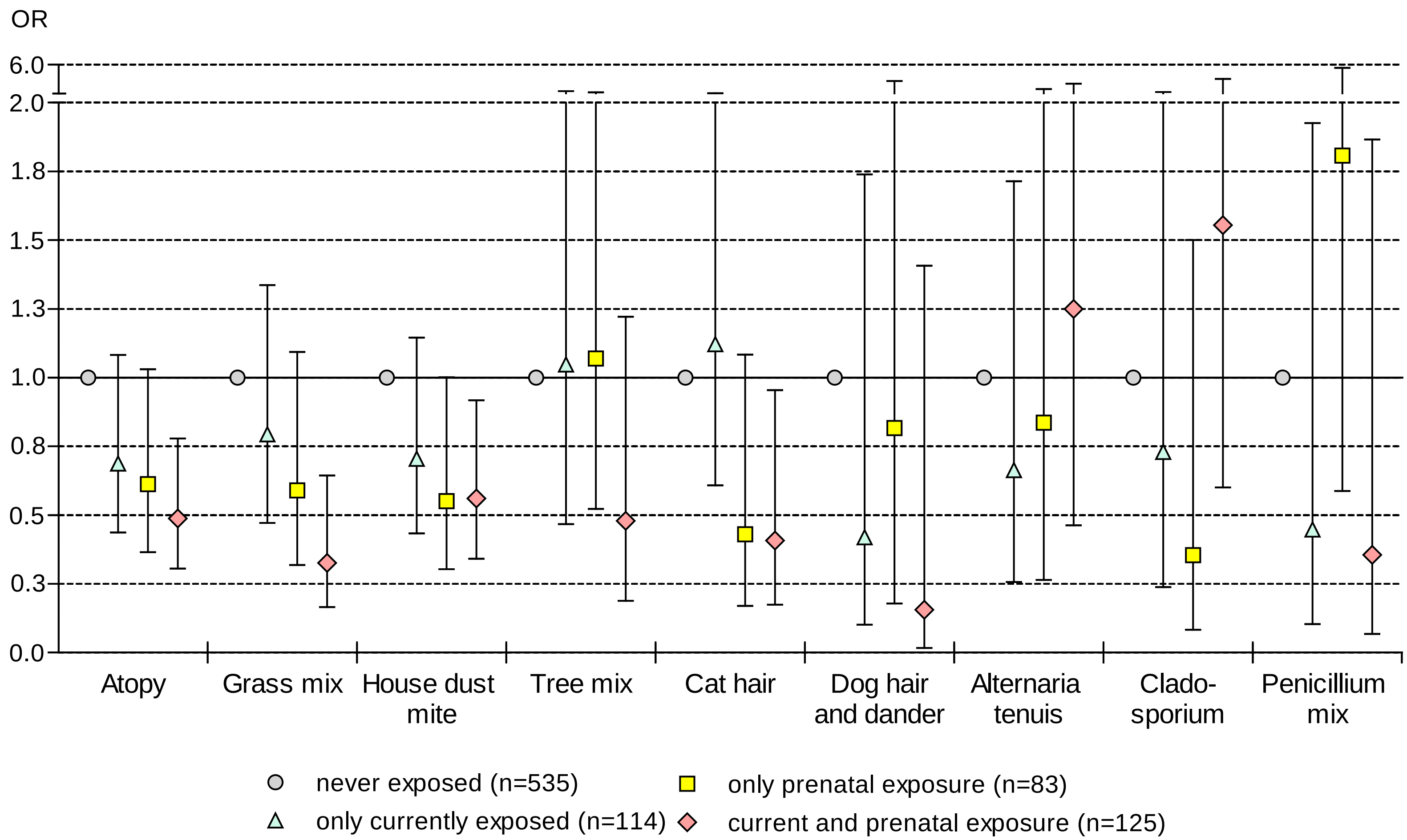
- Blackley could therefore be considered to have laid the foundation of what would later become the hygiene hypothesis (Douwes et al., 2009)

INDEPENDENT AND JOINT EFFECTS OF CURRENT AND PRENATAL ANIMAL EXPOSURE IN NZ FARMERS' AND RURAL REFERENCE CHILDREN - DOUWES ET AL., 2008



O, never exposed (n=1124; reference group); Δ only currently exposed (n=247); only prenatal exposure (n=168); ◊ current and prenatal exposure (n=231)

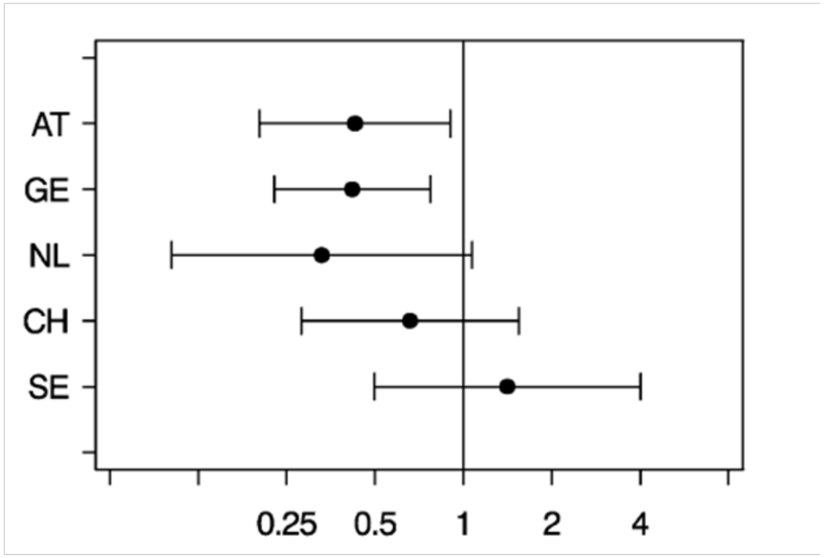
ANIMAL EXPOSURE AND ATOPY IN A SUBPOPULATION



ATOPY AND FARM EXPOSURE IN FARMERS CHILDREN, THE PARSIFAL STUDY (EGE ET AL., JACI 2006)

Adjusted ORs for maternal work in stables during pregnancy

	Atopic sensitization (≥3.5 kU/L) (n = 285/2086)
Current farm exposure*	0.96 (0.63-1.46), P = .854
Regular contact with farm animals ever	0.76 (0.51-1.15) P = .194
Farm milk consumption ever	0.76 (0.52-1.11), P = .162
Stable exposure in pregnancy†	0.58 (0.39-0.86), P = .007



	TLR2	TLR4	CD14
Current farm exposure*	1.04 (0.69-1.55), P = .851	0.93 (0.66-1.3), P = .671	1.01 (0.66-1.54), P = .964
Regular contact with farm animals ever	1.09 (0.75-1.58), P = .650	0.92 (0.67-1.25), P = .577	0.97 (0.65-1.43), P = .866
Farm milk consumption ever	1.04 (0.77-1.42), P = .813	1.06 (0.81-1.4), P = .656	1.16 (0.83-1.64), P = .385
Stable exposure in pregnancy†	1.44 (1.04-1.98), P = .027	1.4 (1.07-1.83), P = .015	1.66 (1.18-2.33), P = .003

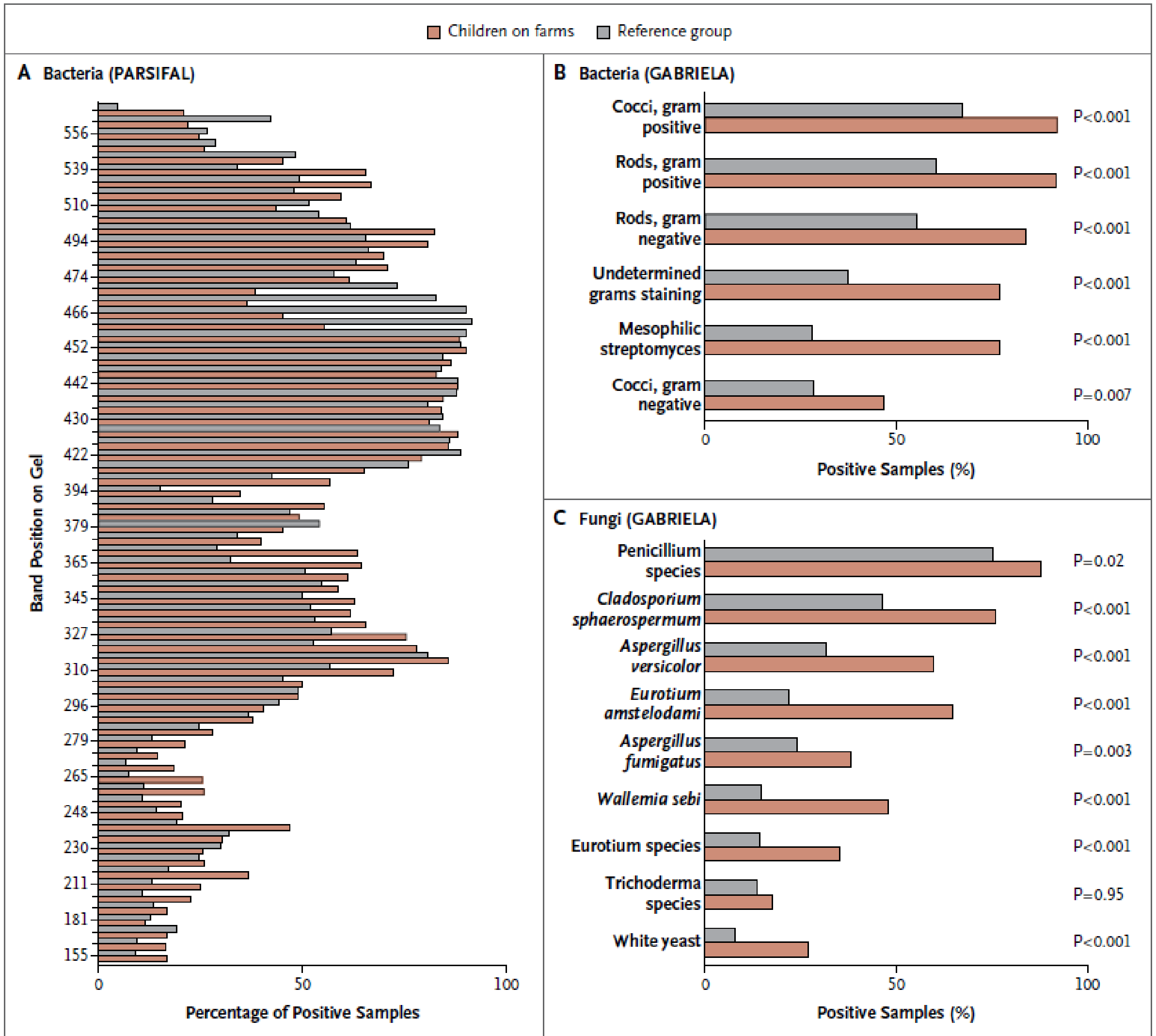


Figure 2. Detection of Environmental Microorganisms in Dust Samples in the PARSIFAL Study and GABRIELA.

In the PARSIFAL study (Panel A), samples of mattress dust were screened for bacterial origin with the use of single-strand conformation polymorphism (SSCP) analysis, with positive samples defined as those with detectable SSCP bands. In GABRIELA (Panels B and C), settled dust from children's rooms was evaluated for bacterial and fungal taxa with the use of culture techniques. The listed microbes were present in at least 10% of all samples.

Exposure to Environmental Microorganisms and Childhood Asthma

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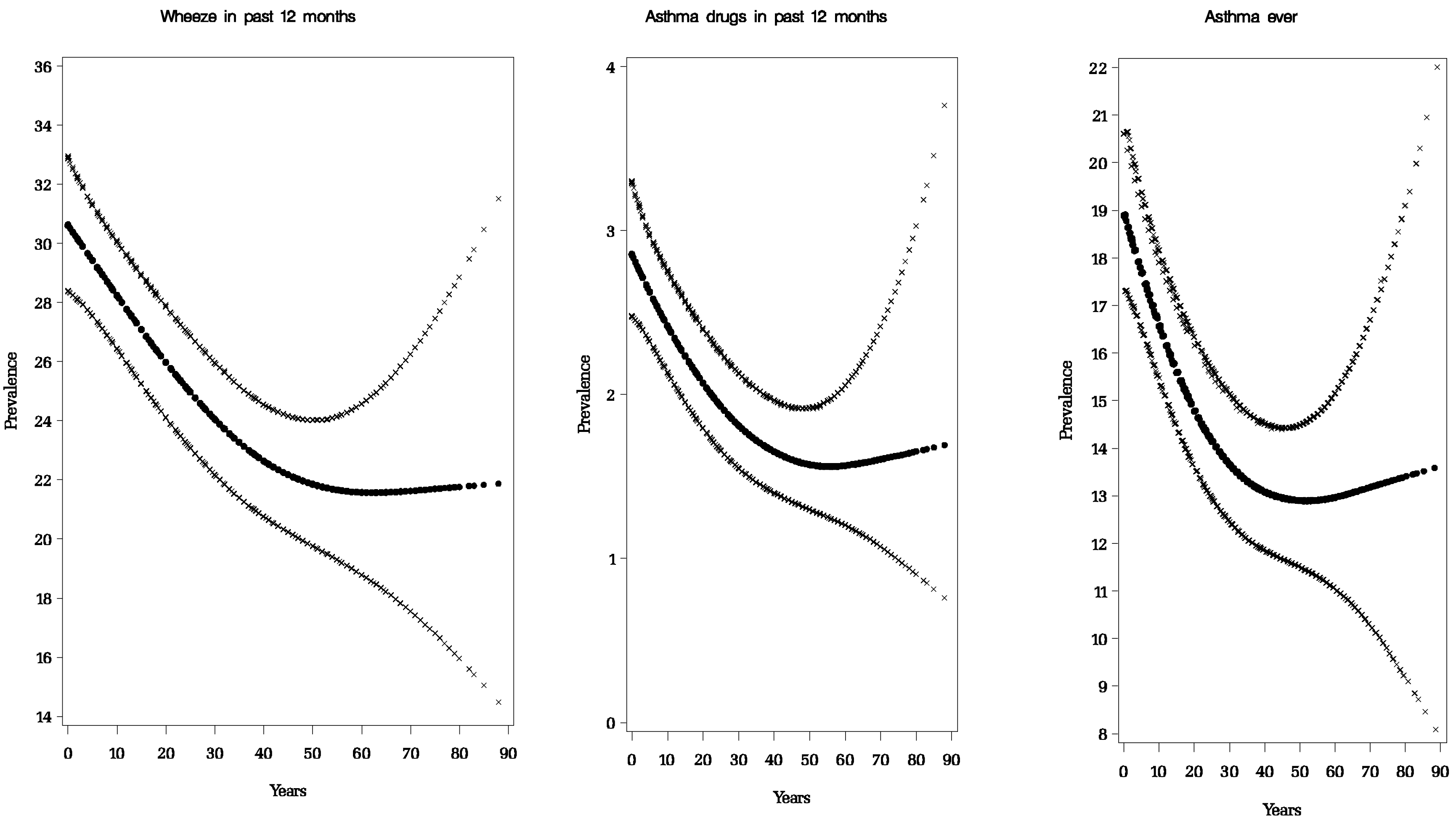
NUMBER OF YEARS OF EXPOSURE TO A FARMING ENVIRONMENT IN CHILDHOOD AND ADULTHOOD (DOUWES ET AL., 2007)



ATOPIC SENSITISATION AND ENDOTOXIN EXPOSURE IN SWINE FARMERS (PORTENGEN ET AL., 2005)

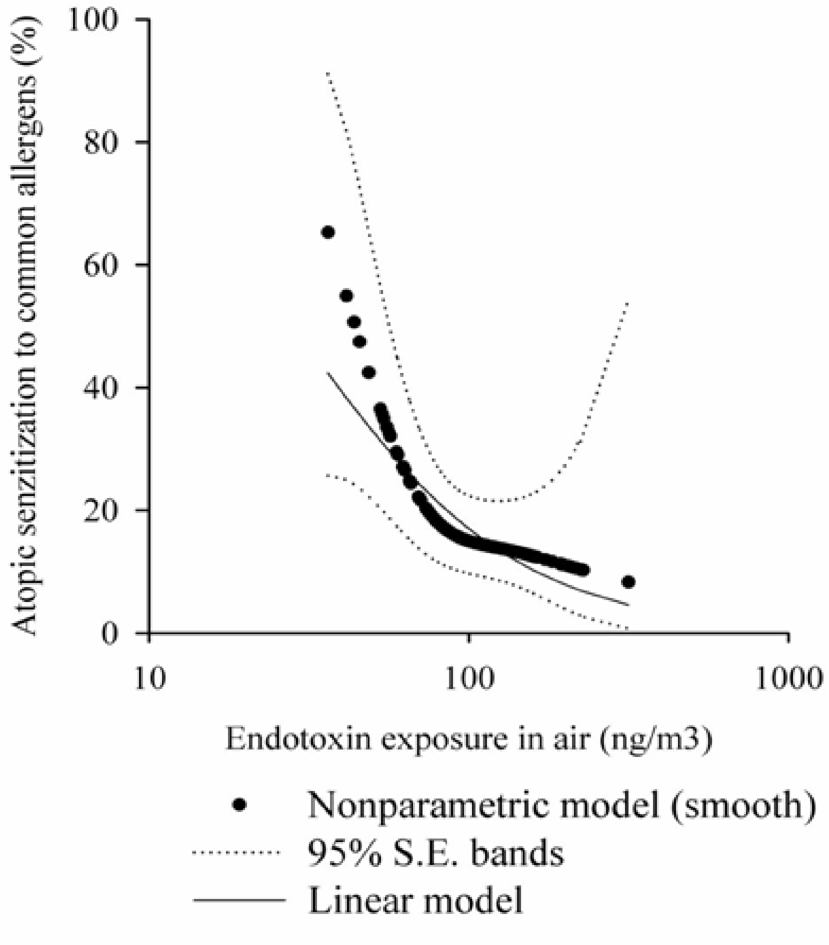
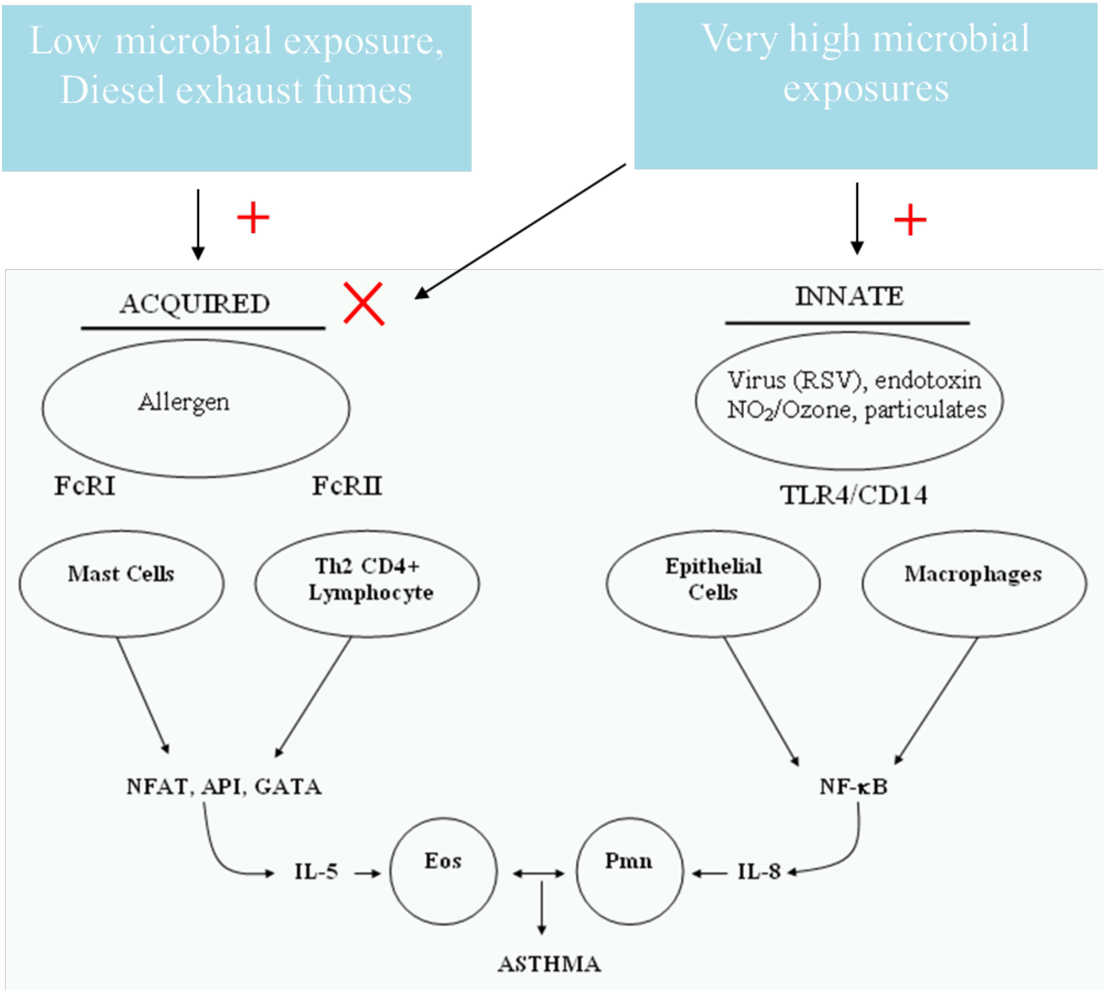


FIGURE 1

ACQUIRED AND INNATE IMMUNE PATHWAYS LEADING TO ASTHMA (DOUWES ET AL., 2002)

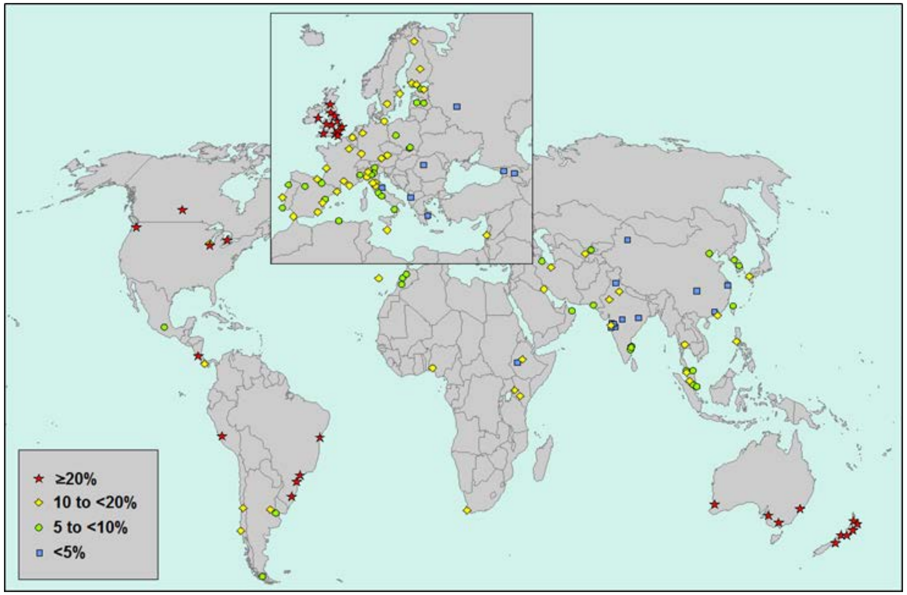


DOES UNPASTEURISED MILK CONFER PROTECTION AGAINST ALLERGIES AND ASTHMA?

- Consumption of unpasteurised farm milk in farmers' and non-farmers' children has been shown to be protective in several studies
- The protective effects appear independent from concomitant exposures to (other) microbial sources
- Probiotic bacteria or other currently unidentified non-microbial components in farm milk may play a role.
- the Russian Nobel-prize laureate Elias Metchnikoff (1845-1916) proposed that consumption of fermented milk may result in better health and an increased life span (Douwes et al., 2009).
- Like Blackley's findings (1873), Metchnikoff's hypothesis was based on observations in farmers

WHAT IS “WESTERN LIFESTYLE”?

- Greater allergen exposure? - No
- More Air pollution? - No
- “Cleaner” environment? Maybe → Lack of microbial stimulation
- Move from rural to urban living? Maybe



RESEARCH AT THE INTERFACE OF COMMUNICABLE AND NON-COMMUNICABLE DISEASES

- Opportunity for IDREC to fill a gap
  - Cancer, respiratory, autoimmune disease, gut immunology
  - Exposure assessment of infectious agents

Thank you

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