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PERSPECTIVES

SCIENCE AND SOCIETY

Farm living: effects on childhood asthma and allergy

Erika von Mutius and Donata Vercelli

Abstract | Numerous epidemiological studies have shown that children who grow up on traditional farms are protected from asthma, hay fever and allergic sensitization. Early-life contact with livestock and their fodder, and consumption of unprocessed cow's milk have been identified as the most effective protective exposures. Studies of the immunobiology of farm living point to activation and modulation of innate and adaptive immune responses by intense microbial exposures and possibly xenogeneic signals delivered before or soon after birth.

The prevalence of asthma, hay fever, atopic dermatitis and allergic sensitization is higher in affluent, Western countries than in developing countries. A rise in the prevalence of these conditions has also occurred in the last decades of the twentieth century[1]. From a

In these areas, most farms are involved in dairy production, but may also keep other animals, such as horses for horse-back riding, pigs for meat and poultry for egg production. In addition, some farmers raise sheep and goats. Most farmers also grow

Allergy-protective farm exposures

Several studies have identified some of the exposures associated with a farming lifestyle that contribute to the reduced risk of asthma and allergies in farm children, namely contact with livestock, mostly cattle, pigs and poultry; contact with animal feed such as hay, grain, straw and silage; and the consumption of unprocessed cow's milk[4,6–9]. These exposures had an independent protective farm effect, which indicates that inhalation and ingestion are the two main routes of exposure. Other differences in lifestyle, such as duration of breast feeding, family and sibship size, day care, pet ownership, other dietary habits, parental education and a family history of asthma and allergies, did not account for the protective farm effect. However, the timing of this exposure was crucial, with the strongest effects observed for exposures that occurred *in utero* and during the first years of life[7,10]. Maternal contact with increasing numbers of farm animal species[10–12], work in barns[11,12] and stables[10,13], and the consumption of

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Farm living: effects on childhood and adulthood asthma and allergy

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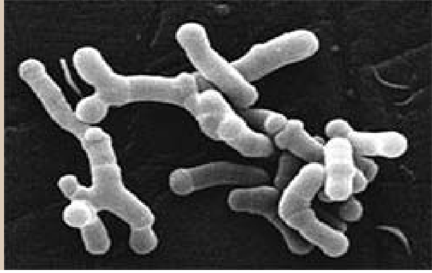
Farm living: effects on childhood and adulthood asthma and allergy



- Background
- Farming and asthma/Hygiene hypothesis
- Timing of exposure
- The New Zealand farmers and asthma study
- Conclusions and interpretation

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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

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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.

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Urbanisation and childhood asthma* in Africa (Weinberg 2000)

Reference	Country	Group	N	Prevalence (%)
Niekerk et al., 1979	S Africa	Urban	695	3.17
		Rural	671	0.14
Keeley et al., 1991	Zimbabwe	Urban high SES	726	5.8
		Urban low SES	642	3.1
		Rural	687	0.1
Addo Yobo et al., 1997	Ghana	Urban rich	599	4.7
		Urban poor	220	2.2
		Rural	270	2.7
Ng'ang'a et al., 1998	Kenya	Urban middle class	331	10.3
		Urban poor	242	9.1
		Rural plantation	140	12.9
		Rural peasant	339	3.2

* Exercise induced bronchospasm

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Cattle and pigs in and around the house protect against allergies in Nepal and Africa (Shaheen et al., 1996; Melson et al., 2001)

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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)

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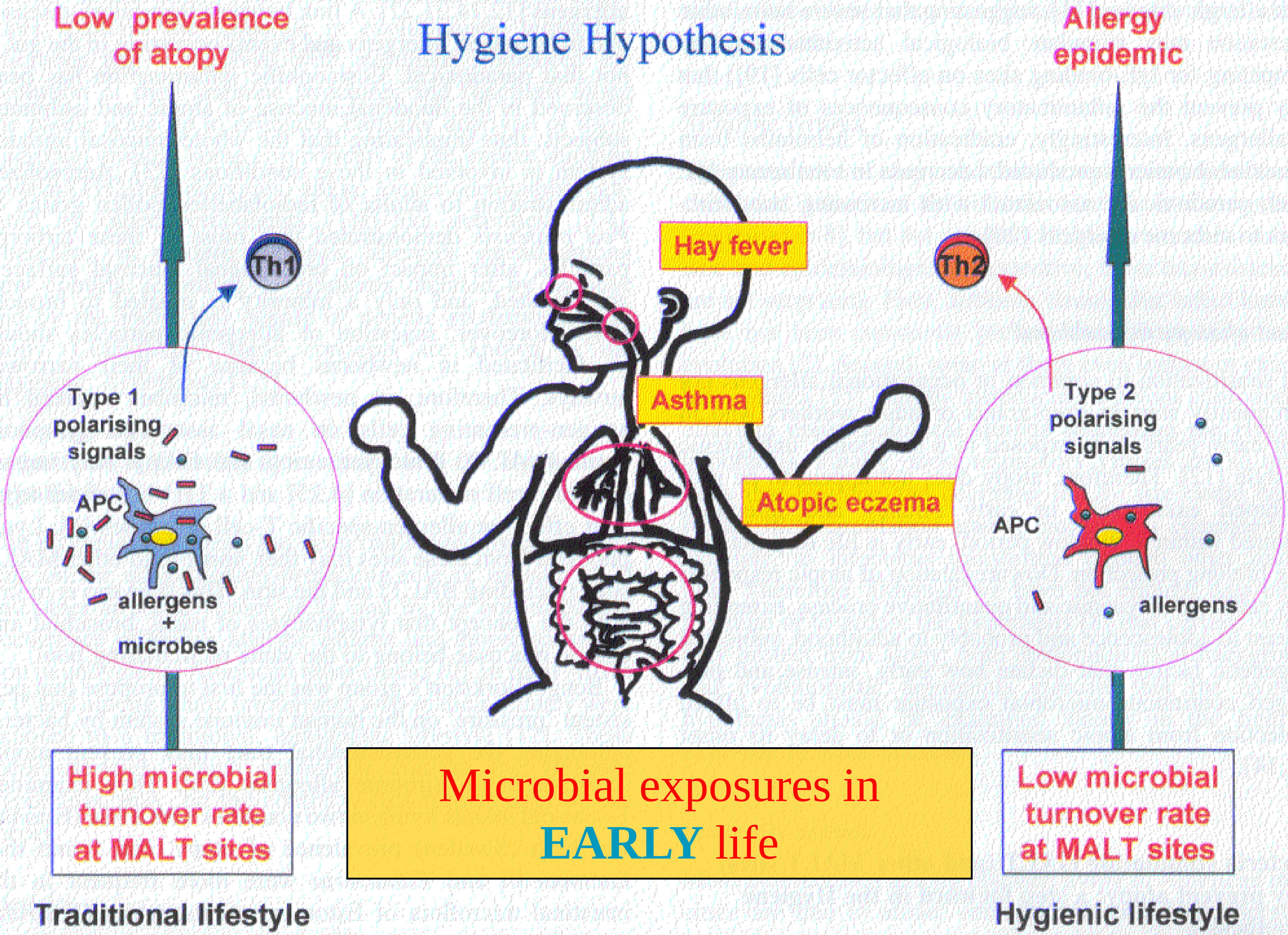

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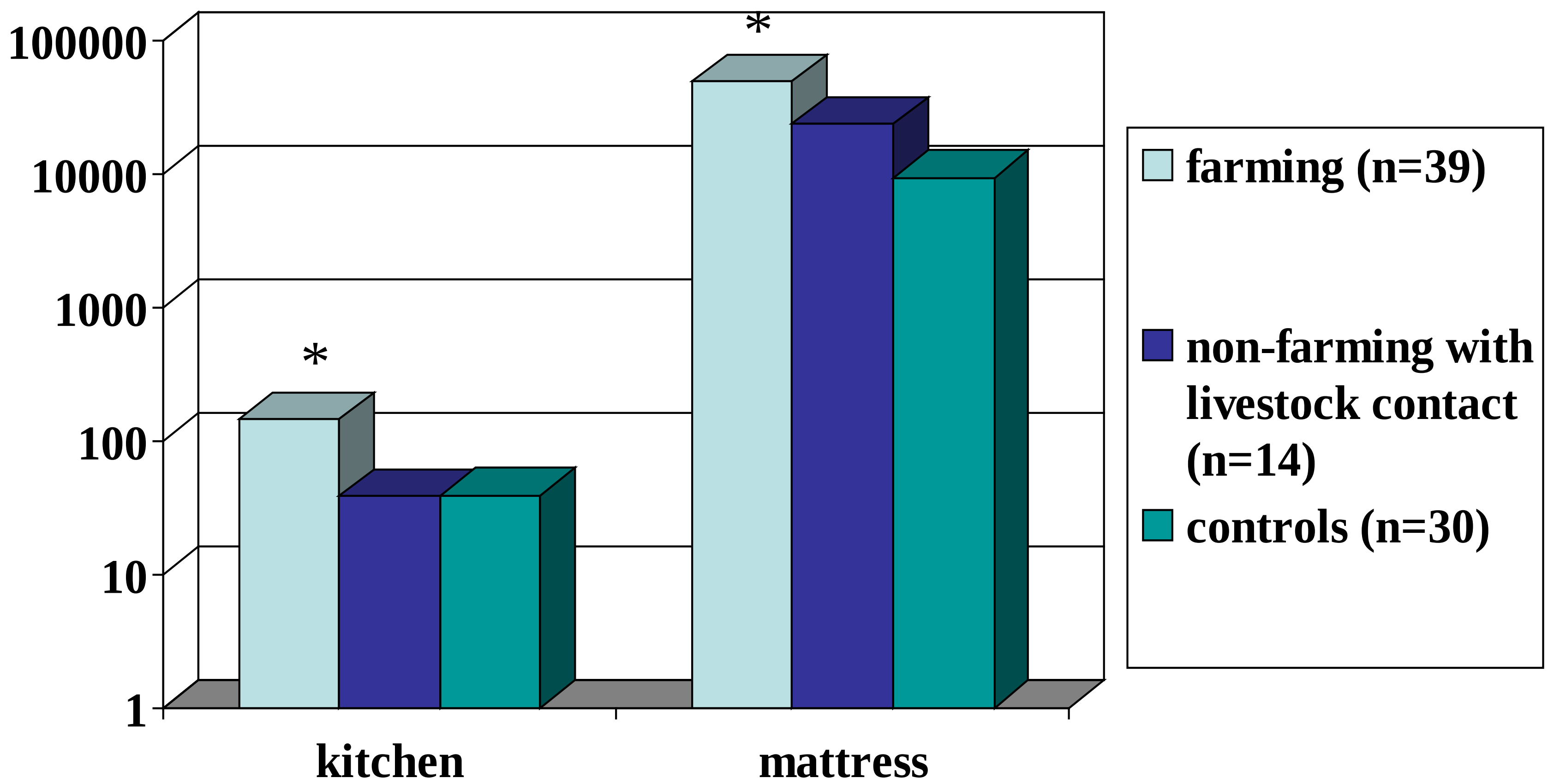
Endotoxin levels (EU/mg) in farming and non-farming families



(Von Mutius, 2000)

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Mattress endotoxin, atopy, hay fever, and asthma in 6-13 yr olds from farming and non-farming families (Braun-Fahrländer et al., 2002)

Health outcome	Exposure to farming during first year of life	Current endotoxin exposure
	OR (95% CI)	
Hay fever	0.26 (0.13-0.52)*	0.61 (0.40-0.95)*
Sneezing and itchy eyes	0.55 (0.31-0.97)*	0.53 (0.36-0.77)*
Atopic sensitisation	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)*
Non-atopic asthma	0.48 (0.16-1.41)	1.22 (0.60-2.46)
Atopic wheeze	0.59 (0.28-1.23)	0.66 (0.41-1.07)
Non-atopic wheeze	0.43 (0.19-0.97)*	1.23 (0.73-2.06)

* $p<0.05$; lowest versus highest quartile

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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

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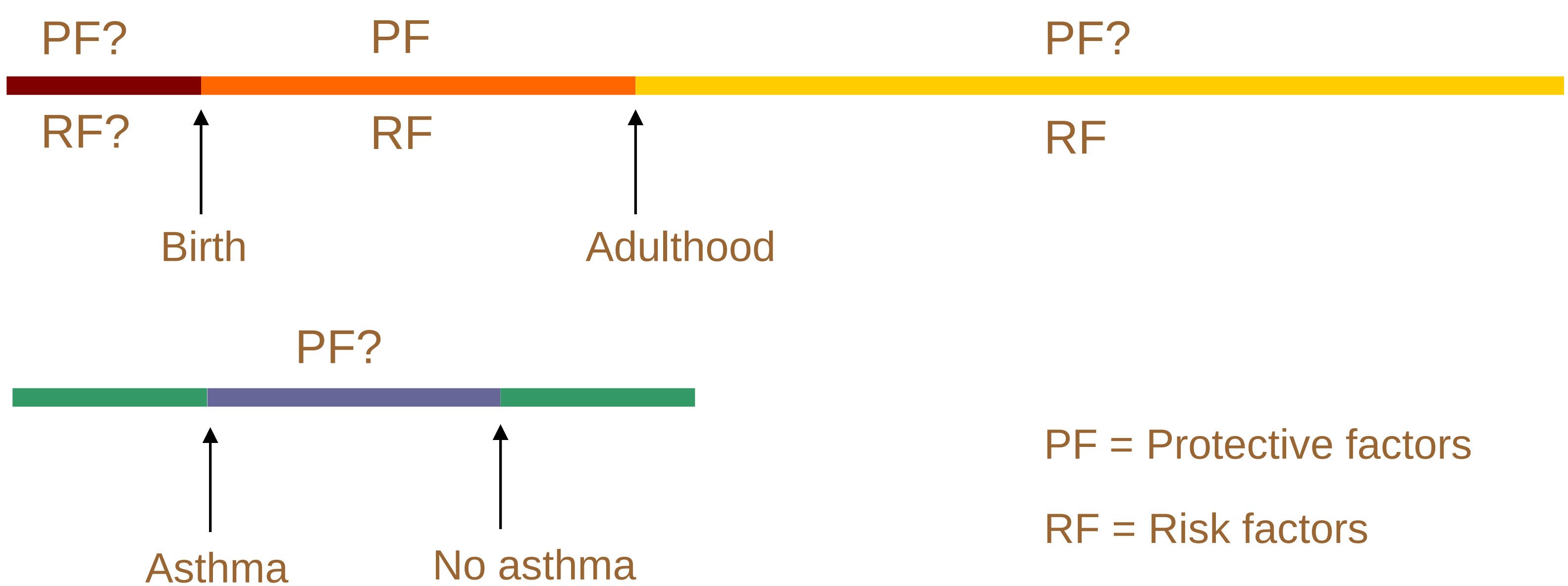
Asthma a "*biological Freudianism*"?

- Rene Dubos. Biological Freudianism. Lasting effects of early environmental influences. *Pediatr* 1966;38:789-800
- Do asthma and allergies originate in early life?
- Is the immune system fixed after the first few years of life?
- Can risks be modifies in later life?
- Is continued exposure required?
- Is it reversible?



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Atopic sensitisation and endotoxin exposure in swine farmers (Portengen et al., 2005)

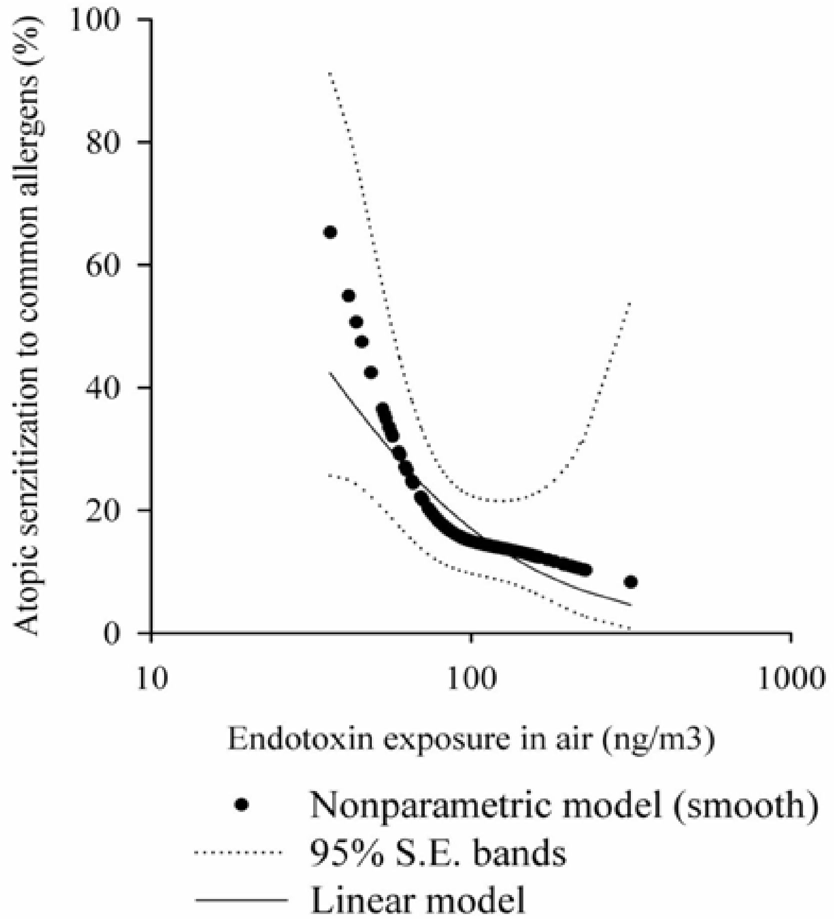
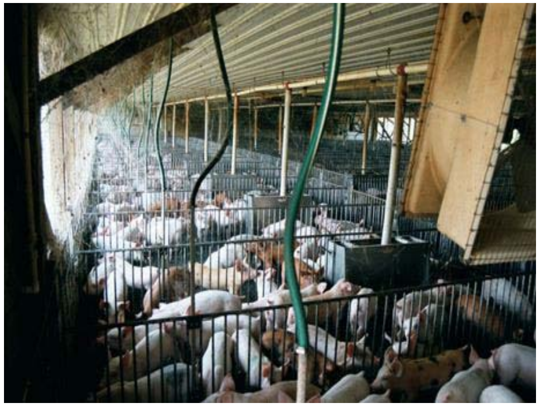


FIGURE 1



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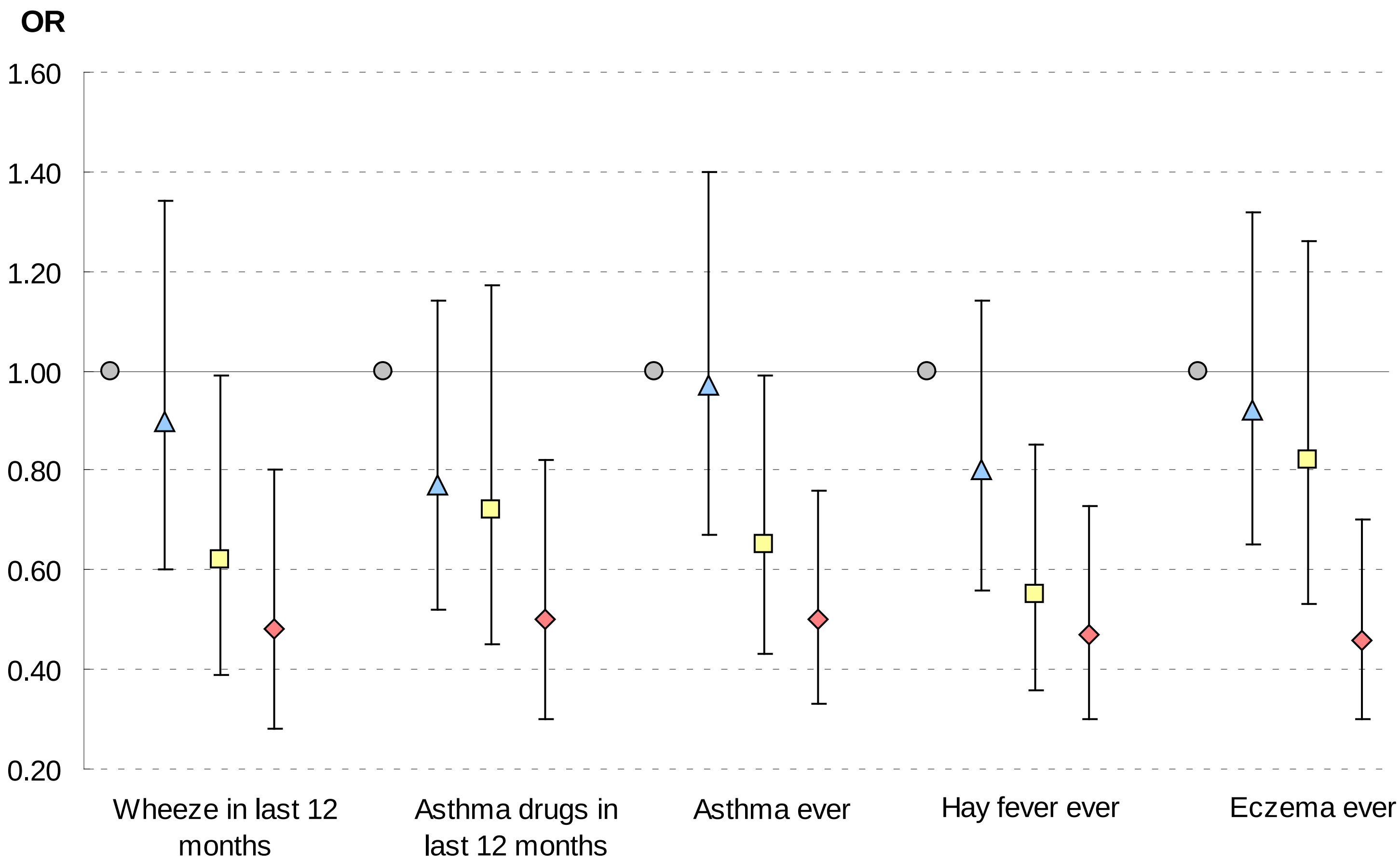
Independent and joint effects of current and prenatal animal exposure in NZ farmers' and rural reference children (Douwes et al., 2008)

Analyses were adjusted for age, sex, ethnicity, mother's education level, ETS, and farm type



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

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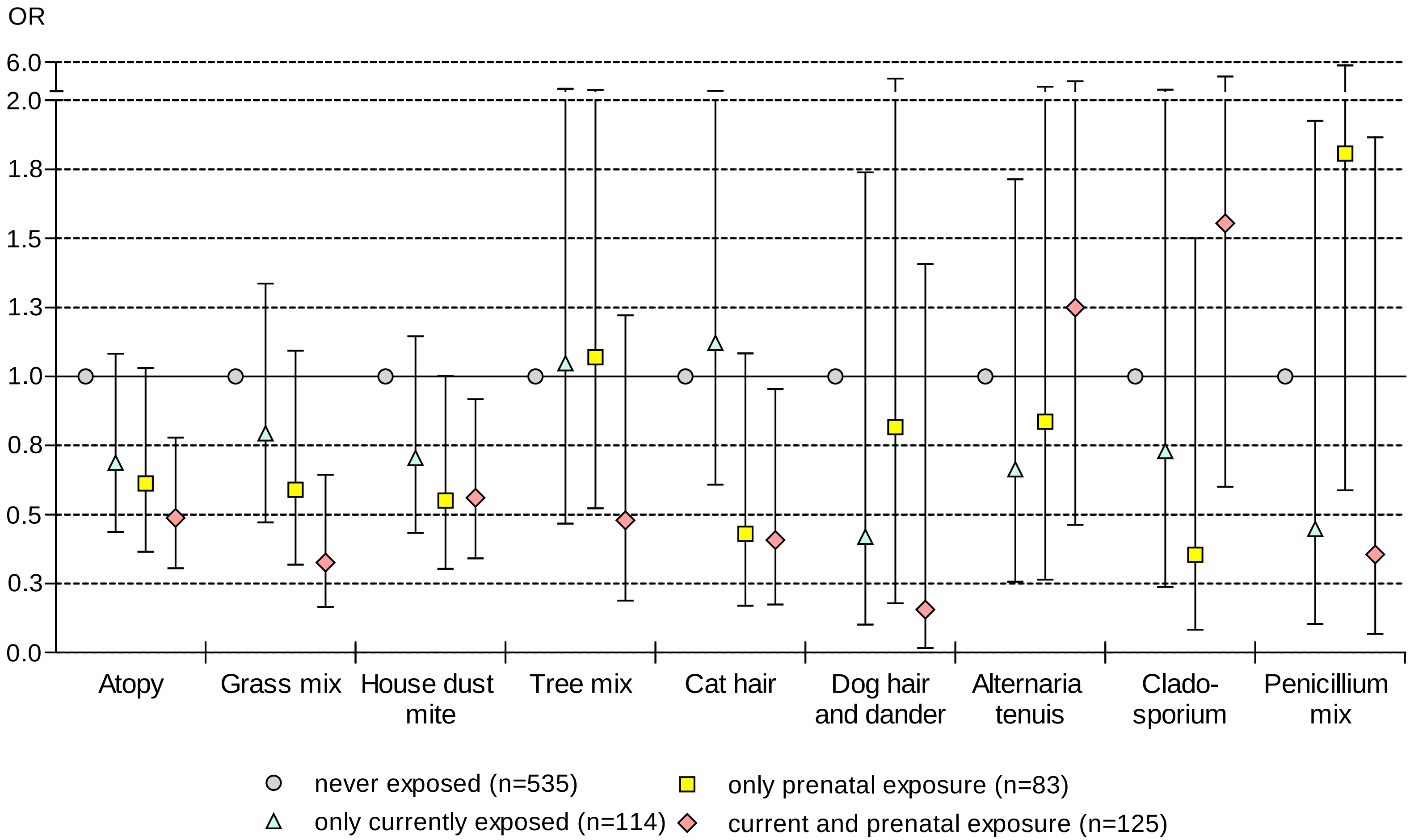
Animal exposure and atopy in a subpopulation

Analyses were adjusted for age, sex, ethnicity, mother's education level, ETS, and farm type



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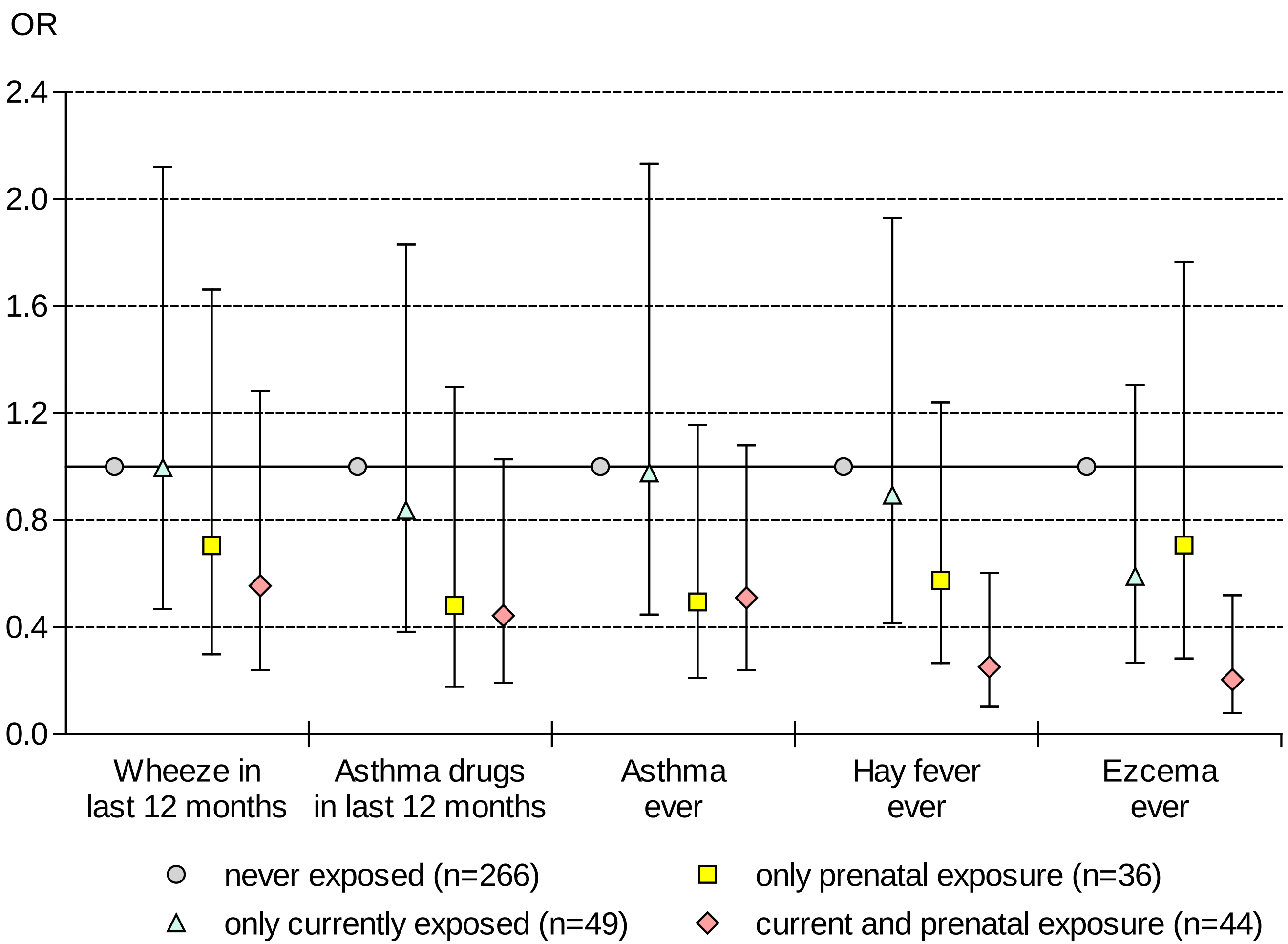
Animal exposure and symptoms in atopics

Analyses were adjusted for age, sex, ethnicity, mother's education level, ETS, and farm type



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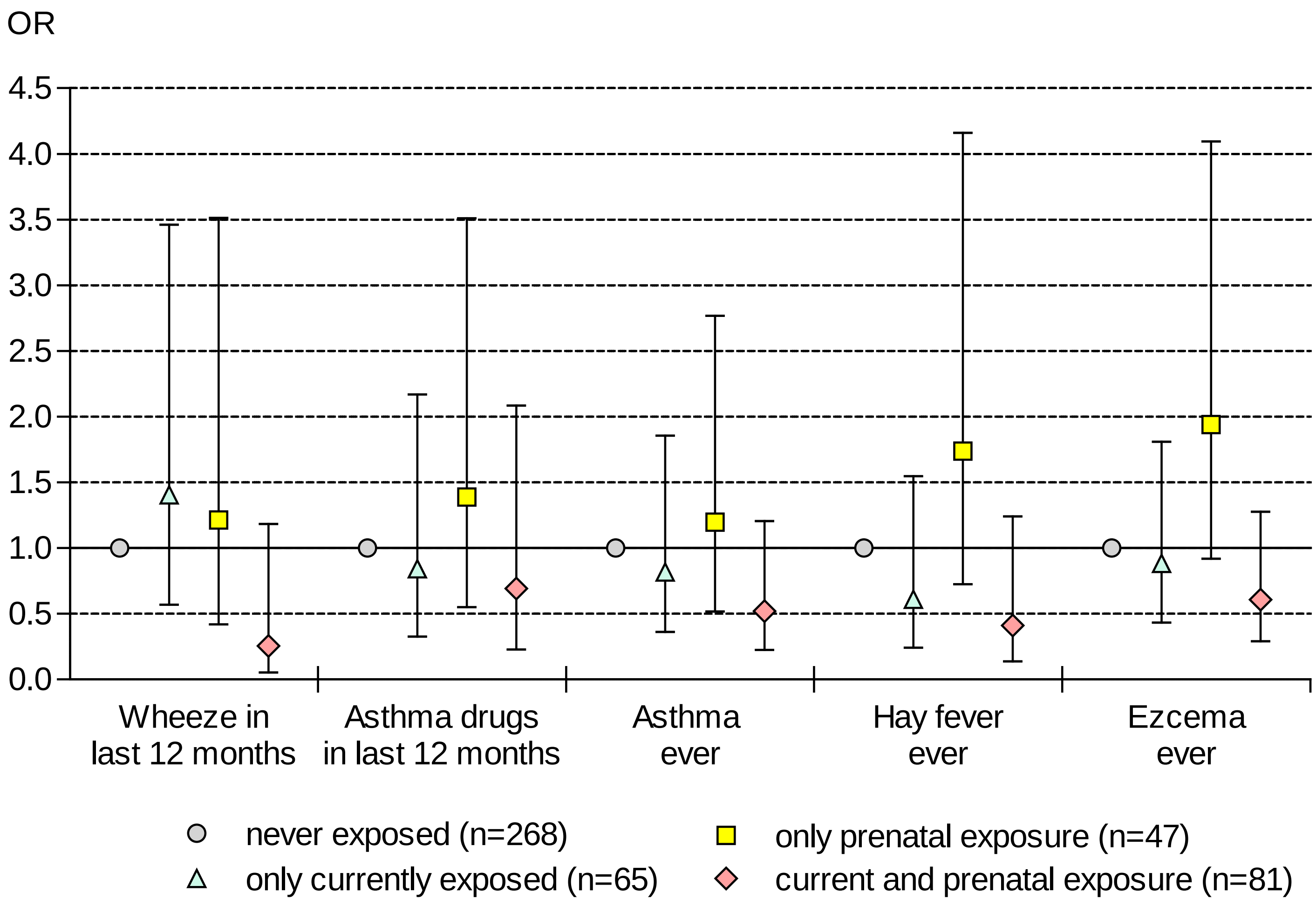
Animal exposure and symptoms in non-atopics

Analyses were adjusted for age, sex, ethnicity, mother's education level, ETS, and farm type



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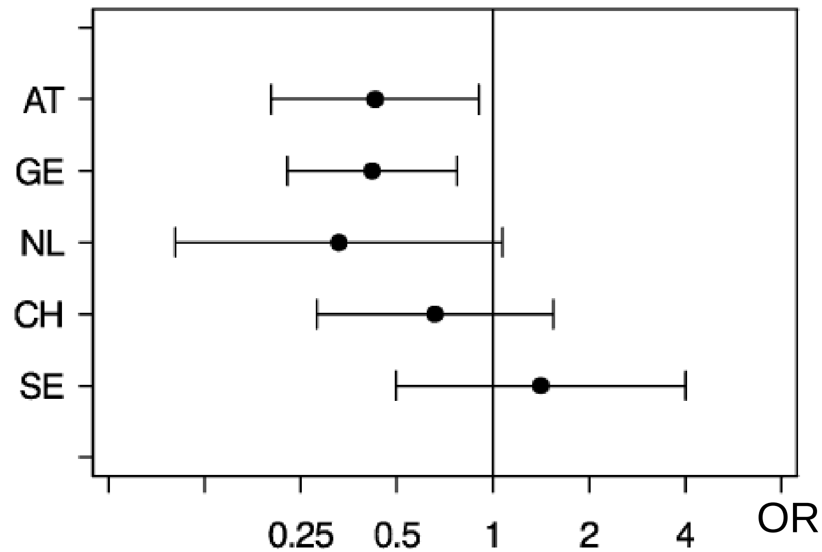
Atopy and farm exposure in farmers children, the PARSIFAL study (Ege *et al*., JACI 2006)

Adjusted ORs for maternal work in stables during pregnancy

	Atopic sensitization ($\geq$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

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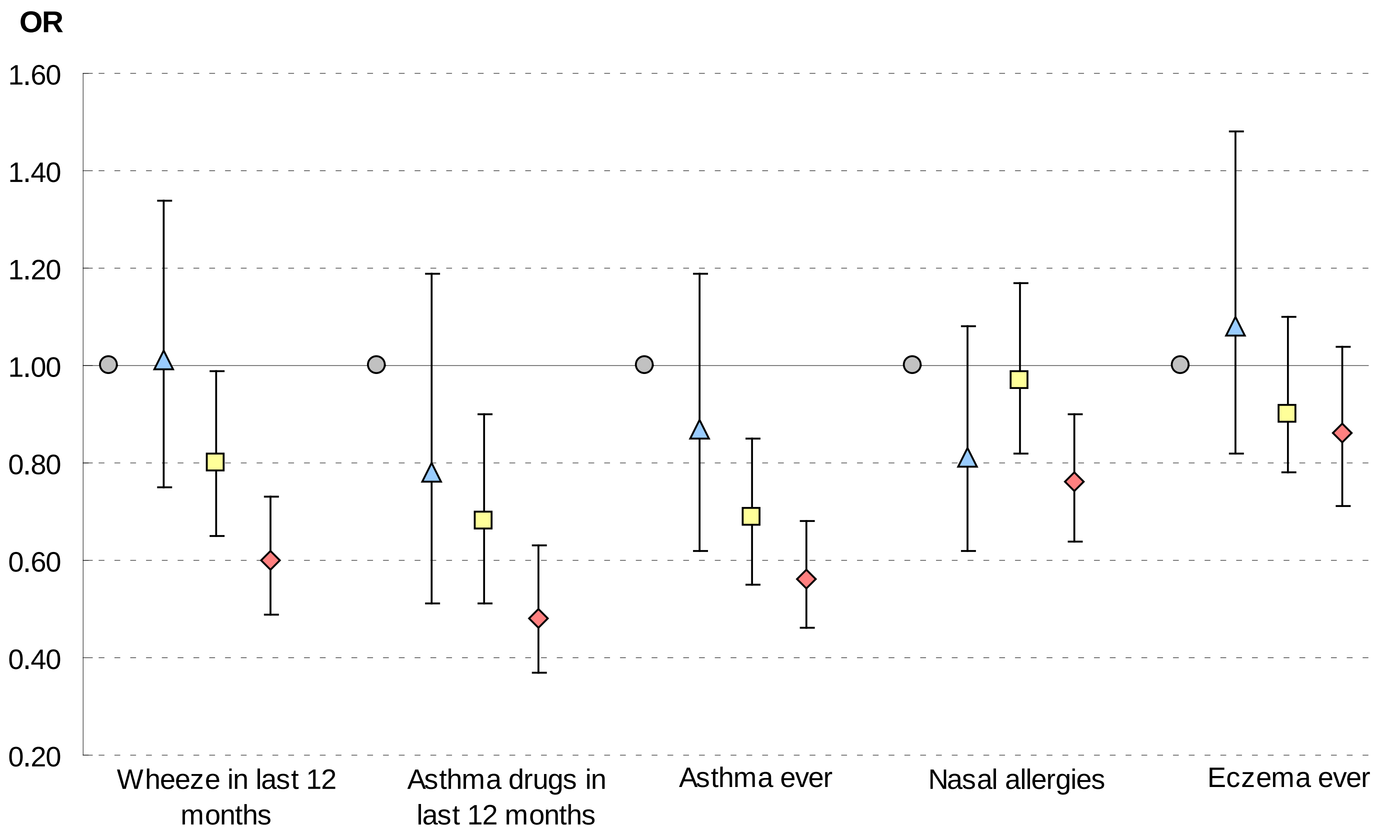
The independent and joint effects of *current* and *childhood* exposure in adult farmers (Douwes et al., 2007)

Adjusted for age, sex, ethnicity and smoking



O, never exposed (n=1017; reference group); Δ only exposed in childhood (n=297); □ only currently exposed (n=1478); ◊ current and childhood exposure (n=2784)

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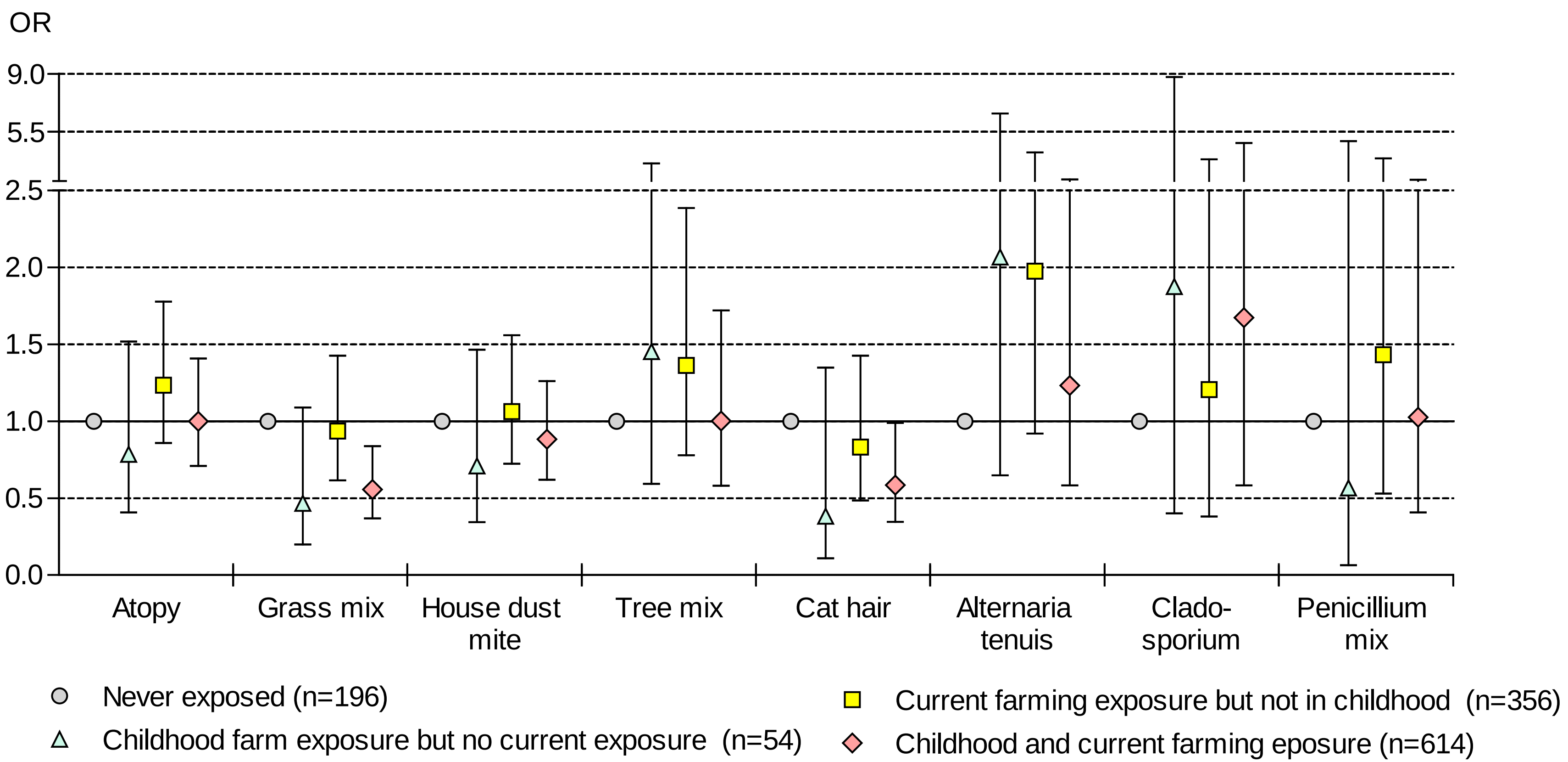
Farming and atopy in a subpopulation

Analyses were adjusted for age, sex, ethnicity, and smoking



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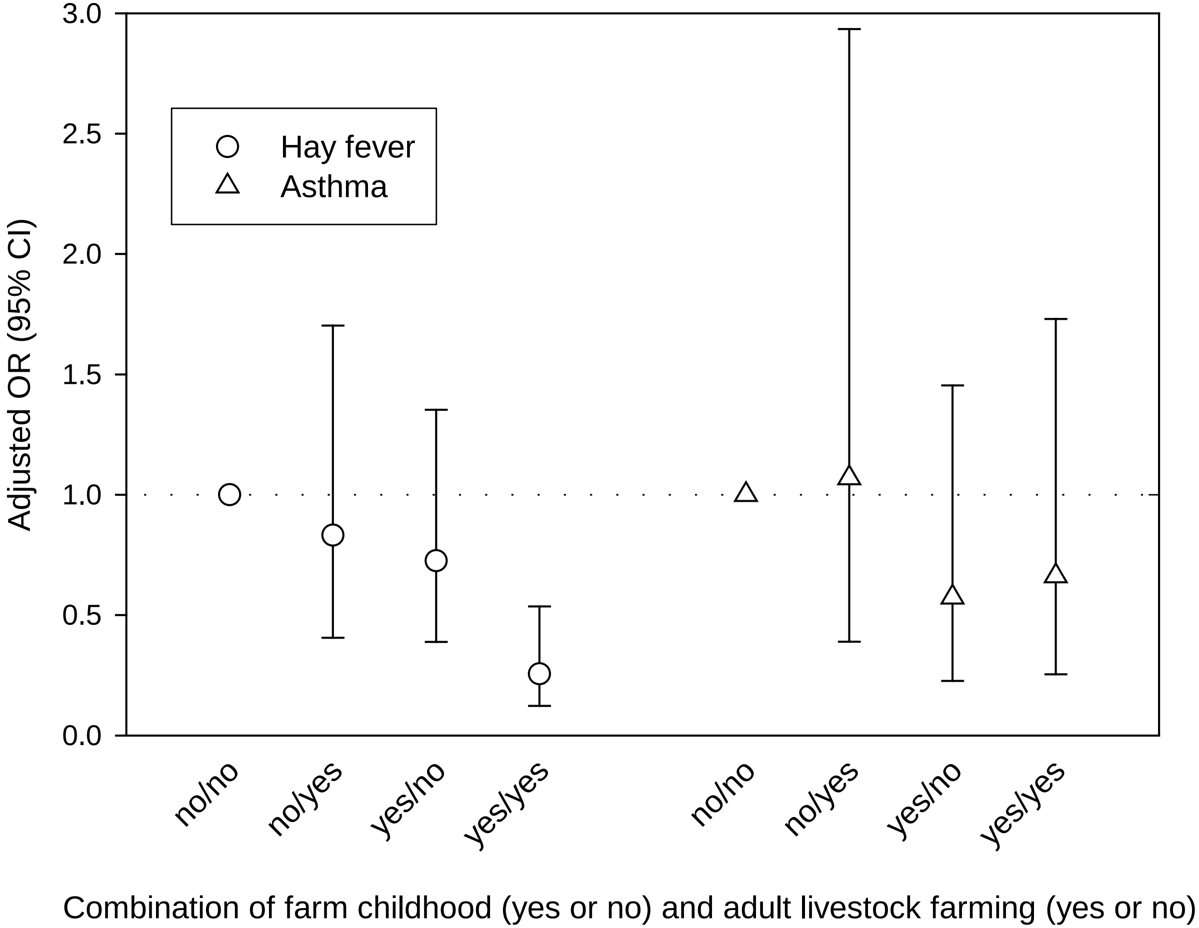
Farm/animal contact and hay fever in adults in The Netherlands (Smit et al., 2007)



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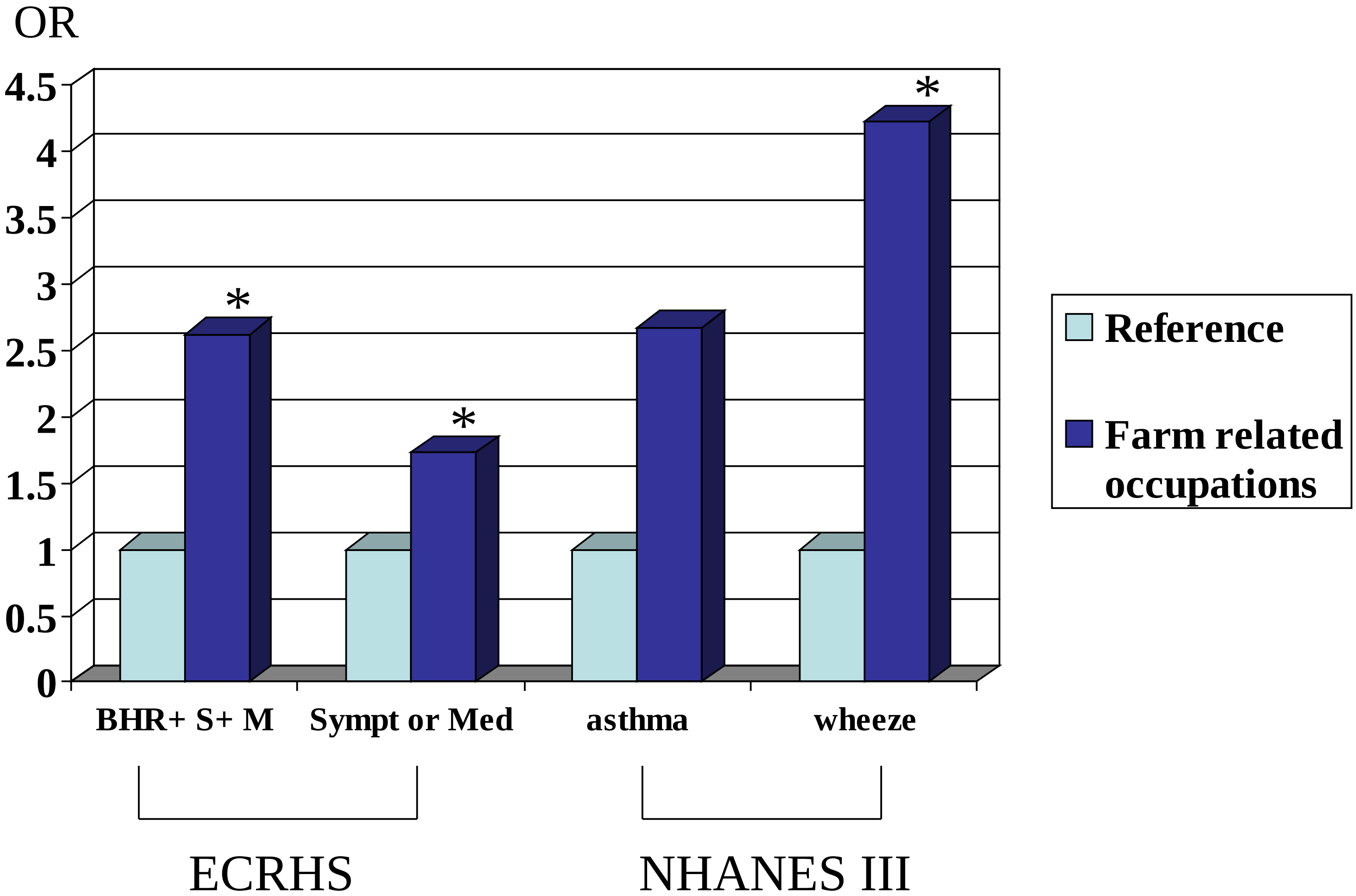
Population based studies of work related asthma and wheezing (ECRHS, NHANES III)

(Kogevinas et al., Lancet 1999; Ahmed et al., Am J Ind Med 2003)



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Livestock farming in New Zealand and Europe

New Zealand

Europe

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U-shaped dose-response? (Douwes et al., 2009)

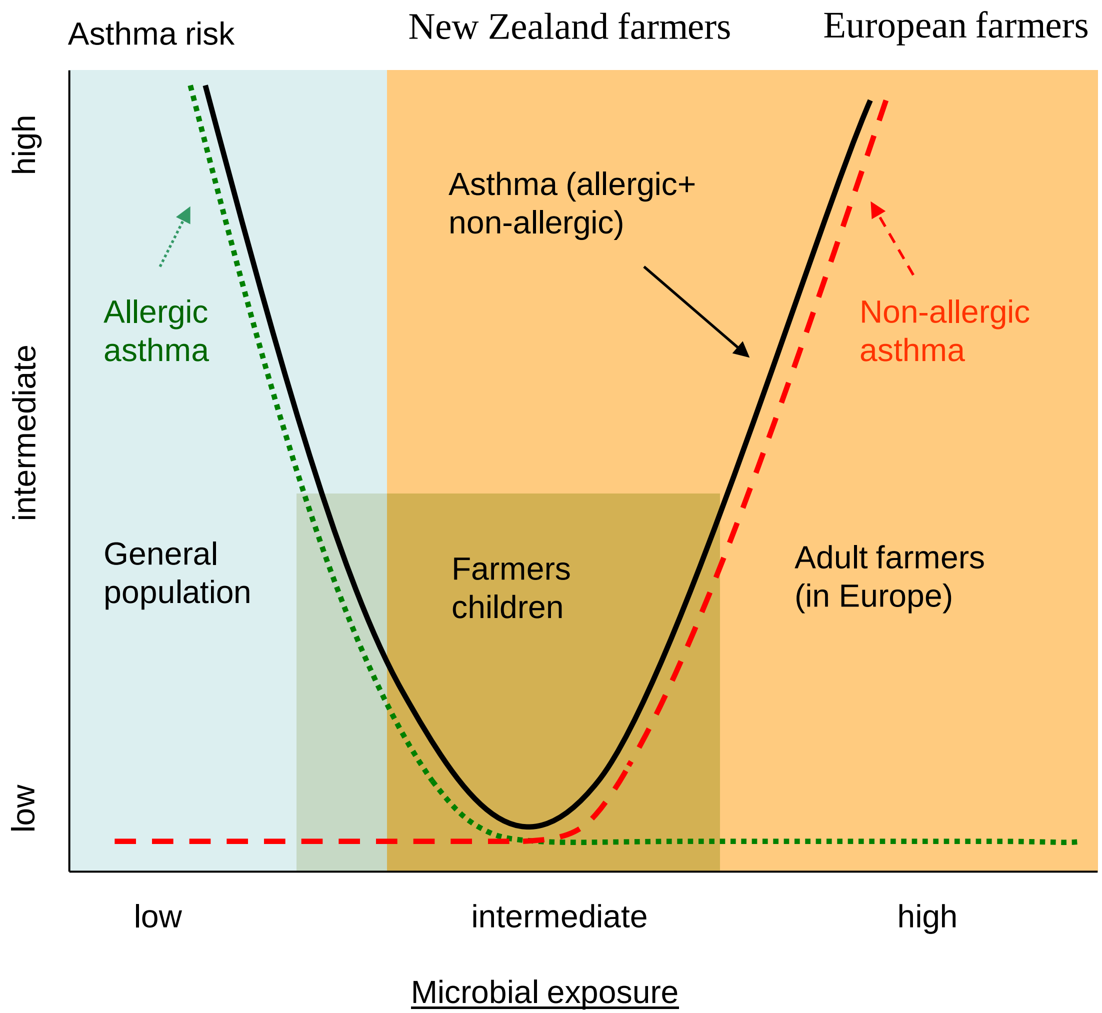

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Table 1 Overview of epidemiological studies indicating adverse respiratory effects related to environmental endotoxin exposure

Reference	Population	N	Exposure*	Health effect
Occupational studies:				Acute respiratory effects:
48	Pig farm workers	40	180 ng/m^3	Cross-shift decline in FEV_1 and MEF_{25}
49	Slaughter house workers	23	20–1500 ng/m^3	Cross-shift decline in FEV_1 and FVC; increased prevalence of respiratory symptoms
50	Animal feed workers	119	29 ng/m^3	Cross-shift decline in MMEF and MEF_{50}; cross-week decline in FEV_1, MEF_{25}, MMEF and MEF_{50}
51, 52	Fibreglass workers	130	0.4–759 ng/m^3	Cross-shift decline in PEF and FEV_1; increased amplitude of PEF; increased prevalence of respiratory symptoms and symptoms of fever, joint pains, and influenza-like symptoms
53	Potato processing workers	61	21–56 EU/m^3	Cross-shift decline in FEV_1 and MMEF
54	Potato processing workers	97	534 EU/m^3	Cross-shift decline in PEF; increased prevalence of respiratory symptoms
				Chronic respiratory effects:
55	Cotton mill workers	443	2–550 ng/m^3	Decline in FEV_1; increased prevalence of chronic bronchitis and byssinosis
56	Pig farm workers	183	130 ng/m^3	Decline in FEV_1 and FVC; increased prevalence of respiratory symptoms
57	Cotton mill workers	253	9–126 ng/m^3	Decline in FEV_1 and FVC; increased prevalence of respiratory symptoms
58	Animal feed workers	315	25 ng/m^3	Decline in FEV_1, FVC, PEF, MEF_{75}, MEF_{50}
59	Cotton mill workers	34	20–320 ng/m^3	Increase in bronchial hyperresponsiveness
60	Pig farm workers	54	11332 EU/ m^3	Decline in FEV_1 and FVC; increased prevalence of cough and chronic bronchitis
61	Grain workers	410	2859 EU/ m^3	Decline in FEV_1; increased prevalence of respiratory symptoms
62†	Farm workers (pig farms/others)	168/127	588/410 EU/m^3	Longitudinal decline in FEV_1 and MMEF
63†	Pig farm workers	171	105 ng/m^3	Longitudinal decline in FEV_1
64†	Grain and animal feed workers	140	3.6–99.0 ng/m^3	Longitudinal decline in FEV_1 and MMEF
65†§	Cotton mill workers	366	–3200 EU/m^3	Longitudinal decline in FEV_1 and FVC
Indoor studies:				
20	Adult asthmatic patients	28	2.59 ng/mg	Decline in FEV_1 and FEV_1/FVC; increase in asthma medication and symptoms
66	Adult asthma (40)/rhinitis (29) patients	69	1.78 ng/mg	Decline in FEV_1, and FEV_1/FVC; increase in asthma medication and symptoms
67	Children (50% with asthma)	20	1–100 EU/mg	Increase in asthma medication and symptoms in asthmatic children
22	Children (50% with airway symptoms)	148	24.9 EU/mg	Increased PEF variability in atopic children with asthma symptoms‡
68†	Infants	499	100 EU/mg	Increased prevalence of wheeze during first year of life

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MEF_{25}, MEF_{50}, MEF_{75} = maximum expiratory flow rates at 25%, 50% and 75% of the vital capacity; MMEF = maximum mid expiratory flow; PEF = peak expiratory flow.
*Exposure is expressed as the mean exposure (or range of (mean) exposures if no overall mean is given) in ng or endotoxin units per m^3 or per mg of house dust; one endotoxin unit is approximately 0.1 ng (the exact conversion factor varies depending on the source of endotoxin for calibration).
†Longitudinal study (all other studies were cross sectional studies)
‡Association between endotoxin exposure and PEF variability disappeared after adjusting for pets in the home.
§15 year follow up of study by Kennedy *et al* in cotton mill workers.

Thorax 2002;**57**:86–90

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Atopy and asthma in 1614 Norwegian adult farmers (Eduard et al., Thorax 2004)

	Asthma	Atopy	Atopic asthma	Non-atopic asthma
	Adjusted ORs			
Fungal spores				
- Low	*Ref*	*Ref*	*Ref*	*Ref*
- medium	1.3	1.0	0.6	1.6
- high	1.2	1.0	0.3*	1.7*
Endotoxin				
-Low	*Ref*	*Ref*	*Ref*	*Ref*
- medium	1.0	1.1	0.6	1.1
- high	1.2	0.8	0.3*	1.6

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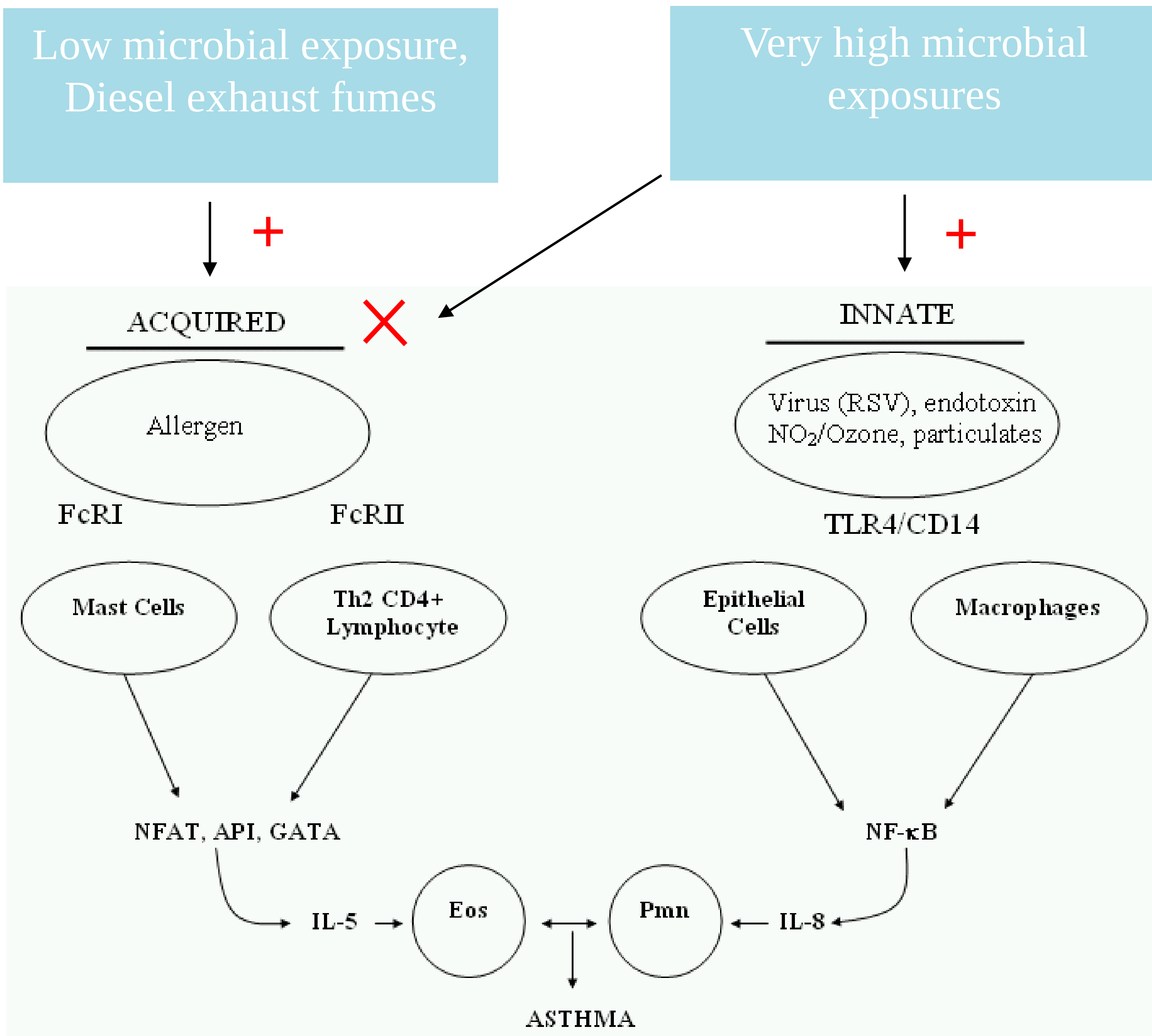
Acquired and innate immune pathways leading to asthma
(Douwes et al., 2002)



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The protective effects of farming on allergies and asthma: lasting effects of early environmental influences?

- Maybe, but effects may not last for ever;
- Continuous exposure may be required;

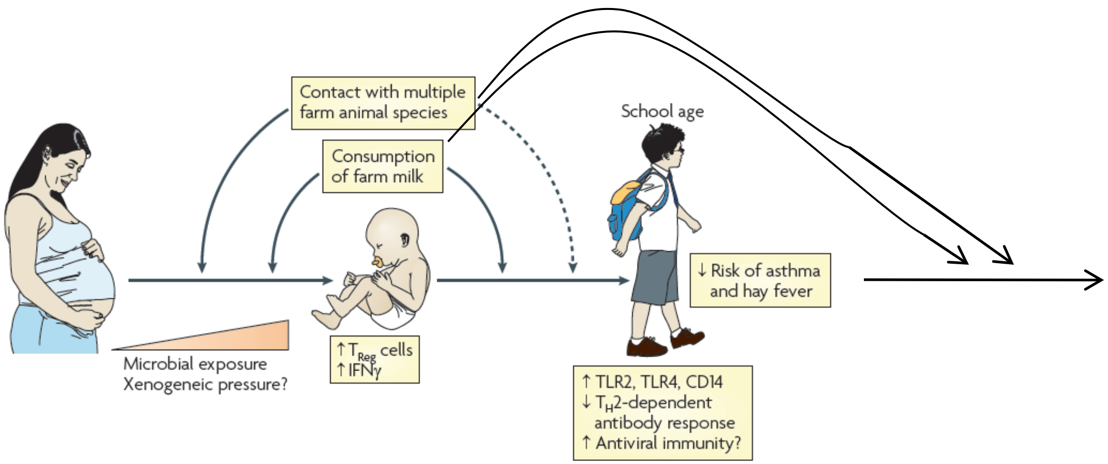

Figure 1 | **A working model of the immunobiology of farm exposure.** Contact with multiple animal species, combined with consumption of farm milk, results in strong microbial exposure of, and possibly xenogeneic pressure on, women who carry out farming duties during pregnancy. These combined exposures, which occur at a crucial time for programming immune responses, upregulate regulatory T (T_{Reg}) cell function and interferon-γ (IFNγ) production at birth, which in turn enhance innate immune responses (through increased expression of pattern-recognition receptors), and dampen T helper 2 (T_H2) cell-dependent allergic inflammation in early childhood. Exposure to animals and farm milk in early life reinforces the protective effects of prenatal exposures. The ability to produce high levels of IFNγ at birth may also ensure effective responses to respiratory viral infections in early life, thereby counter-acting the contribution of these infections to increased asthma susceptibility. TLR, Toll-like receptor.

- The role of atopy remains unclear;
- Studies of farming families have considerable potential to lead to realistic and effective interventions, even if their specific nature is unclear at this stage.

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