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IDReC Infectious Disease Research Centre

(MICROBIAL) BIODIVERSITY AND NON-COMMUNICABLE DISEASES

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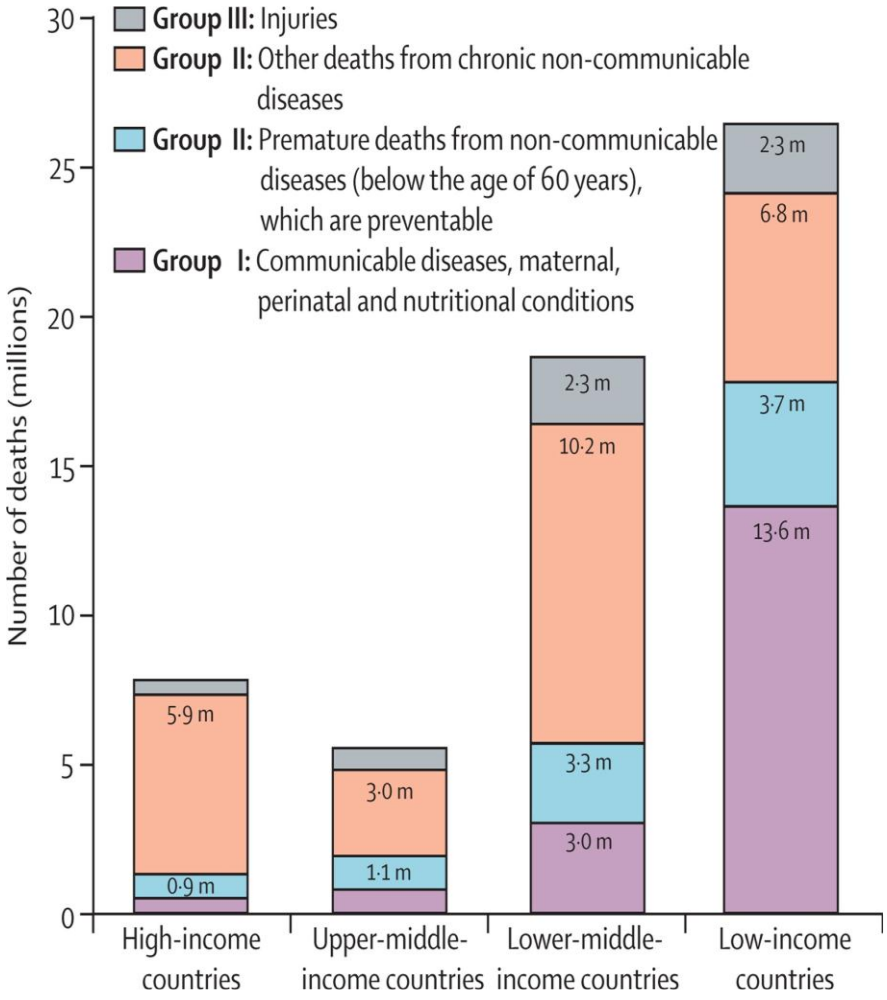
(MICROBIAL) BIODIVERSITY AND NON-COMMUNICABLE DISEASES

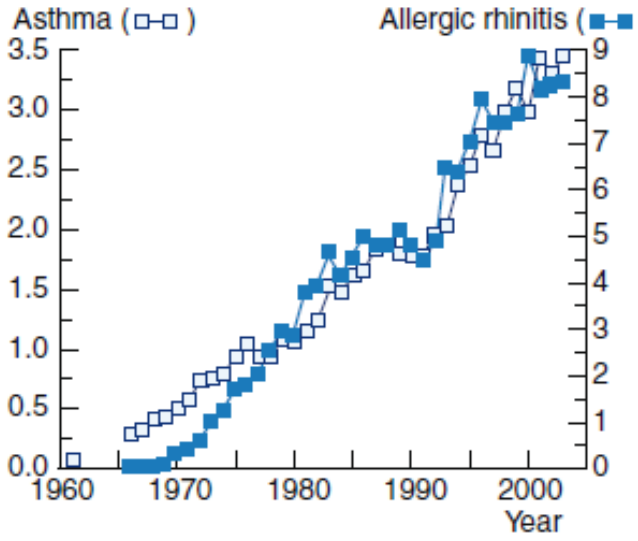
- NCDS a VERY brief introduction
- Pathogens and NCDs
- (Microbial) biodiversity and NCDs
- Microbial diversity and allergies and asthma
    - Environmental exposure
    - Raw milk and probiotics
    - Microbiome
- Conclusions

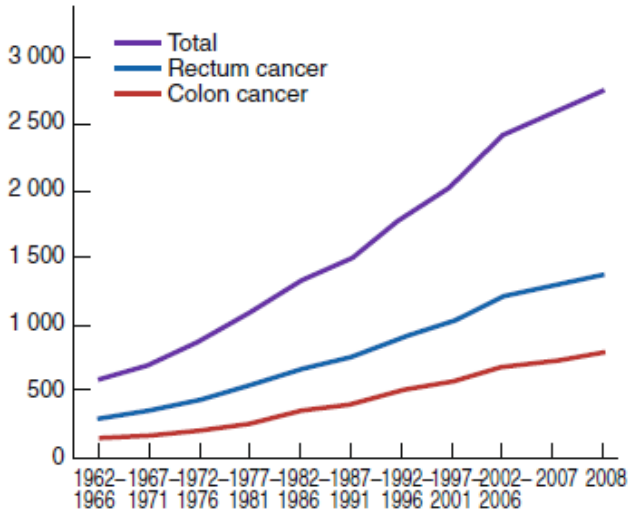
THE GLOBAL BURDEN OF NCDS - LANCET 2010;376:1689-98

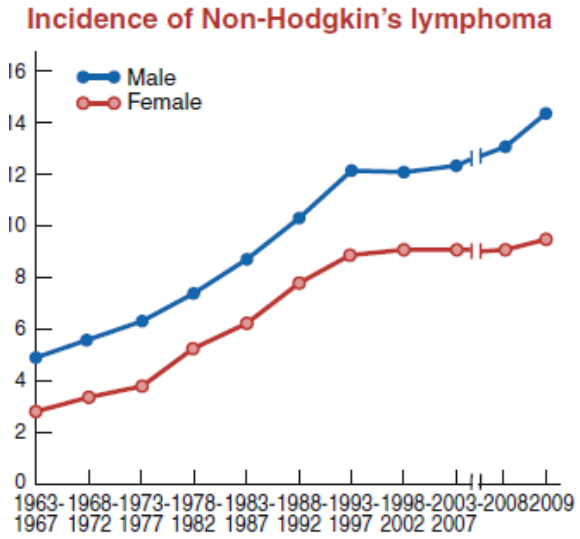
- NCDs have long been the major causes of mortality and morbidity in high income countries (HICs);
- They are now also reaching epidemic levels in low and middle income countries (LMICs);
- Two-thirds of global deaths are due to NCDs;
- Four-fifths of these are in LMICs



THE PREVALENCE OF MANY NCDS (INCL THE MAIN FOUR) HAVE INCREASED CONSIDERABLY IN THE PAST FEW DECADES







Haahtela et al., 2013

THE UN “25X25” STRATEGY (WHO GLOBAL NCD ACTION PLAN 2013-2020) - LANCET 2012;380:1-3

- Four priority diseases:
  - Cardiovascular diseases;
  - Diabetes;
  - Cancer;
  - Chronic respiratory diseases
- Target:
  - 25% reduction in mortality by 2025
- Priority interventions
  - Tobacco control
  - Salt reduction
  - Improved diets and physical activity
  - Reduction in hazardous alcohol intake
  - Essential drugs and technologies

MISSING CAUSES: 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
More to be discovered	• ++++

PATHOGENS AND CANCER

15-20% of all cancers are attributable to infections

- Cervical cancer – HPV
- Stomach cancer – Helicobacter Pylori
- Liver cancer – Aflatoxins

Infections are also associated with respiratory, gastrointestinal and possibly some neurological disorders

- asthma - RSV
- Inflammatory bowel disease – *Mycobact avium paratuberculosis*
- Immunoproliferative small intestinal disease – bacteria/antibiotics?
- ++++

REDUCED ENVIRONMENTAL AND MICROBIAL BIODIVERSITY AND NCDS

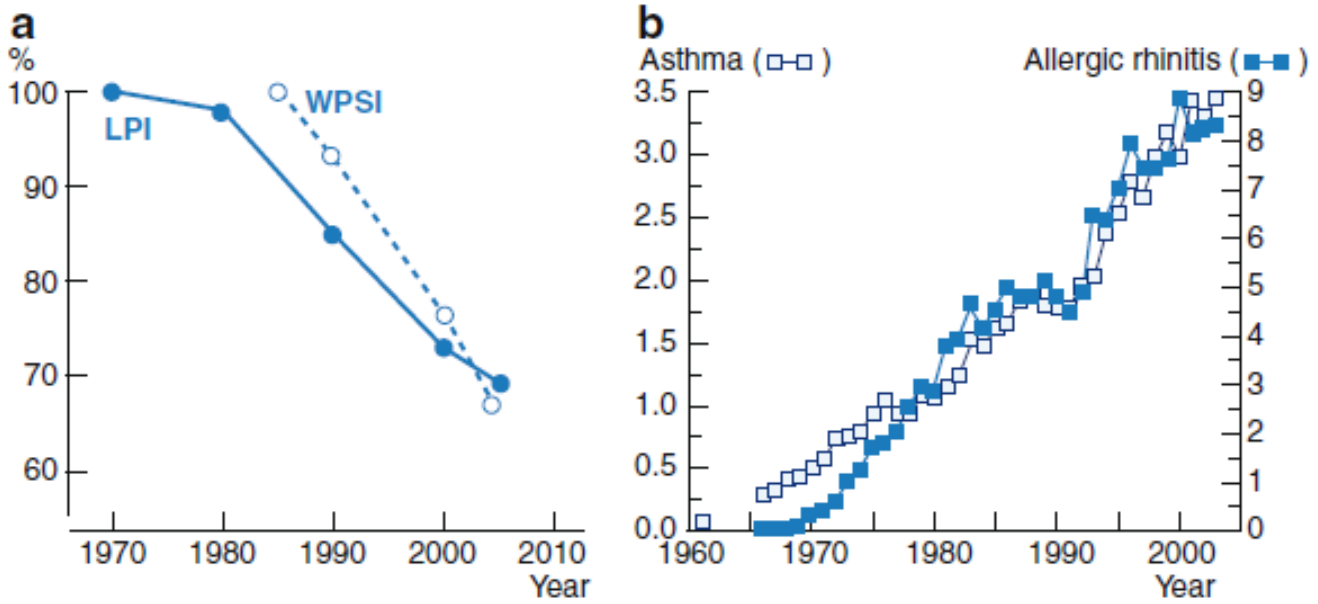


Figure 1 Two global megatrends in biodiversity and public health. (**a**) Declining biodiversity (percentage change) since 1970 as measured by two indices. WPSI=Waterbird Population Status Index; LPI=Living Planet Index [14]. (**b**) Increasing trends in the prevalence of inflammatory civilization diseases, asthma and allergic rhinitis among military conscripts in 1966-2003 [165] as an example (modified from ref. [14]).

Haahtela et al., 2013

REDUCED ENVIRONMENTAL AND MICROBIAL BIODIVERSITY: ASTHMA AND ALLERGIES

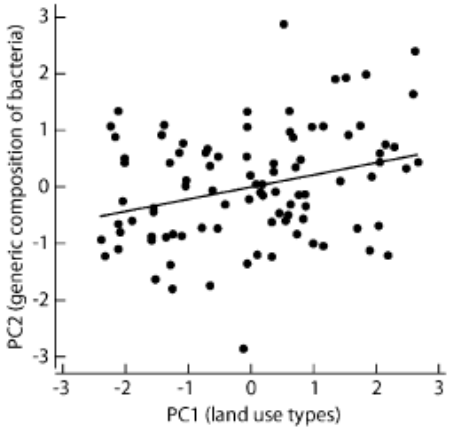


Fig. 1. Relationship between the generic composition of skin microbiota and land use types around the home. The vertical axis shows $PC2_{bac}$, which

- Living near forests and agricultural land is positively associated with skin microbiota diversity, in particular proteobacteria ;
- Living near forests and agricultural land is inversely associated with atopy;
- Living near flowering native plants is inversely associated with atopy;
- proteobacteria on the skin are inversely associated with atopy and IL-10 expression;

Hanski et al., 2012

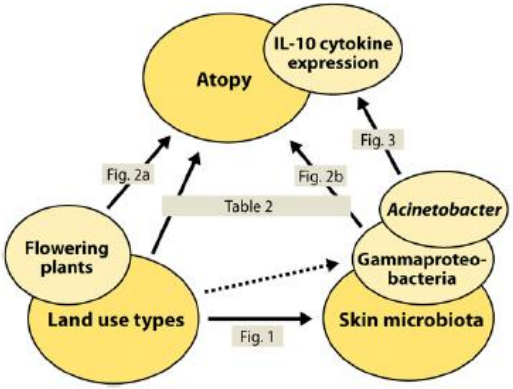


Table 2. Logistic regression models of atopy

	Stepwise model			Regression model	
Variable	Deviance	Difference	*P*	Coefficient	*P*
Constant	158.0			−0.58	0.023
Land use types, $PC1_{env}$	117.6	40.4	<0.0001	−0.52	0.0059
Flowering plants	107.4	10.1	0.0014	−0.10	0.0016
Gammaproteobacteria	100.9	6.5	0.011	−0.31	0.015
P value of the model				0.20	
Positive cases/*N*				38/94	

REDUCED MICROBIAL BIODIVERSITY AND NCDS

- Gut microbial diversity is inversely associated with:
  - Obesity and metabolic diseases; →
  - Autism, depression, anxiety, stress
  - Inflammatory diseases:
    - Gastrointestinal disease such as inflammatory bowel disease and colon cancer
    - Autoimmune disease (e.g. rheumatoid arthritis)
    - Allergies and asthma

- Gut microbial diversity is positively associated with exercise →

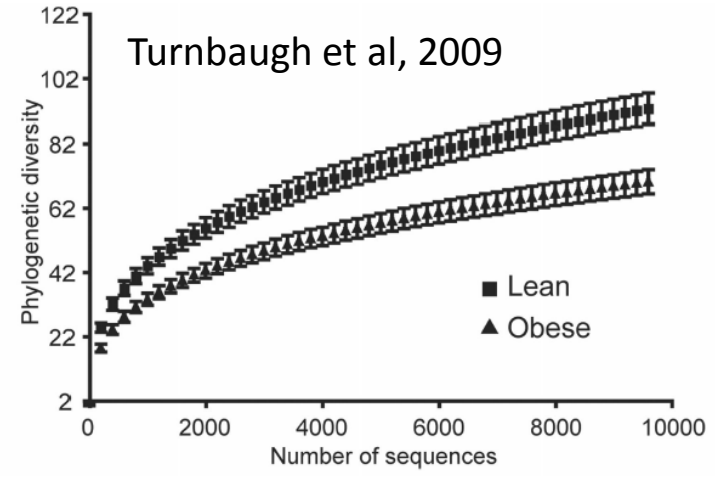
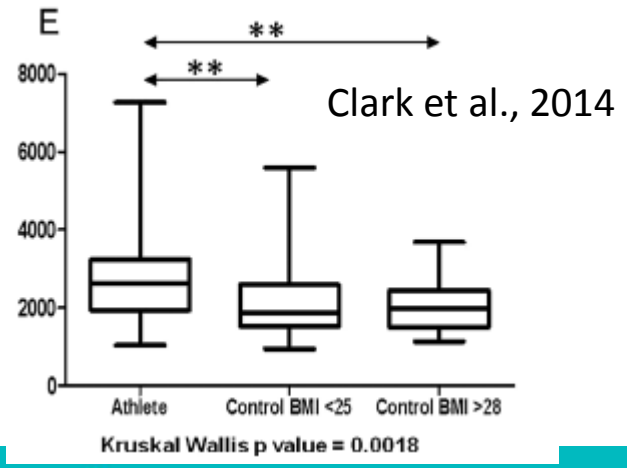


Figure 1. 16S rRNA gene surveys reveal familial similarity and reduced diversity of the gut microbiota in obese individuals



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UNIVERSITY OF NEW ZEALAND

REDUCED MICROBIAL BIODIVERSITY: OLDER SIBLINGS

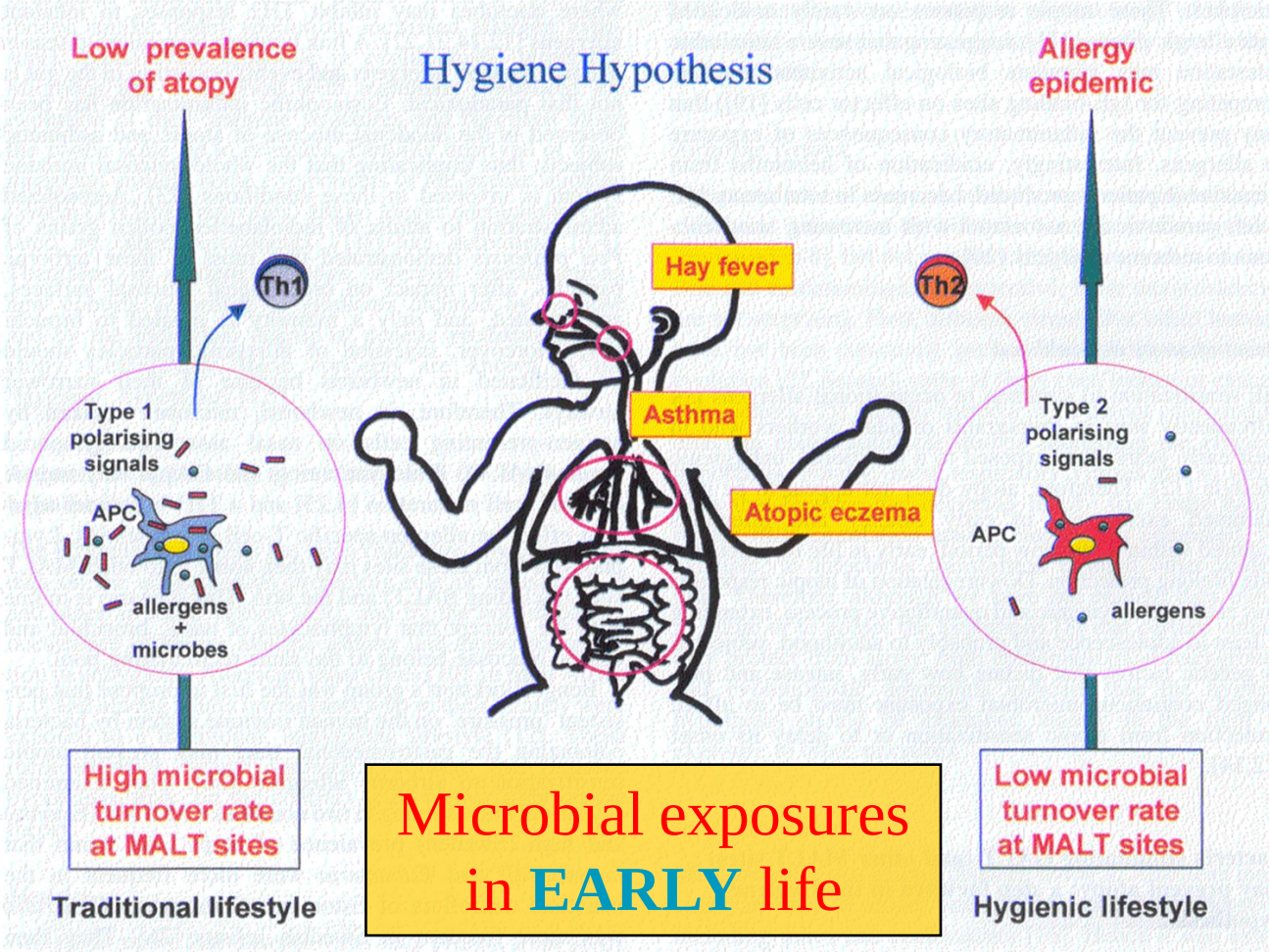
	Prevalence of hay fever in previous year							
	At age 23				At age 11			
	Crude*	Crude†	Adjusted‡	χ²§	Crude*	Crude†	Adjusted‡	χ²§
No of older children (under 21) in household at age 11‖:								
0	20·4 (910/4 470)	20·5 (810/3 942)	20·4		9·6 (542/5 622)	10·0 (389/3 895)	10·0	
1	15·7 (583/3 703)	15·5 (515/3 323)	15·0		8·4 (398/4 721)	8·3 (273/3 286)	7·9	
2	11·6 (172/1 478)	12·1 (157/1 301)	12·5	80·0	5·4 (106/1 953)	4·8 (62/1 290)	5·0	55·4
3	9·6 (58/606)	9·2 (48/520)	10·6		3·7 (29/777)	3·3 (17/511)	4·0	
4+	6·5 (21/322)	6·7 (18/270)	8·6		2·8 (12/436)	1·9 (5/268)	2·6	
No of younger children in household at age 11‖:								
0	17·2 (643/3 746)	17·1 (575/3 354)	17·9		8·8 (422/4 770)	8·6 (286/3 319)	8·9	
1	17·7 (626/3 544)	17·7 (559/3 151)	16·9		8·8 (387/4 414)	8·8 (273/3 120)	8·3	
2	16·0 (303/1 898)	16·3 (273/1 678)	15·7	13·4	7·3 (179/2 436)	7·5 (125/1 657)	7·3	10·7
3	13·9 (117/841)	13·0 (93/714)	13·4		5·9 (67/1 144)	6·1 (43/707)	6·5	
4+	10·0 (55/550)	10·5 (48/459)	12·3		4·3 (32/745)	4·3 (19/447)	5·4	
Total	16·5 (1 744/10 579)	16·5 (1 548/9 356)			8·0 (1 087/13 509)	8·1 (746/9 250)		

Strachan., 1989

Birth cohort: 17,414 subsjects

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 microbes may also be protective



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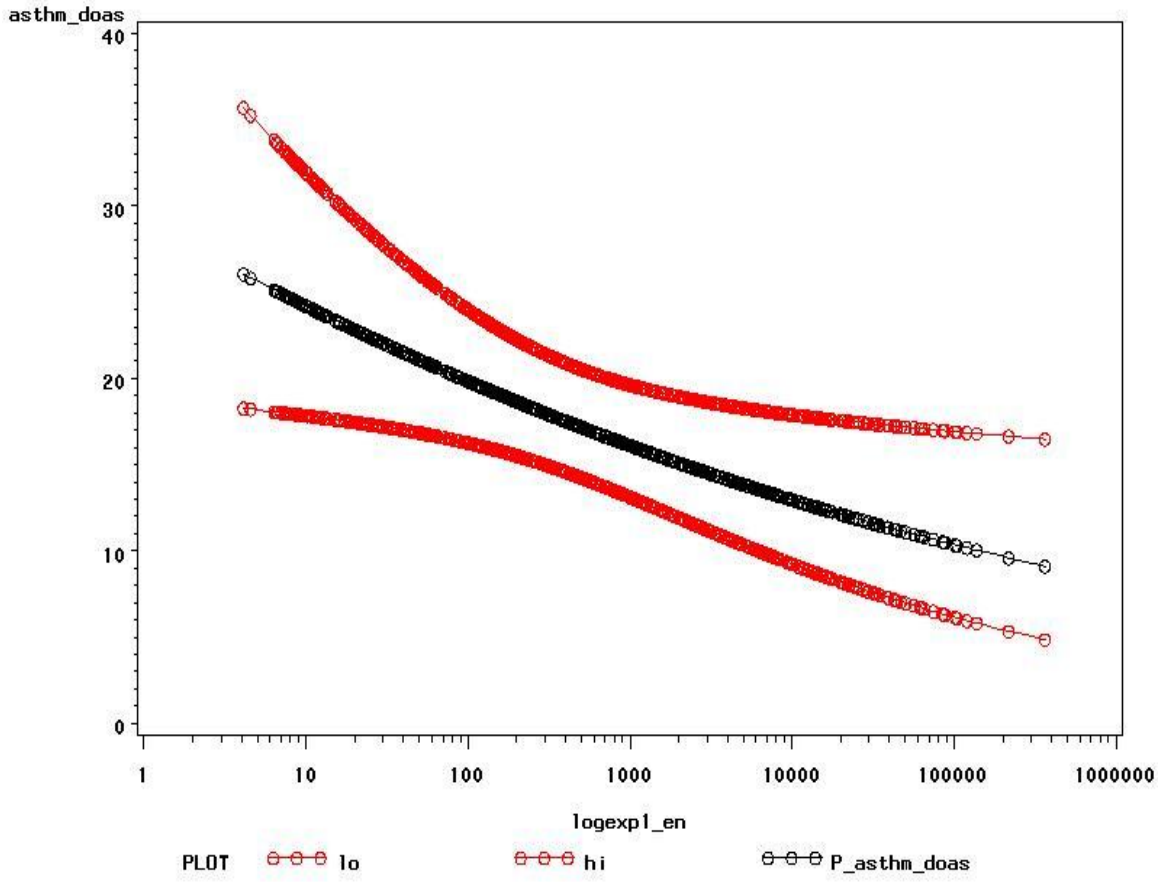
THE BIOLOGY OF THE ATOPIC RESPONSE – PRESTON, J ROYAL NAVY MED SERVICE, 1970

This disorder, hay-fever, seems therefore to have appeared in England amongst the upper social classes in about the time of George IV, when aristocratic living conditions had become more hygienic and just before the time when such episodes as the Broad Street Pump cholera outbreak (1854) drew the attention of the privileged to the poor hygienic conditions in English cities, which resulted in the 1884 Commission to enquire into the overcrowding in London and ultimately to the Housing of the Working Classes Act of 1884. It is salutary to note that it was not until 1890 when the great northern out-fall sewer was built along the north bank of the Thame that there was any means of sewage disposal in Westminster other than direct discharge into a tidal river. Certainly it seems that atopic rhinitis dates from the time when hygienic disposal of sewage, with freedom from infection with some intestinal nematodes, became a feature of English life.

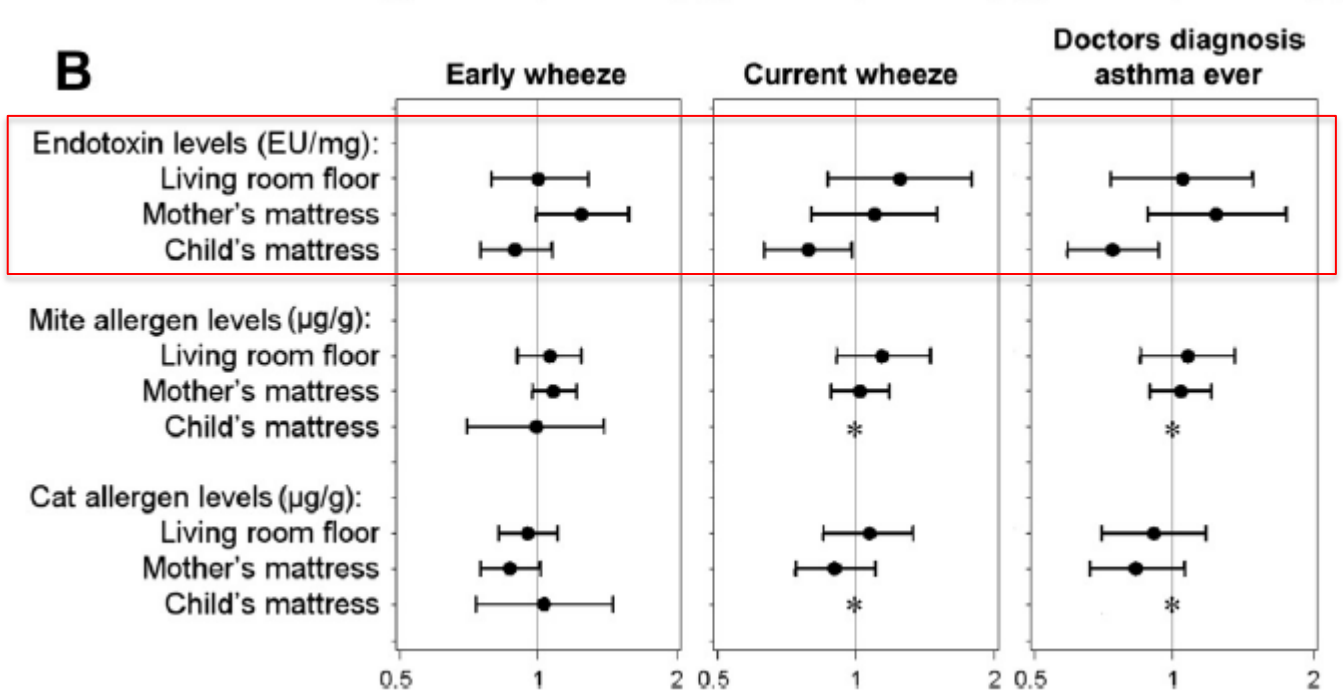
ENDOTOXIN EXPOSURE AT 12 MONTHS AND DOCTOR'S DIAGNOSED ASTHMA AT 48 MONTHS (DOUWES ET AL., 2006)

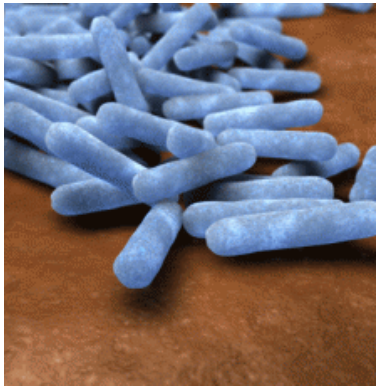


PAULA BIRTH COHORT STUDY

ILLI ET AL., ANN ALLERGY ASTHMA IMMUNOL 2014;112:132-139

- Endotoxin levels at 3 months and symptoms at age 5.





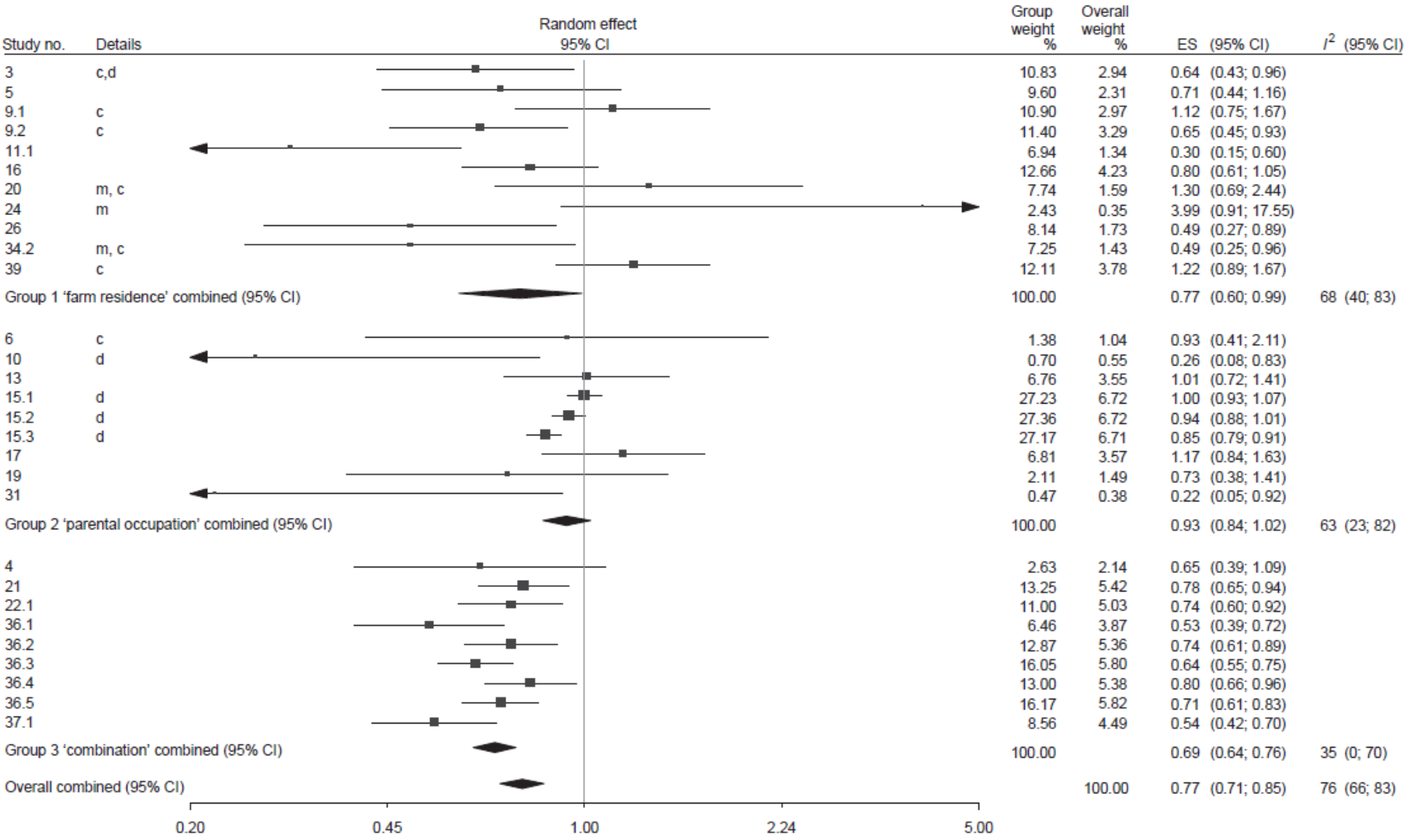
EFFECT OF ENDOTOXIN AND ALLERGENS ON NEONATAL LUNG FUNCTION (ABBING-KARAHAGOPIAN ET AL., 2012)

- Lung function before age 2 months, N=298
- Mattress mite allergens and endotoxin
- No associations between allergen exposure and lung function and symptoms
- Mattress dust endotoxin was associated with a significant increase in neonatal respiratory compliance

Table 4 Crude and adjusted associations *between endotoxin concentrations in the child's mattress dust, neonatal lung function, and respiratory symptoms and eczema during the first year of life

	Crude		Adjusted†	
	Beta	95% CI	Beta	95% CI
Lung function (N = 298)				
Compliance	2.44	0.45; 4.42	2.31	0.33; 4.29
Resistance	−0.31	−0.74; 0.13	−0.32	−0.77; 0.14

reduced environmental and microbial biodiversity: farming and asthma. Genuneit J. Pediatr Allergy Immunol 2012: 23: 509–518.



CAUSAL EXPOSURES: FARM ANIMALS

Table 4. Changes in the odds ratio (OR) at the various stages of fitting the logistic regression model for the association of living on a farm and allergic sensitization

	n	OR	95% CI	*P*-value
Crude	1006	0.48	0.30–0.75	0.001
+ Predefined confounders*	899	0.48	0.29–0.79	0.004
+ Living conditions*	869	0.48	0.28–0.80	0.005
+ Infection and diet*	786	0.51	0.29–0.89	0.019
+ Regular contact with pets*	786	0.54	0.31–0.96	0.036
+ Regular contact with livestock and poultry*	786	0.75	0.37–1.52	0.426

Riedler et al., 2000

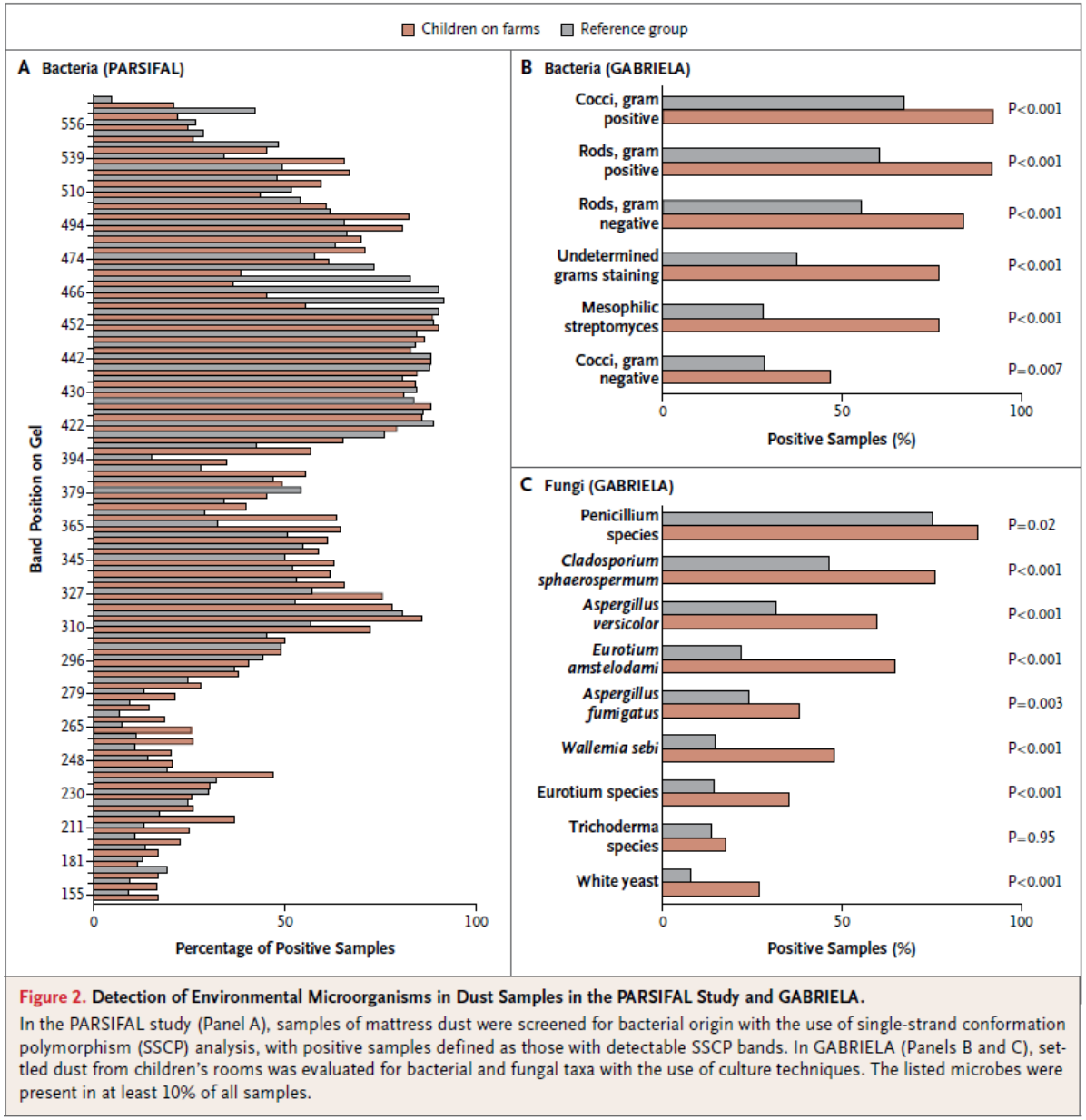


Figure 2. Detection of Environmental Microorganisms in Dust Samples in the PARSIFAL Study and GABRIELA.

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

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

The NEW ENGLAND JOURNAL of MEDICINE

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The NEW ENGLAND JOURNAL of MEDICINE 364;8:2011

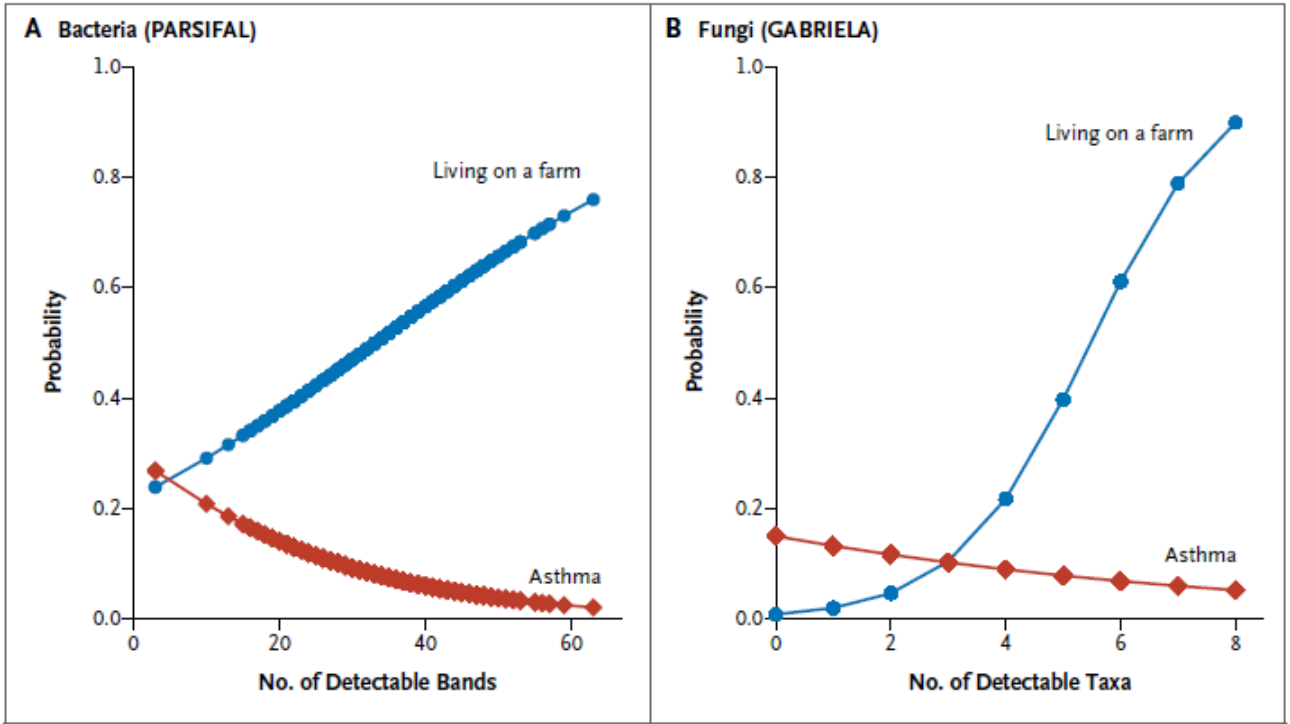


Figure 3. Relationship between Microbial Exposure and the Probability of Asthma.

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

DO FARMERS HAVE AN ALTERED MICROBIOME? A STUDY IN THE OLD ORDER AMISH (ZUPANICIC ET A., 2012)

- Gut microbiota sequencing in 310 Amish;
- In men, the occupation of farming (n=44) was over-represented among those with the *Prevotella*-dominated network (71.4%) compared to either the *Bacteroides*-dominated (21.4%) or *Firmicutes*-dominated (36.5%) networks;
- The distribution of networks did not differ within any other occupational class;
- Of interest, gut microbiota of various livestock species contain a high relative abundance of the xylanolytic bacterial species *Prevotella;*
- Could transmission of microbes across host species explain the protective effects of animal exposure on allergies and asthma?

EXPOSURE TO FARMING IN EARLY LIFE AND ASTHMA AND ALLERGY IN 6-13 YR OLDS FROM FARMING AND NON-FARMING FAMILIES (RIEDLER ET AL., 2001)

	Stables and **farm milk** in 1st year of life	Stables and/or **farm milk** *after* 1st year of life	Neither stables nor farm milk exposure
Asthma diagnosis	1% OR 0.14*	11% OR 0.88	12% Reference
Wheeze	3% OR 0.17*	9% OR 0.60	15% Reference
Hay fever	3% OR 0.20*	13% OR 0.88	16% Reference
Runny nose and itchy eyes	5% OR 0.27*	12% OR 0.65	20% Reference
Atopy	12% OR 0.32*	29% OR 0.99	33% Reference

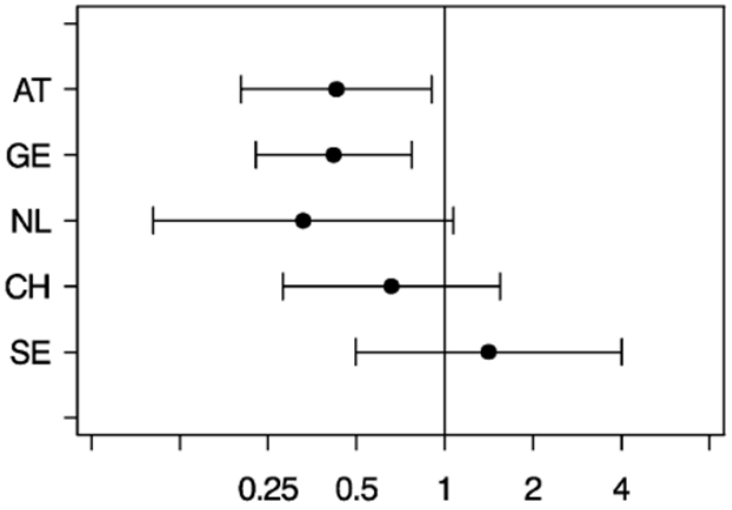
THE PROTECTIVE EFFECT OF RAW MILK CONSUMPTION ON ASTHMA AND ATOPY (BRAUN-FAHRLANDER AND VON MUTIUS, 2010)

Reference	Population	Exposure	Result
Riedler et al, 2001	Rural farm/non-farm children (n=812)	Milk directly from farm	↓ asthma, hayfever, atopy
Waser et al, 2007	Rural farm/non-farm children, steiner, peri urban (n=14,893)	Milk directly from farm	↓ asthma, hayfever, atopy
Perkin and strachan, 2006	Rural farm/non-farm children (n=4767)	Unpasteurised milk	↓ eczema, atopy → asthma
Barnes et al, 2001	Rural farm/non-farm children (n=929)	Unpasteurised milk	↓ atopy
Radon et al, 2004	Rural farm/non-farm adults (n=321)	Raw, unboiled farm milk	↓ atopy
Wickens et al, 2002	Farm children/children from small towns	Unpasteurised milk	↓ atopic eczema

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), $P = .003$

DO RAW MILK DRINKERS HAVE AN ALTERED MICROBIOME: A POPULATION BASED STUDY IN NEW ZEALAND

Health Research Council of New Zealand

- Cross sectional survey of 300 families who regularly drink raw milk;
- Reference population: 150 families who drink pasteurised milk
- Questionnaire, lung function, exhaled NO, skin prick tests, blood/serum
- Stool samples: gut microbiome (not funded)

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PROBIOTICS AND ALLERGIES: EVIDENCE FROM CLINICAL TRIALS – ALLEN ET AL., 2014

Table 3 Secondary outcomes according to intervention group

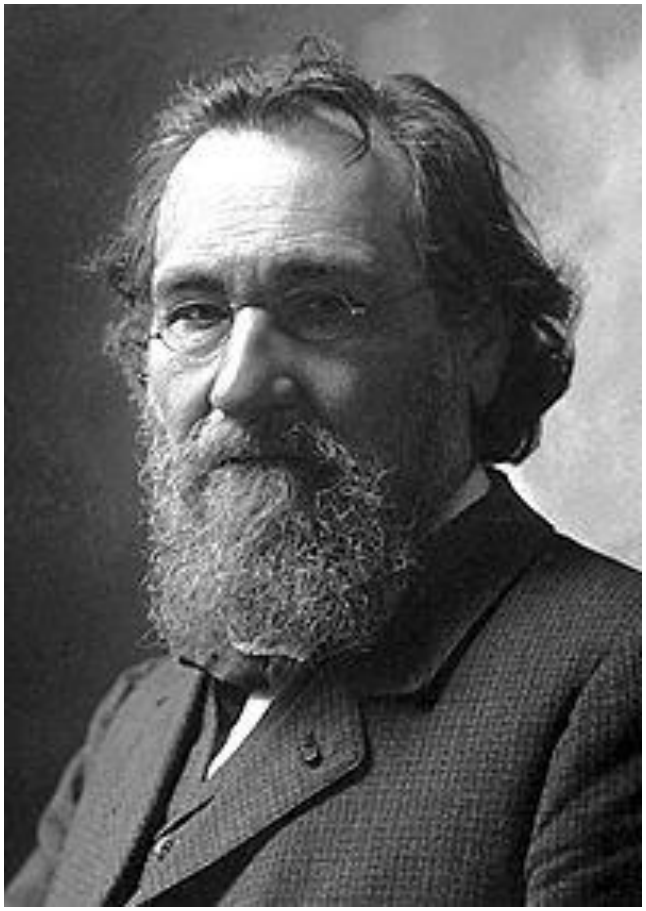
Variable	Probiotic arm	Placebo arm	OR (95% CI)	p Value*
SPT† positive at 6 m	6/151 (3.97%)	16/147 (10.88%)	0.34 (0.13 to 0.89)	0.023
▶ cow's milk	0/148 (0.0%)	5/147 (3.40%)	–	0.030*
▶ egg	5/148 (3.4%)	14/147 (9.5%)	0.33 (0.11 to 0.95)	0.032
▶ house dust mite	1/151 (0.66%)	0/147 (0.0%)	–	0.51*
▶ cat	0/151 (0.0%)	2/145 (1.4%)	–	0.24*
▶ grass	1/150 (0.67%)	0/147 (0.0%)	–	0.49*
SPT† positive at either 6 m or 2 yrs	18/171 (10.5%)	32/173 (18.5%)	0.52 (0.28 to 0.98)	0.036
▶ cow's milk	1/171 (0.6%)	6/173 (3.5%)	0.16 (0.02 to 1.4)	0.12*
▶ egg	9/171 (5.3%)	19/173 (11.0%)	0.45 (0.2 to 1.0)	0.052
▶ house dust mite	9/171 (5.3%)	11/173 (6.4%)	0.82 (0.3 to 2.0)	0.66
▶ cat	3/171 (1.8%)	7/173 (4.0%)	0.42 (0.1 to 1.7)	0.20
▶ grass	2/171 (1.2%)	2/173 (1.2%)	1.0 (0.14 to 7.2)	0.99*
Skin				
▶ Atopic eczema at 6 m	4/151 (2.7%)	13/147 (8.8%)	0.28 (0.089 to 0.88)	0.021
▶ Severity of eczema at 6 m clinic‡; median, (IQR)	14.3 (7.5–17.9)	14.4 (10.6–24.9)	–	0.46
▶ Atopic eczema at 2 yrs	9/171 (5.3%)	21/173 (12.1%)	0.40 (0.18 to 0.91)	0.024
▶ Severity of eczema at 2 yr clinic‡; median (IQR)	11.1 (7.2–20.1)	14.2 (7.2–14.2)	–	0.85
▶ All reported eczema§,¶	119/214 (55.6%)	132/226 (58.4%)	0.90 (0.61 to 1.3)	0.55

Lactobacillus salivarius and *paracasei;* and *Bifidiobacterium animalis subspecies lactis* and *bifidium*

ILYA ILYICH MECHNIKOV (1845 – 1916) NOBEL PRIZE FOR MEDICINE IN 1908

- Observation: regular consumption of lactic acid bacteria (naturally present in raw milk) in fermented dairy products such as yoghurt was associated with enhanced health and longevity in Bulgarian peasants
- Mechnikov laid the foundation for modern probiotics (FAO/WHO: "*live microorganisms which when administered in adequate amounts confer a health benefit on the host*")

- Anukam et al., 2007



REDUCED MICROBIAL BIODIVERSITY: ANTIBIOTIC USE IN EARLY LIFE

Table 1—*Risk of Asthma at Age 7 Years Following Antibiotic Use in the First Year of Life, Adjusted for Respiratory and Nonrespiratory Infections

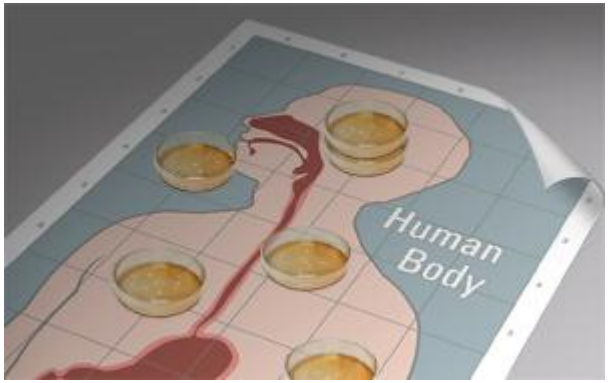
Variables (Reference Group)	Model 1	Model 2	Model 3	Model 4
Courses of antibiotics (none)				
1–2	1.27 (1.06–1.53)	1.25 (1.04–1.51)	1.27 (1.05–1.53)	1.23 (1.02–1.48)
3–4	1.41 (1.12–1.76)	1.36 (1.08–1.70)	1.40 (1.10–1.78)	1.35 (1.07–1.69)
> 4	1.74 (1.37–2.22)	1.64 (1.29–2.10)	1.72 (1.27–2.34)	1.56 (1.22–2.00)
Each lower respiratory tract infection†		1.05 (1.02–1.09)		
Each upper respiratory tract infection†			1.00 (0.98–1.03)	
Each non-respiratory tract infection‡				1.15 (1.11–1.19)

*Values are given as OR (95% CI). All models were adjusted for gender, urban/rural location, maternal history of asthma, number of health-care visits, and number of siblings.
†For example, zero vs one infection, one vs two infections, two vs three infections, etc.
‡For example, skin vs urinary tract infection.

Kozyrskyj et al., 2007
Birth cohort study: 13,116 infants followed for 7 years

AIRWAY MICROBIOME AND ASTHMA (LEGATZKI ET AL., 2014)

- Several studies have shown that the airways of asthmatics have an altered bacterial composition compared to airways of healthy airways
- A greater microbial richness and diversity may be present in asthmatic airways i.e. greater abundance of *Proteobacteria* and *Firmicutes*.
- Birth cohort study suggested a role for *Streptococcus pneumonia*, *Haemophilis influenzae*, and *M catarhalis* in early life (associated with asthma in later life; Bisgaard et al., 2011)
- Data largely inconclusive (not many studies have been conducted)



GUT MICROBIOME AND ASTHMA: BISGAARD ET AL., 2011

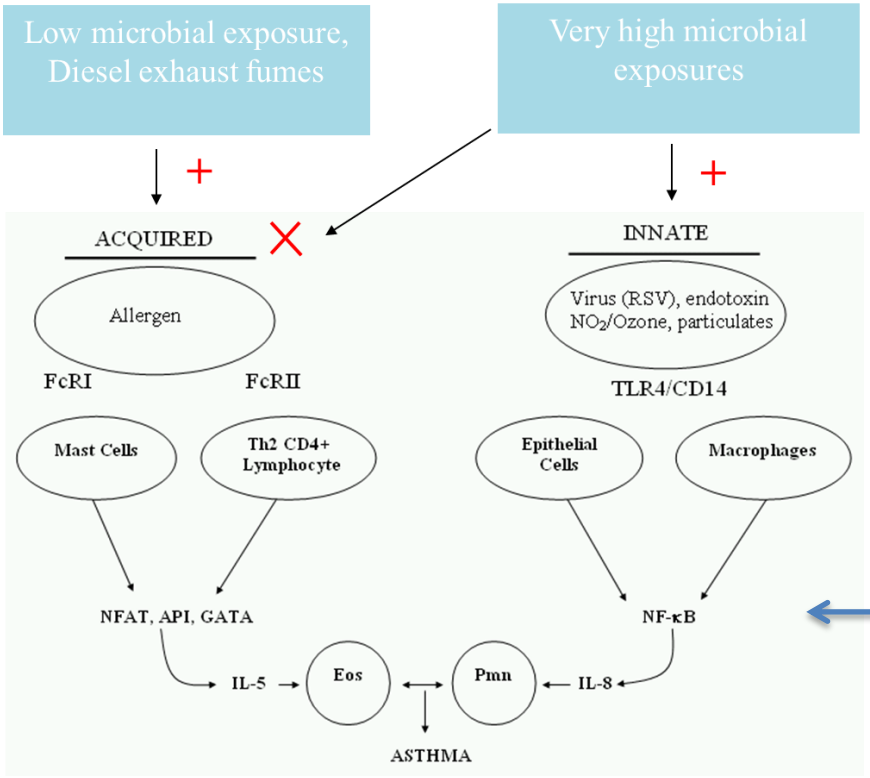
TABLE I. Risk of atopic disease from DGGE band richness in the infant's intestinal flora

End point	Age (y)		Band richness at:	Estimate (95% CL)	*P* value
Repeated assessments		**No.**		**GEE estimate (95% CL)**	
Specific IgE	½, 1½, 4, and 6 y	910	1 mo	−0.106 (−0.202 to −0.098)	.031
			12 mo	−0.093 (−0.179 to −0.070)	.034
			Average	**−0.196 (−0.324 to −0.069)**	**.0027**
Skin prick test	½, 1½, 4, and 6 y	914	1 mo	−0.054 (−0.155 to 0.047)	>.1
			12 mo	−0.114 (−0.224 to −0.005)	.040
			Average	**−0.179 (−0.326 to −0.032)**	**.017**
Peripheral blood eosinophils	½, 1½, 4, and 6 y	836	1 mo	−0.018 (−0.042 to 0.007)	>.1
			12 mo	−0.017 (−0.038 to 0.003)	.10
			Average	**−0.035 (−0.067 to −0.003)**	**.034**
Current disease		**No. positive/no.**		**Odds ratio (95% CI)**	
Allergic rhinitis	7 y	28/162	1 mo	0.78 (0.64 to 0.96)	.016
			12 mo	0.88 (0.76 to 1.02)	.08
			Average	**0.71 (0.56 to 0.91)**	**.007**
Current asthma	6 y	27/229	1 mo	1.01 (0.86 to 1.19)	>.1
			12 mo	0.98 (0.85 to 1.12)	>.1
			Average	**0.98 (0.79 to 1.21)**	**>.1**
Time to onset		**No. positive/no.**		**Hazard ratio (95% CI)**	
Atopic dermatitis	0-6 y	127/253	1 mo	0.96 (0.89 to 1.03)	>.1
			12 mo	1.00 (0.95 to 1.06)	>.1
			Average	**0.97 (0.89 to 1.06)**	**>.1**

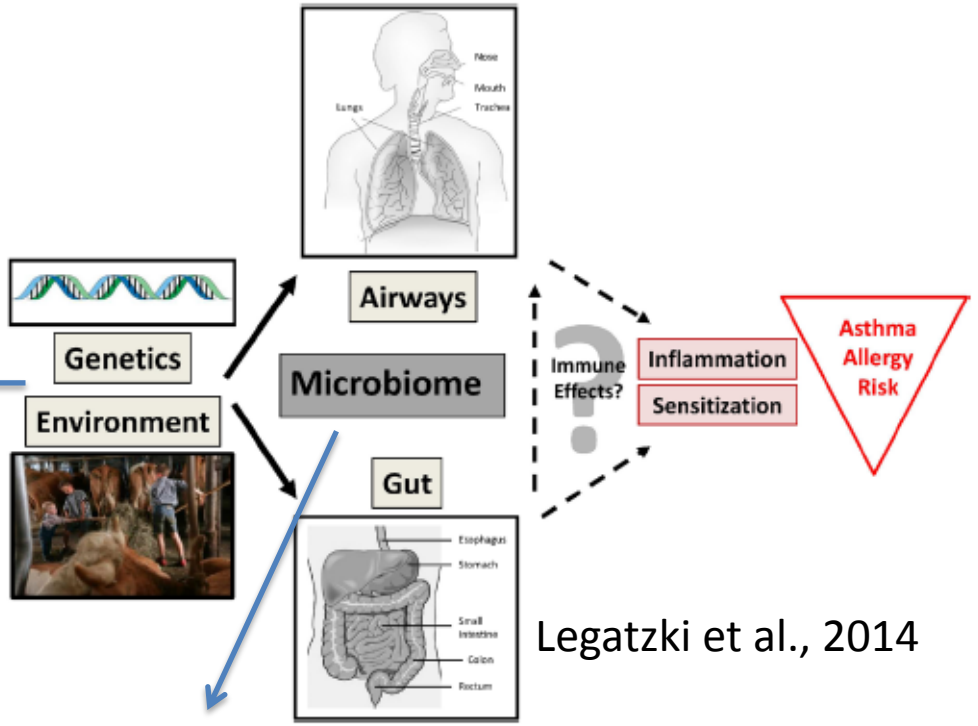
The independent effects of band richness at 1 and 12 months were analyzed together as explanatory variables in the same model. The average band richness was analyzed separately (in boldface).
CL, Confidence limit.

- Evidence for allergies/atopy most consistent
- Evidence for asthma is mixed

ENVIRONMENTAL AND MICROBIAL BIODIVERSITY AND ALLERGIES AND ASTHMA: MECHANISMS?



Douwes et al., 2002



Legatzki et al., 2014

Microbiome causally related to new onset disease or a secondary epiphenomenon?

CONCLUDING COMMENTS…

- There appears to be an association between environmental, exogenous and endogenous microbial biodiversity, and NCDs, but we are currently only at the beginning of understanding these complex relationships.
- Clinical application is still unclear, but the microbiome is potentially modifiable, and if associations are causal, then there is significant potential for it to be used for improved preventive and treatment options.
- Pre and probiotics are currently extensively tested for treatment of atopic dermatitis, hay fever and asthma (and other inflammatory diseases) with mixed success;
- Faecal transplantation as a therapeutic tool is increasingly reported in the scientific literature for treatment of refractory infections with *Clostridium difficile* and as a suggested treatment for ulcerative colitis Crown's disease and the metabolic syndrome.
- An important opportunity to develop novel research at the interface of communicable and non-communicable diseases

Thank you

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