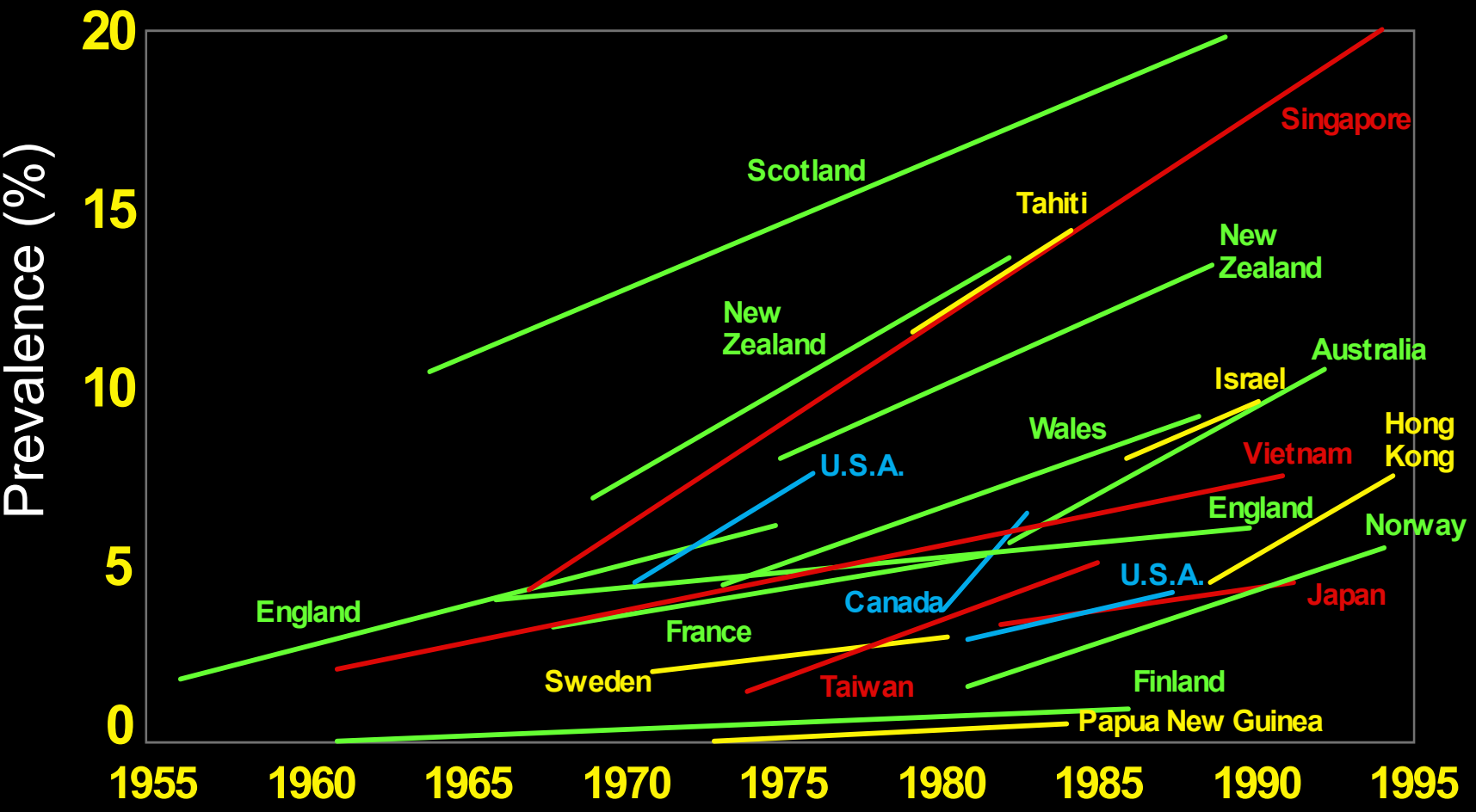
MANCHESTER 1824

The University of Manchester

Risk Factors for Allergic Sensitisation and Asthma

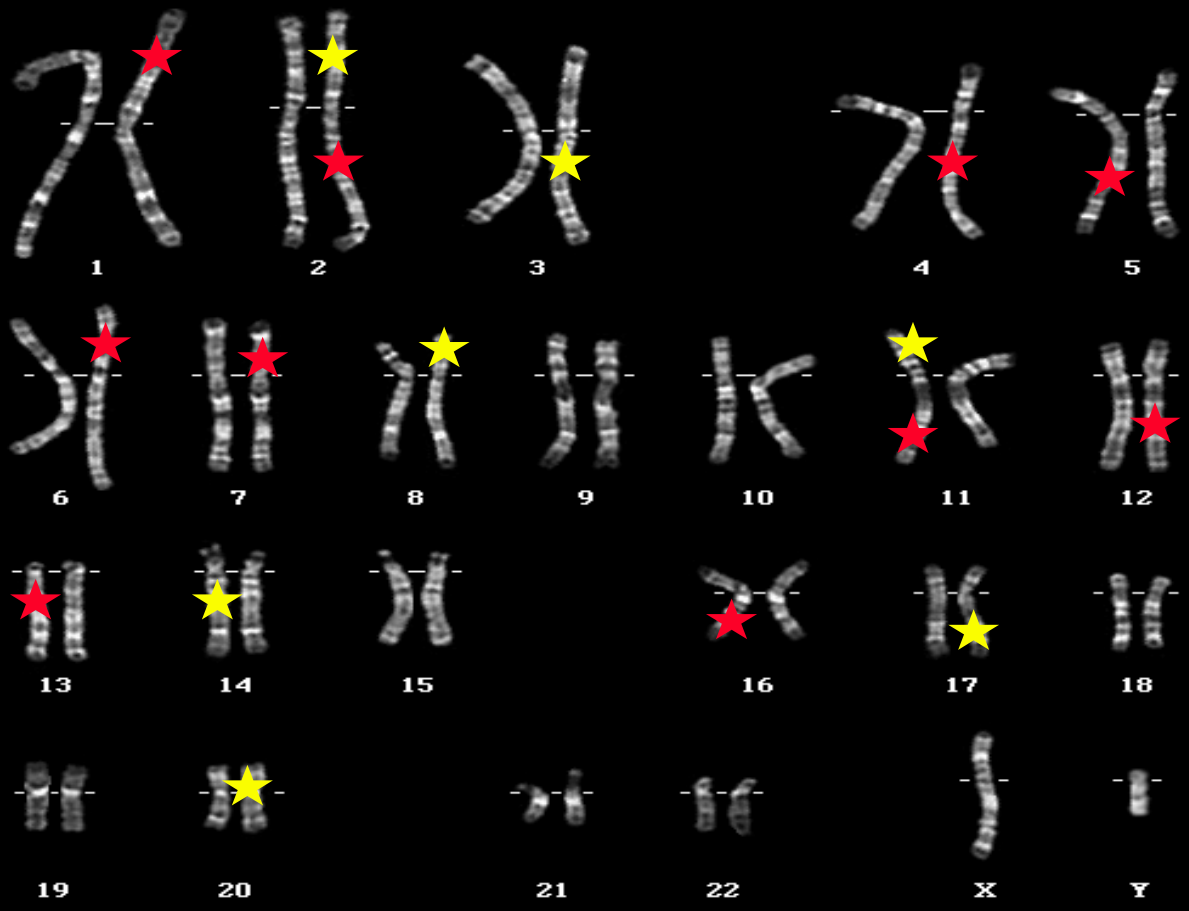
Adnan Custovic MD DM MSc PhD
Professor of Allergy
North West Lung Centre
Manchester, UK

Asthma has increased in prevalence



Beasley R, JACI 2000; 105: S466-472

Asthma is heritable – and complex



Linkage in 1 study

Linkage in >1 study

Environment And Respiratory Allergic Diseases

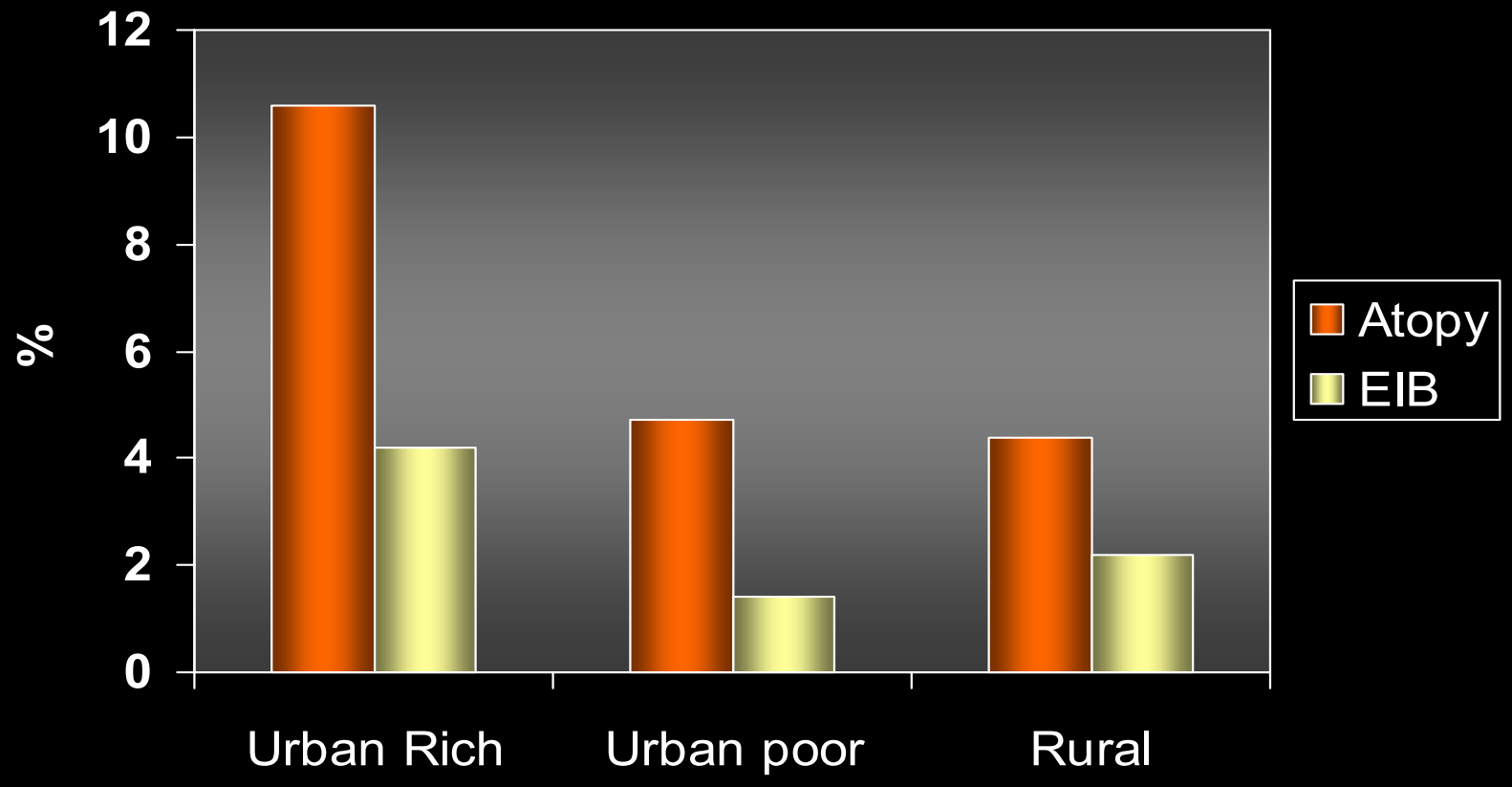
- Environment – everything that is not me
  - Albert Einstein
- Hygiene hypothesis
- The role of environmental allergen exposure

Hygiene Hypothesis

- Improved hygienic conditions
- ↓
- Less microbial exposure during early childhood
- ↓
- Slower post-natal maturation of the immune system
- ↓
- Delayed development of the optimal balance between TH-1 and TH-2-like immune response

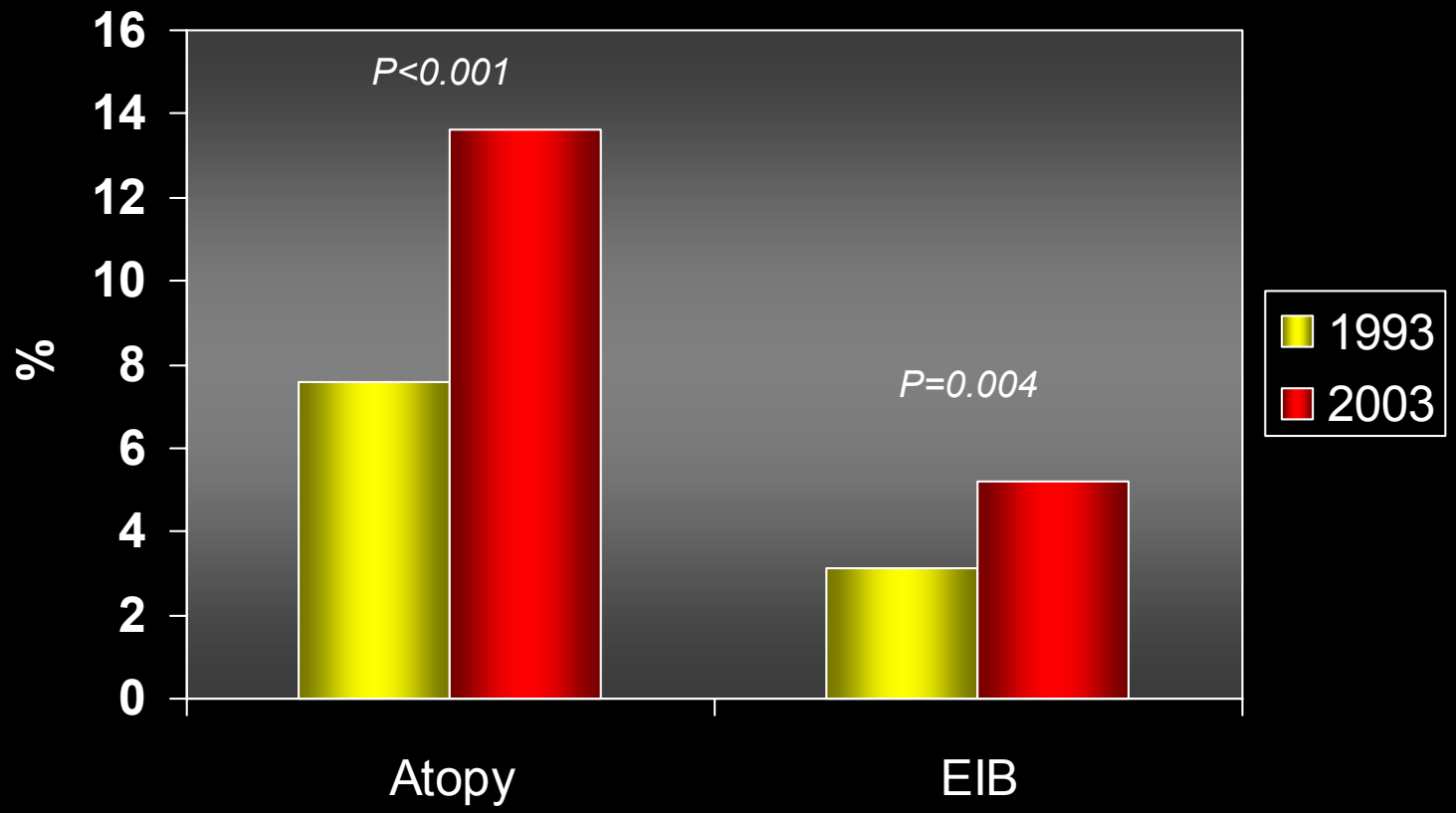
North Atlantic Ocean
South Atlantic Ocean
Indian Ocean
Arabian Sea
Mediterranean Sea
Black Sea
Caspian Sea
Red Sea
Gulf of Guinea
Gulf of Aden
Persian Gulf
Mozambique Channel
Strait of Gibraltar
Tropic of Cancer
Equator
Tropic of Capricorn
GERMANY
POLAND
UKRAINE
KAZAKHSTAN
FRANCE
ROM.
ITALY
PORTUGAL
SPAIN
GREECE
TURKEY
UZBEKISTAN
TURKMENISTAN
AZER.
ARM.
GEO.
SYRIA
IRAQ
IRAN
AFG.
CYPRUS
LEB.
ISRAEL
JORDAN
KUWAIT
QATAR
BAHR.
U.A.E.
OMAN
SAUDI ARABIA
YEMEN
Socotra (YEMEN)
AZORES (PORTUGAL)
MADEIRA ISLANDS (PORTUGAL)
CANARY ISLANDS (SPAIN)
MOROCCO
ALGERIA
TUNISIA
LIBYA
EGYPT
Western Sahara
MAURITANIA
MALI
NIGER
CHAD
SUDAN
ERITREA
DJIBOUTI
ETHIOPIA
SOMALIA
CAPE VERDE
SENEGAL
THE GAMBIA
GUINEA-BISSAU
GUINEA
SIERRA LEONE
LIBERIA
CÔTE D'IVOIRE
BURKINA FASO
GHANA
TOGO
BENIN
NIGERIA
CAMEROON
CENTRAL AFRICAN REPUBLIC
EQUATORIAL GUINEA
SAO TOME AND PRINCIPE
GABON
REP. OF THE CONGO
DEM. REP. OF THE CONGO
UGANDA
KENYA
RWANDA
BURUNDI
TANZANIA
ANGOLA
ZAMBIA
MALAWI
MOZAMBIQUE
ZIMBABWE
BOTSWANA
NAMIBIA
SOUTH AFRICA
SWAZILAND
LESOTHO
MADAGASCAR
COMOROS
SEYCHELLES
MAURITIUS
St. Helena (U.K.)
Ascension (St. Helena)
Scale 1:51,400,000
Azimuthal Equal-Area Projection
0 800 Kilometers
0 800 Miles
Boundary representation is

Atopy And EIB Amongst Urban Rich, Urban Poor and Rural Children in Ghana in 1993



EOD Addo Yobo & A Custovic, Thorax 1997

Atopy and Exercise-Induced Bronchospasm in Ghana: 1993-2003

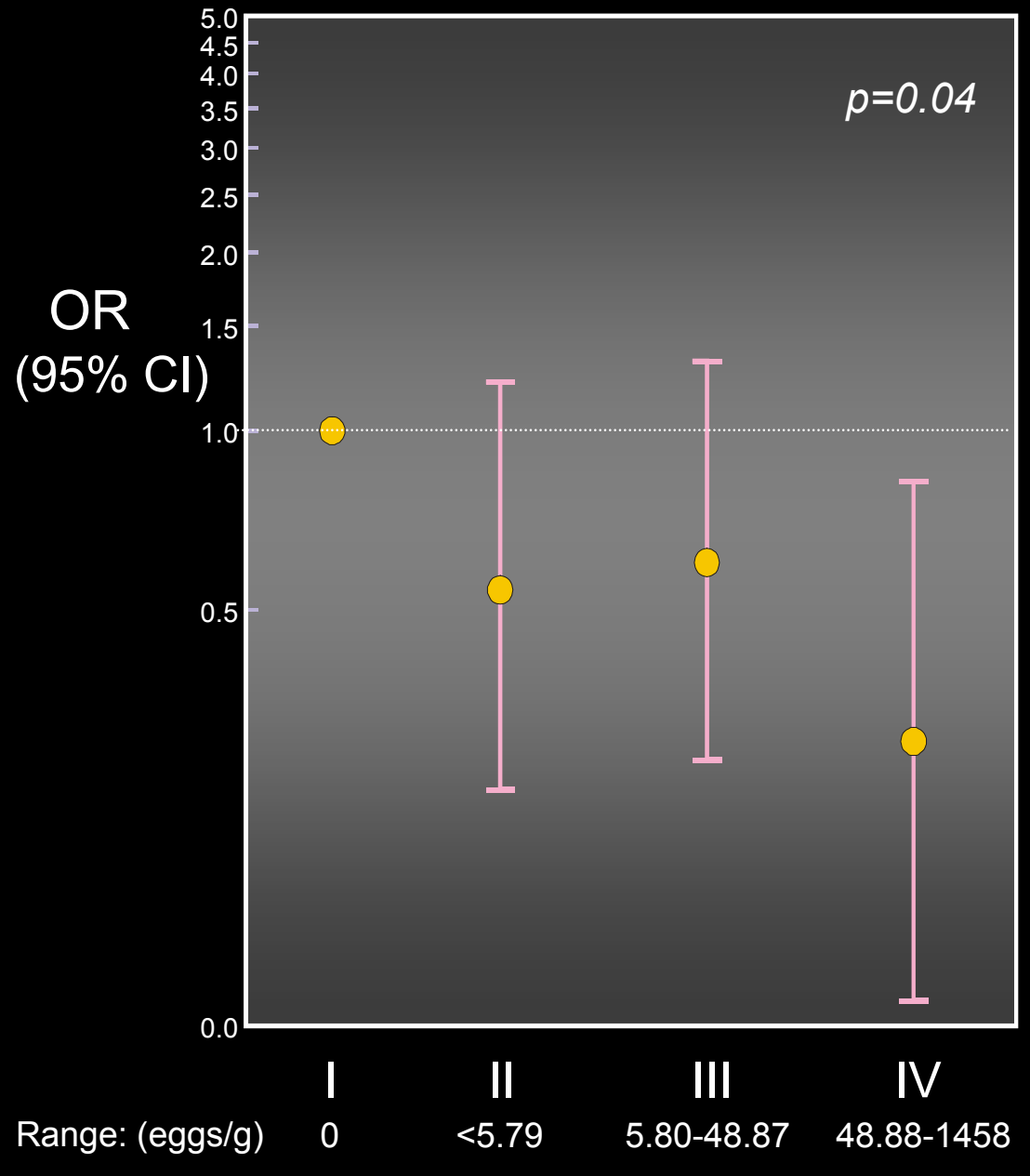


EOD Addo Yobo & A Custovic, 2006

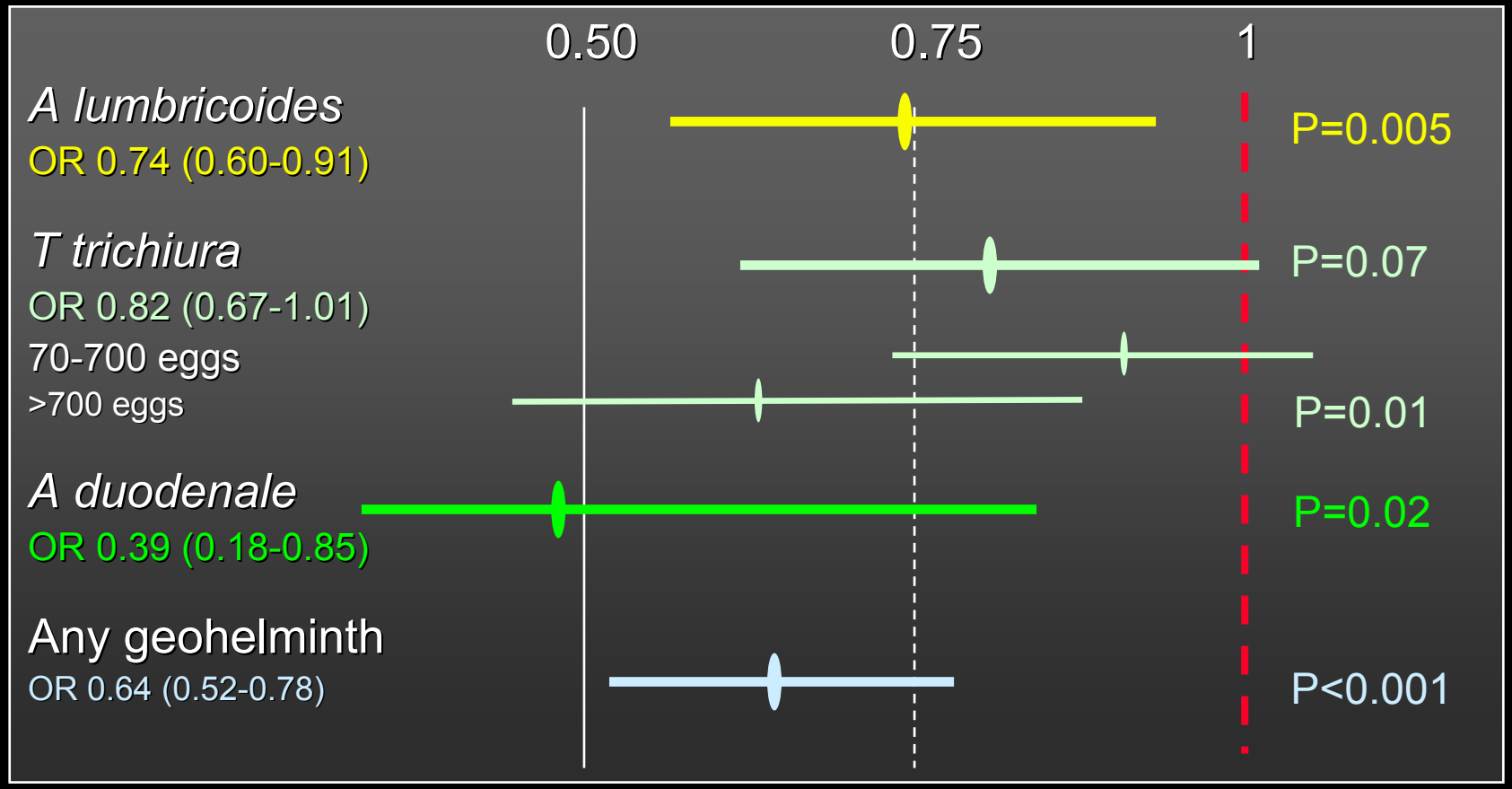
Odds Ratios for Wheeze and Hookworm Quartiles

Scrivener et al

Lancet 2001; 358: 1493-1499

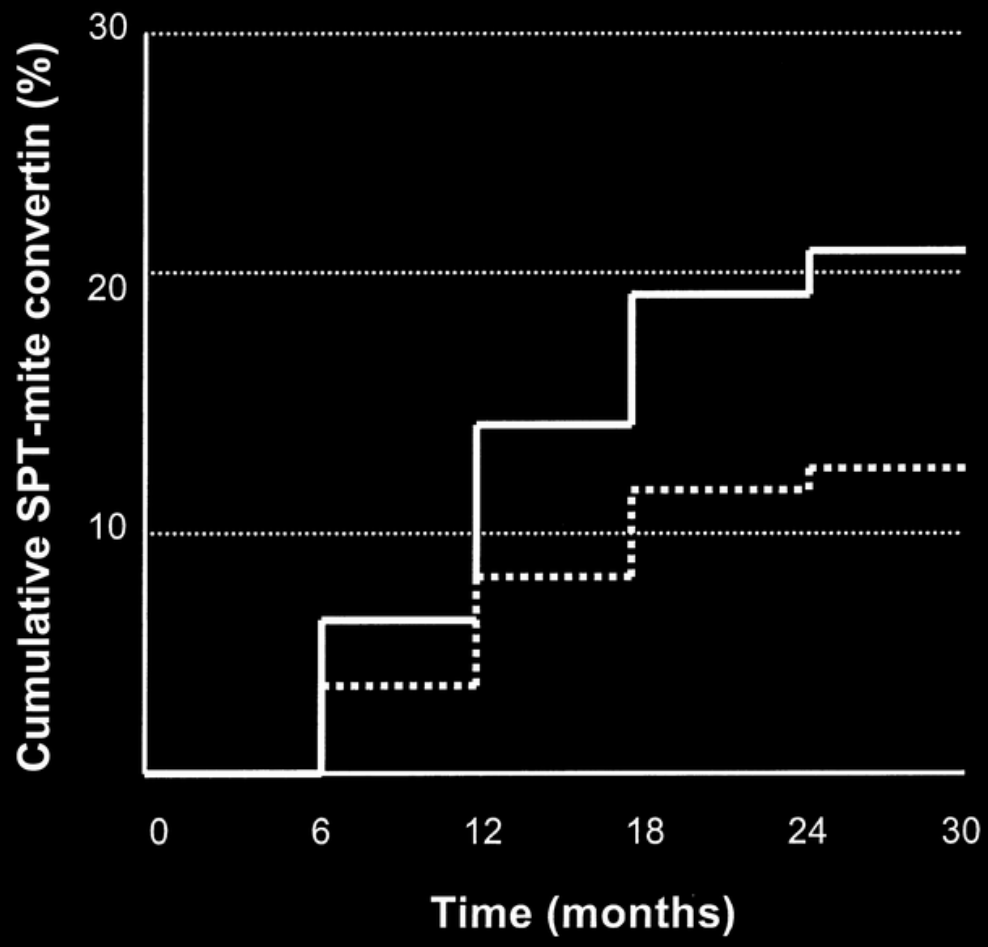


Geohelminthic Parasites are Protective Against Skin Test Reactivity in Ecuador



Cooper PJ et al, JACI 2003; 111: 995-1000

Treatment of Intestinal Helminths Increases Mite Skin-Test Reactivity



Treatment group (163):

Praziquantel +
Mebendazole 3 monthly

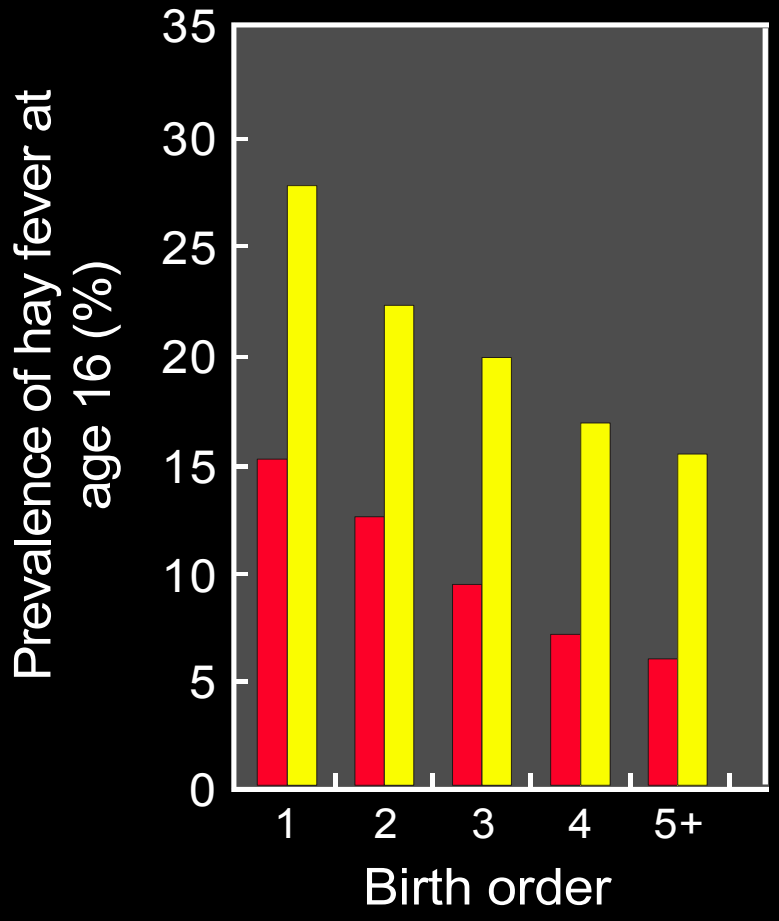
Placebo group (178)

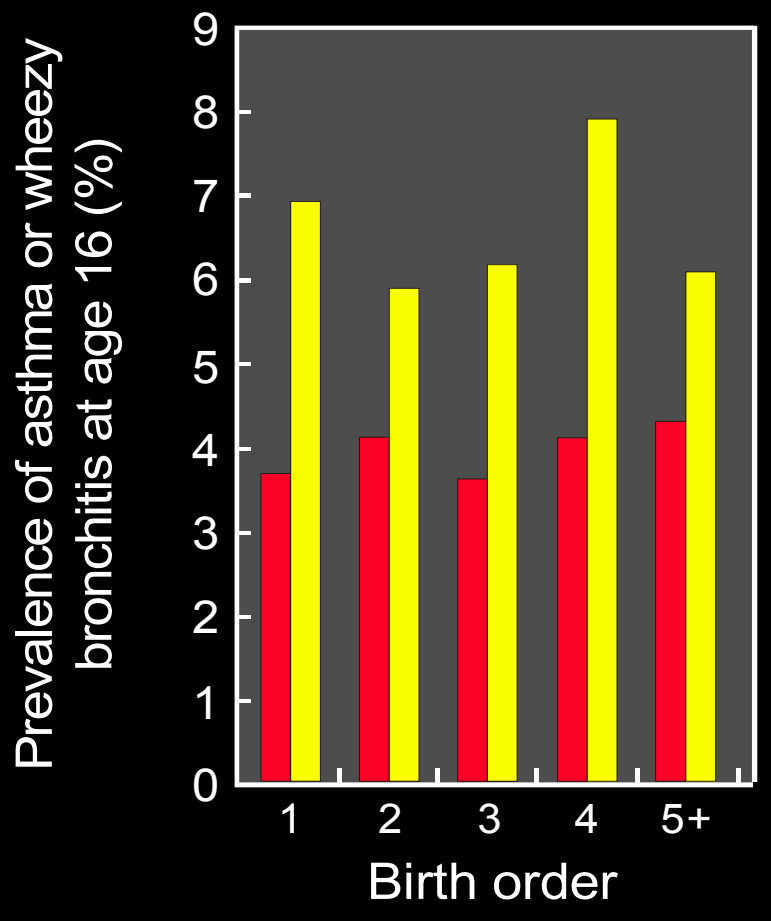
Van den Biggellar et al, JID 2004; 182: 892-900

Inverse Association Between Family Size, Atopy and Asthma

- Number of older siblings more important compared to younger siblings
  - *Strachan, BMJ1989; 299: 1259-60, Strachan et al., Arch Dis Child 1996; 74: 422-6*
- No such difference
  - *Strachan & ALSPAC Study Team, Clin Exp Allergy 1997; 27: 151-5*
- Stronger effect of family size than of birth order
  - *Jarvis et al., Clin Exp Allergy 1997; 27: 240-5*
- Protective effect of greater number of brothers
  - *Svanes et al, J Allergy Clin Immunol 1999; 103: 415-20)*
- Older siblings inversely correlated to atopic disorders only for the children with a history of parental atopy
  - *Mattes et al., Clin Exp Allergy 1998; 28: 1480-6*
- Very little association between asthma and family size
  - *Rona et al., J Epidemiol Community Health 1999; 53: 15-19*

Hay Fever and Asthma at Age 16 in Two British Cohorts by Birth Order





Strachan et al

BCG, Allergy and Asthma

- Association between positive tuberculin responses and less allergy & asthma

But

- Inverse relationship dependant on a small number of children with florid tuberculin response not being allergic
- ? reverse hypothesis correct - the tuberculin reaction size is reduced in asthmatic children because they have lower IFN-γ secretion

Shirakawa et al., Science 1997; 275: 77-9

BCG and Atopy

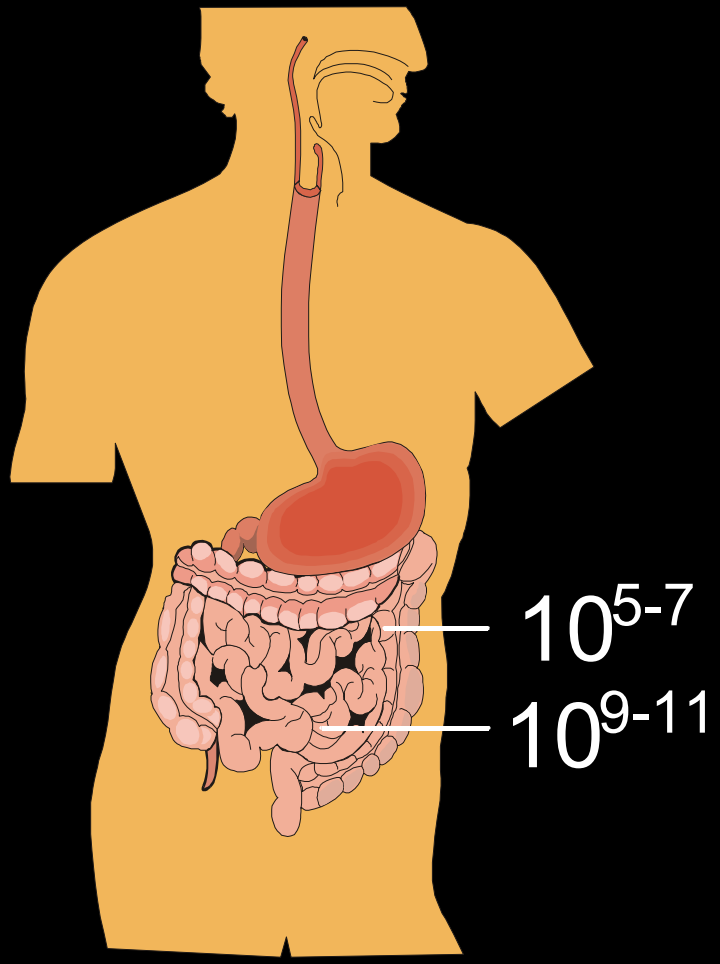
- 216 children with atopic parents who received a BCG vaccination (<6 months of age) and 358 matched controls without a BCG vaccination
- No differences between the 2 groups

But

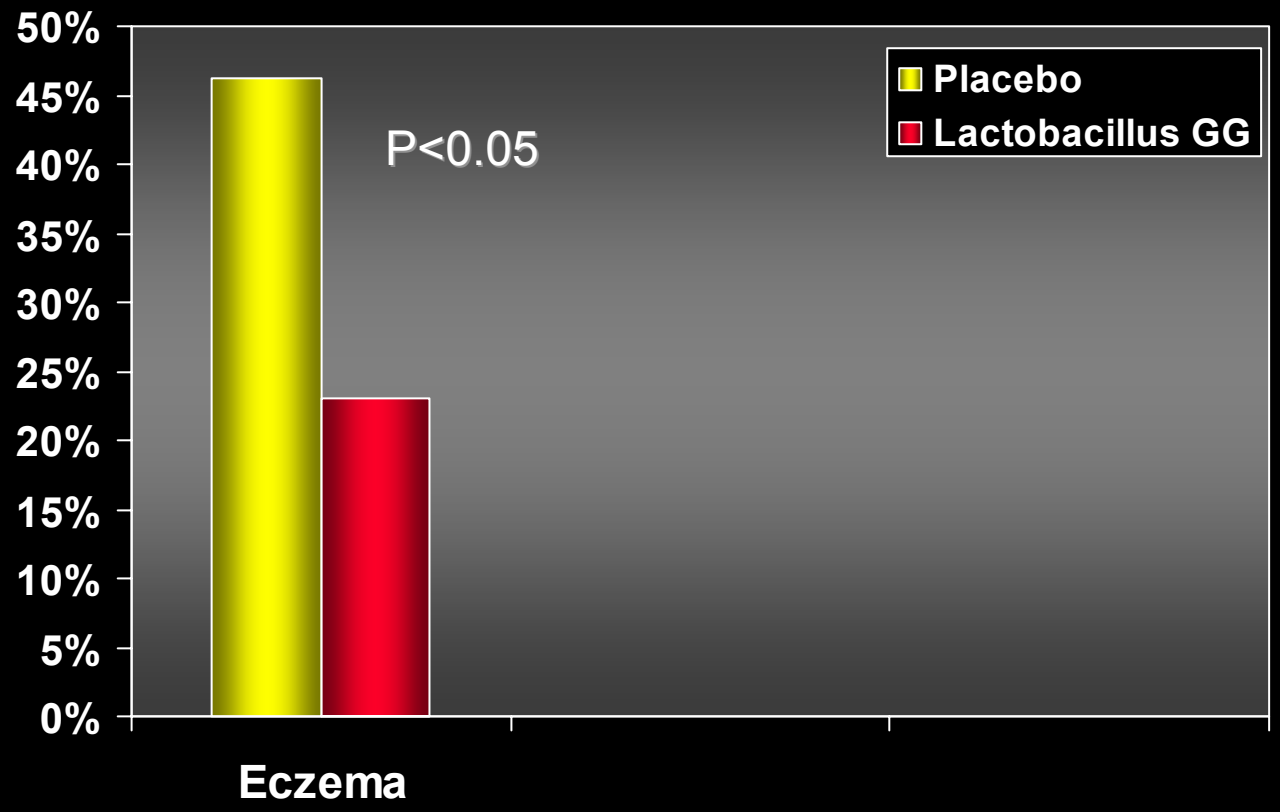
- Powered to detect a 50% reduction in the frequency of atopy in the BCG group
- BCG vaccination alone may produce such a large reduction in disease
- ? timing of the BCG vaccination

Alm et al., Allergy 1998; 53: 537

Gut Microbiota: Large and Continuous Microbial Pressure

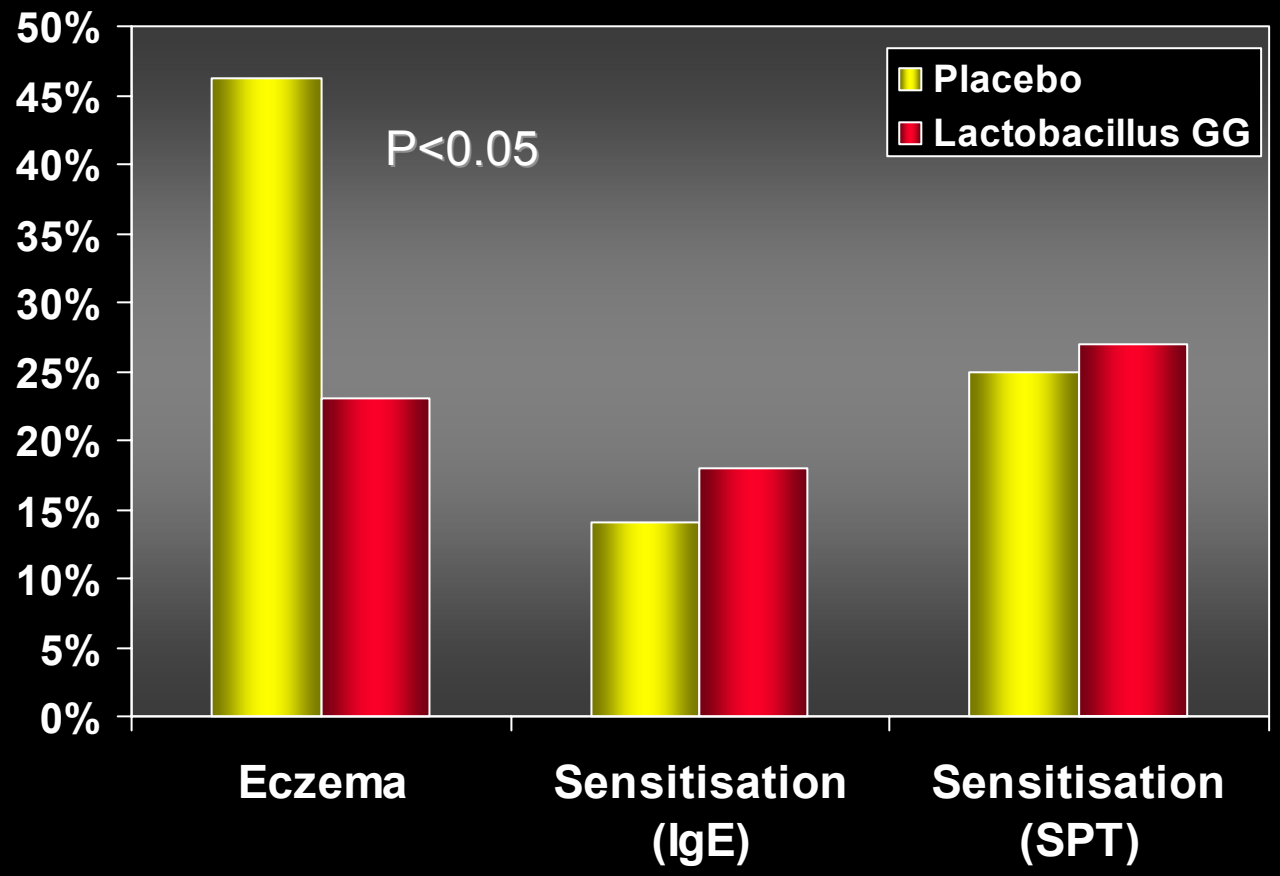


Probiotics in Primary Prevention of Allergic Diseases



Kalliomaki M et al, Lancet 2001; 357: 1076-9

Probiotics in Primary Prevention of Allergic Diseases



Kalliomaki M et al, Lancet 2001; 357: 1076-9

Paradoxical Effects Of Exposure To Domestic Animals

Decreased sensitization to cat amongst cat owners

• Hesselmar, Bjorksten *et al*	Sweden	CEA 1999
• Roost *et al*	ECRHS	JACI 1999
• Sporik *et al*	USA	Thorax 1999
• Custovic *et al*	UK	JACI 2002

Production of IgG and IgG4 (without IgE):

• Platts-Mills *et al*	Lancet 2001
• Erwin *et al*	JACI 2003

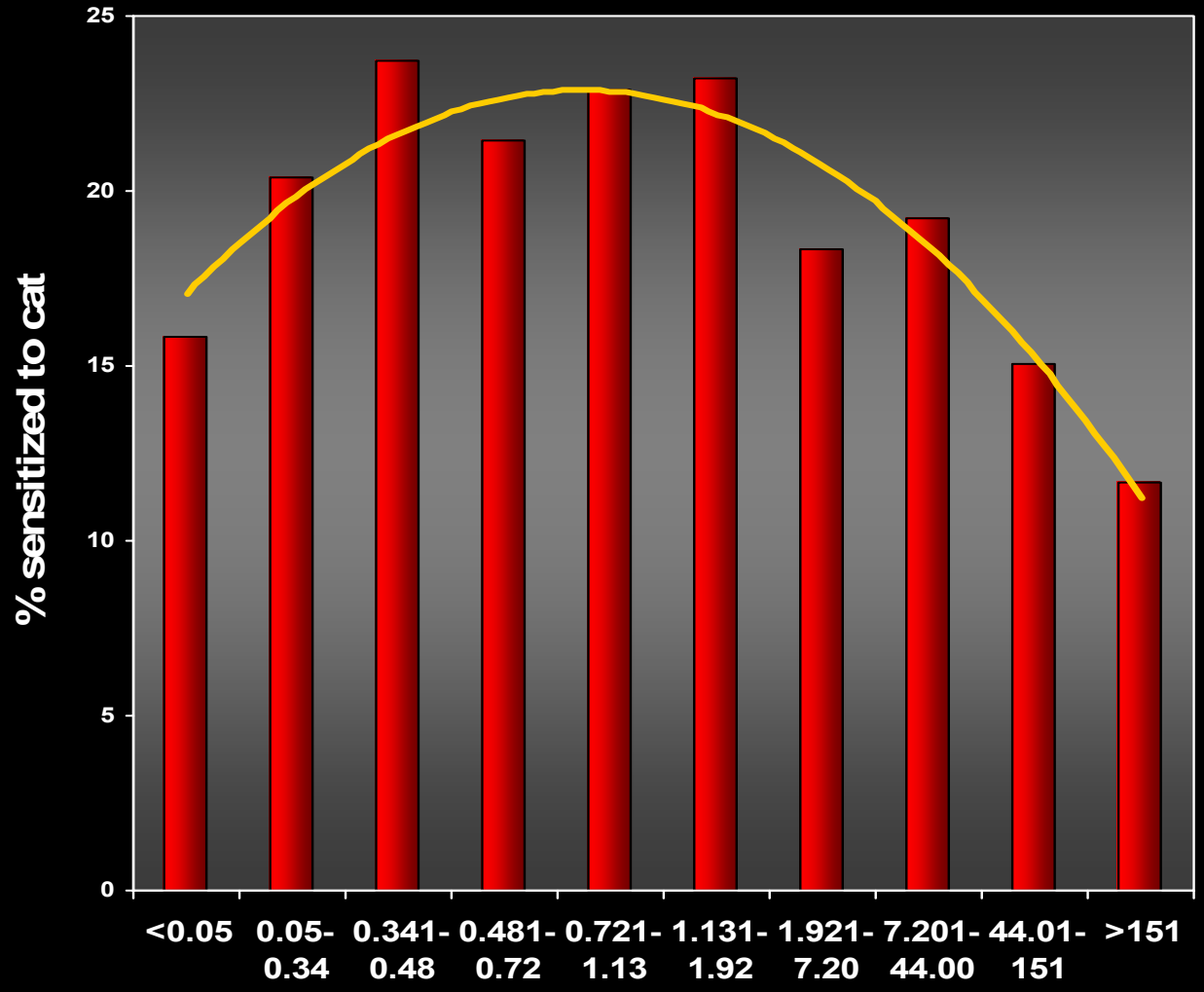
Non-specific effects on other allergens:

• Ownby *et al**	USA	JAMA 2002
• Perzanowski *et al*	Sweden	AJRCCM 2002

** More than one animal.*


sniff
sniff
Lick
Lick
munch
munch
LAP
LAP

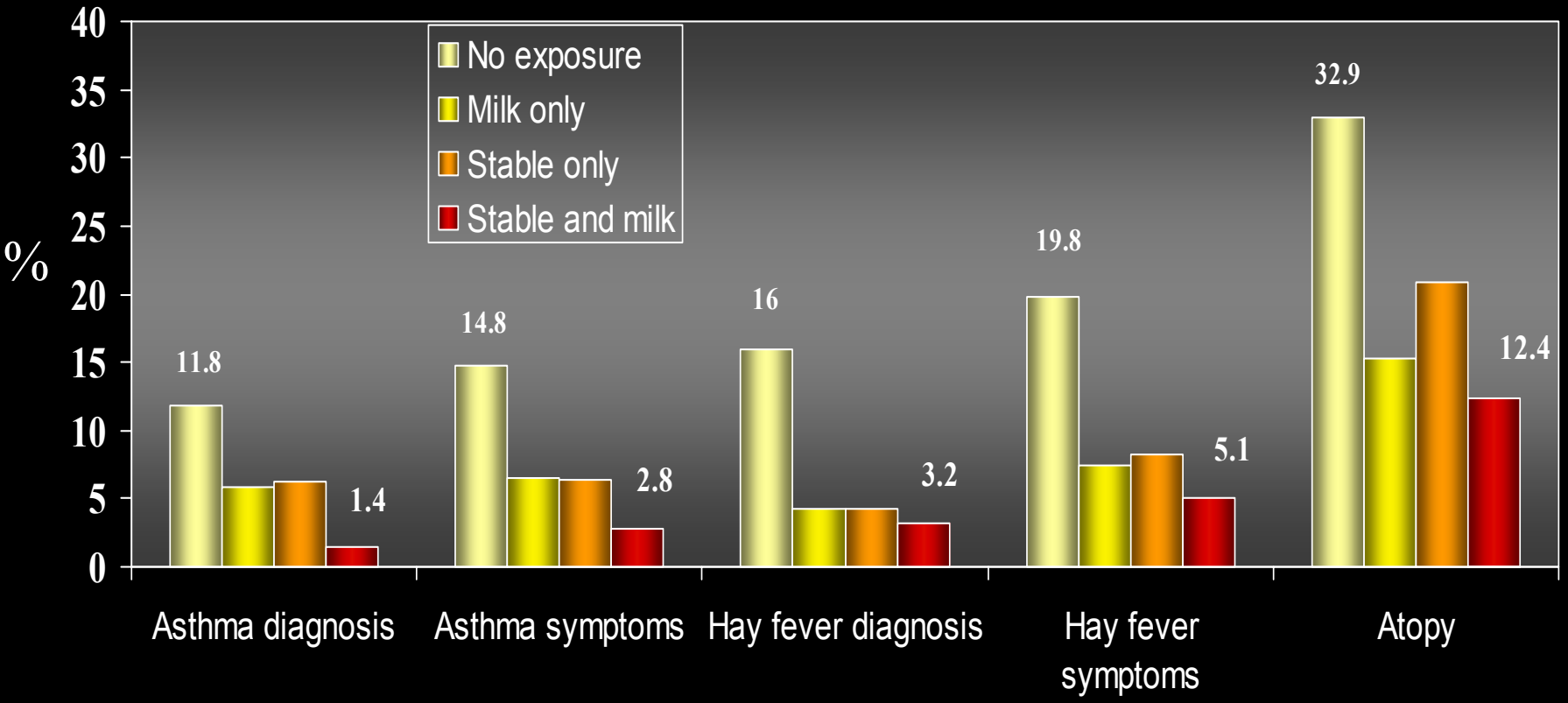
Decreased Risk of Sensitisation to Cats With High Exposure to Cat Allergen



Custovic et al.

J Allergy Clin Immunol 2001; 108: 537-9

Exposure to Stables and/or Farm Milk in the First Year of Life

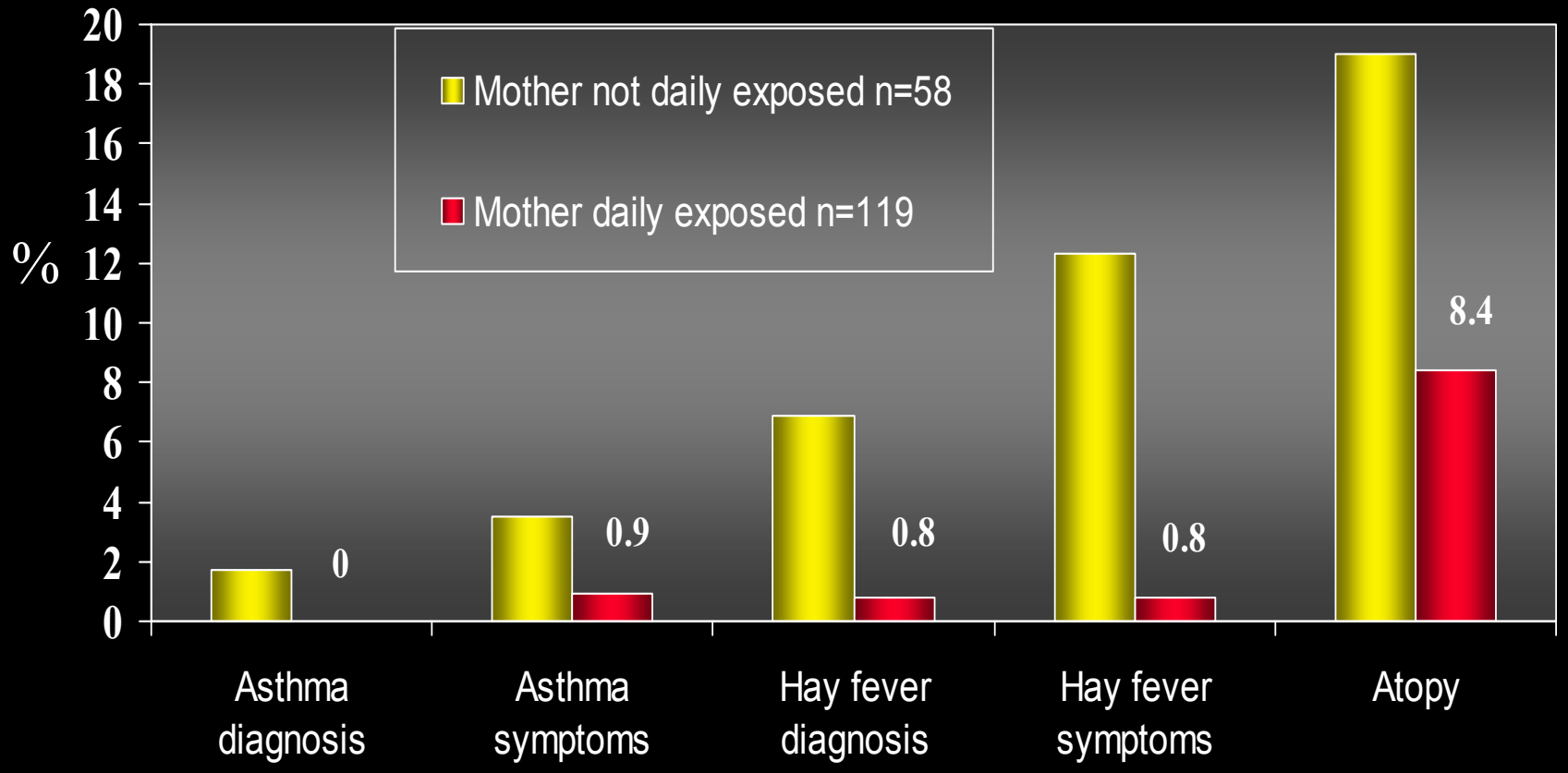


Riedler et al. Lancet 2001

ALEX-Study

Exposure to Farm Environment in Pregnancy

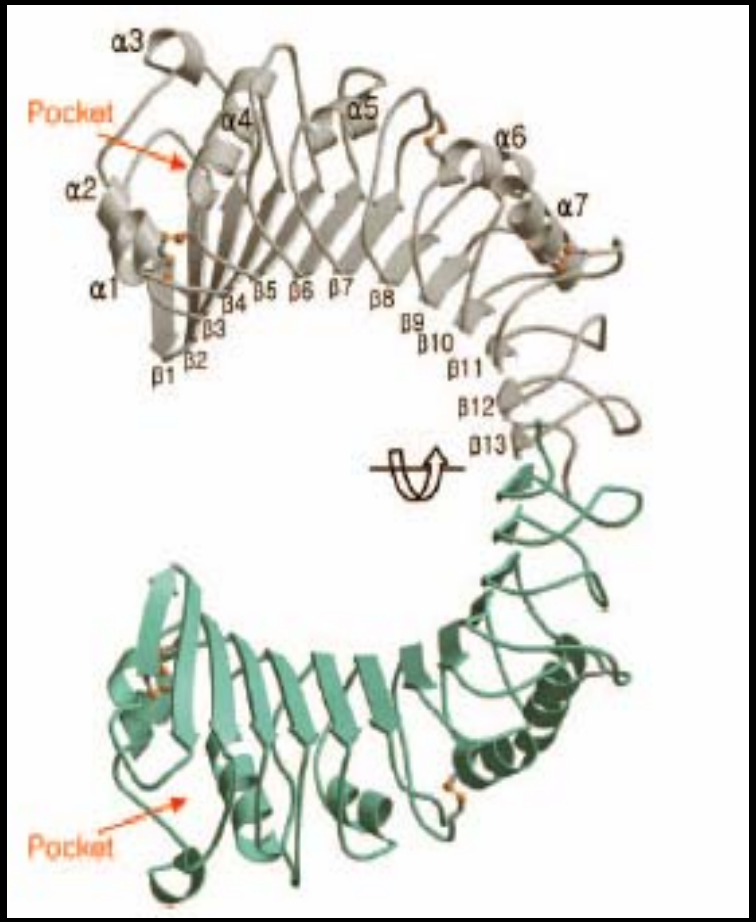
among children exposed to stables and milk in 1. year of life

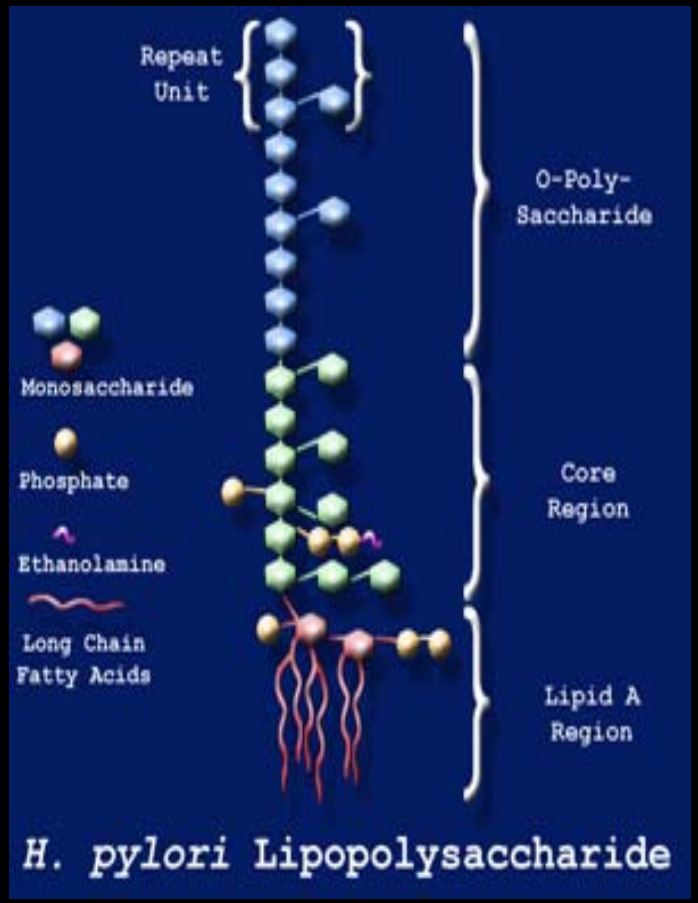


Riedler et al. Lancet 2001

ALEX-Study

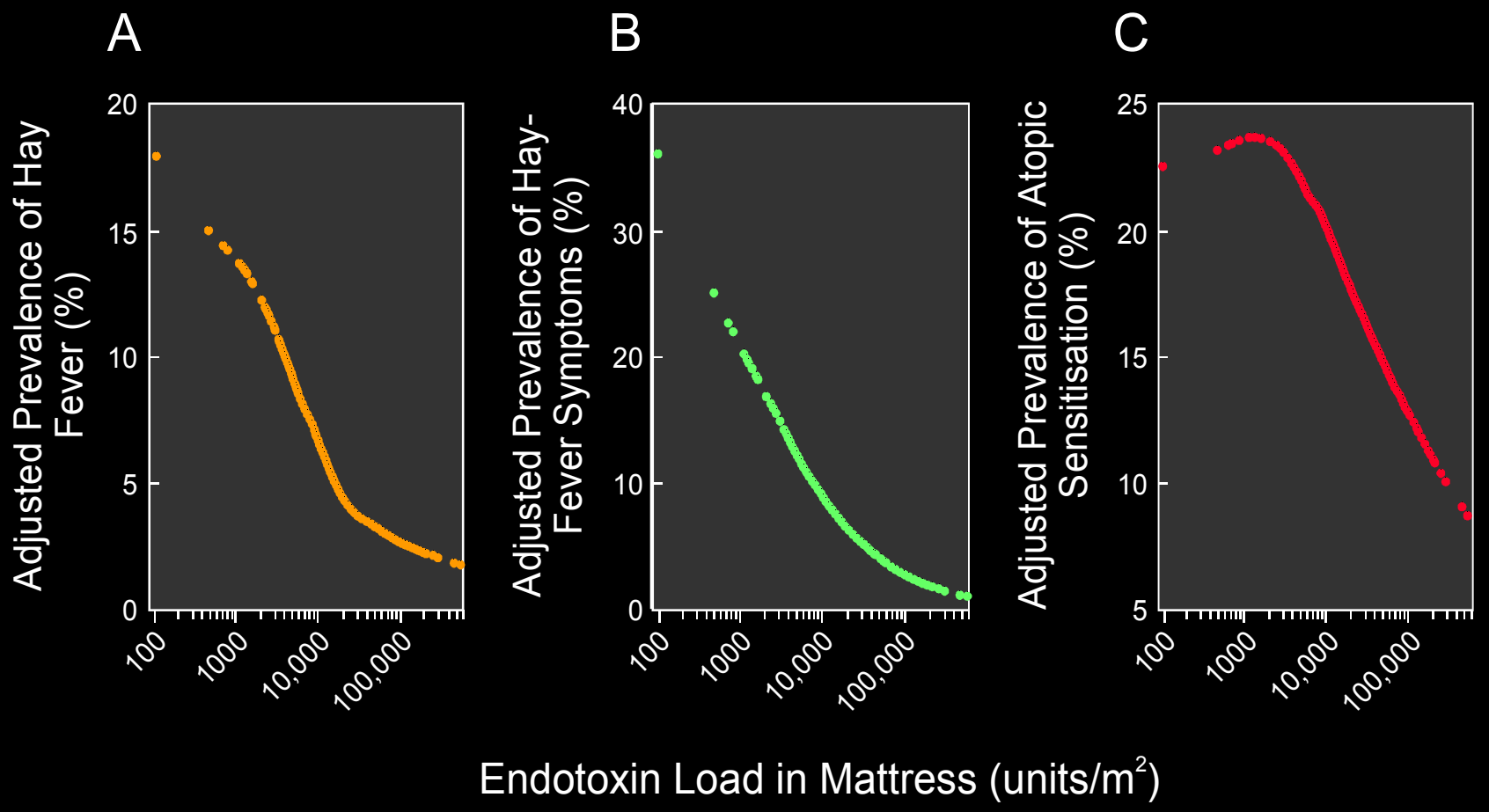
A tale of two molecules



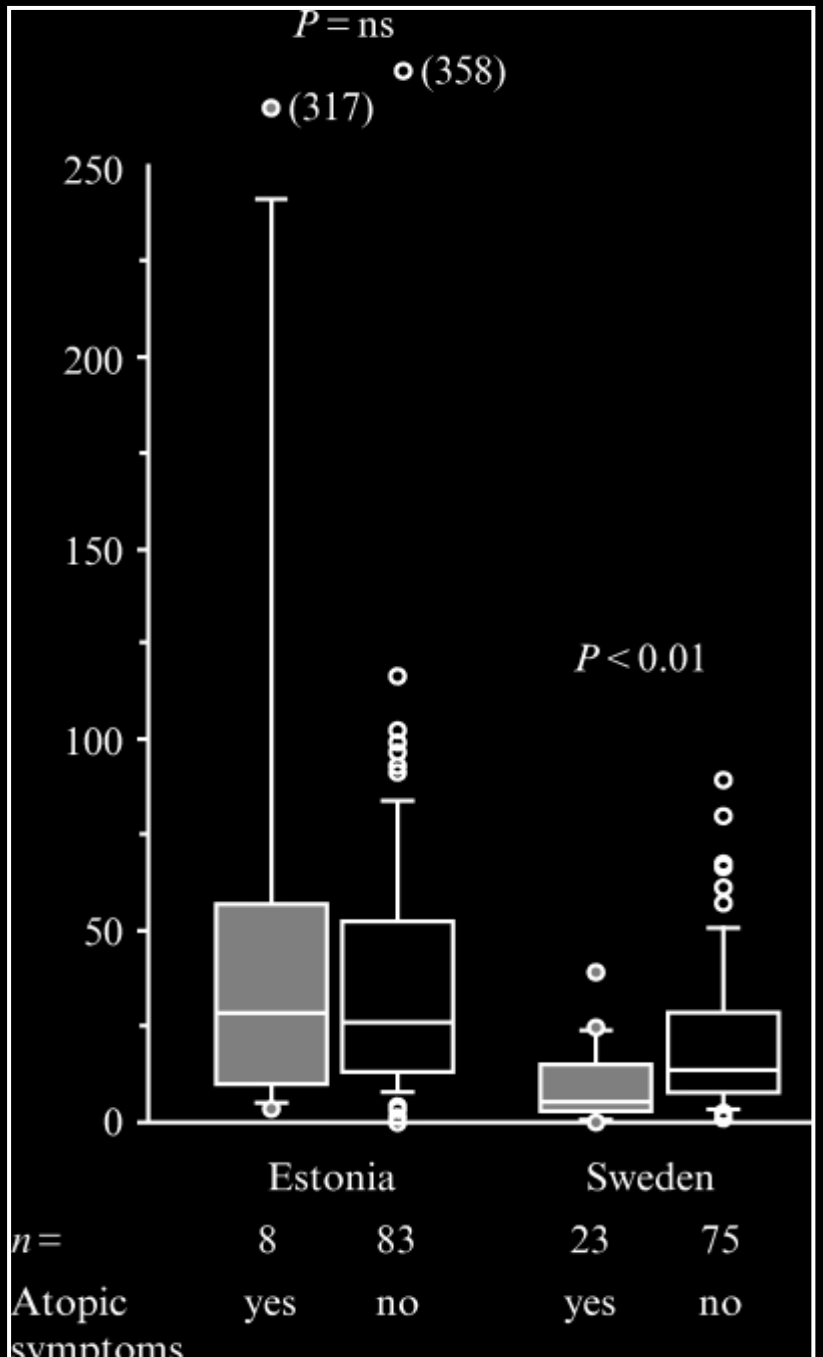


Kim et al JBC 2005

Endotoxin Exposure, Hay Fever & Allergic Sensitisation



Braun-Fahrlander et al. NEJM 2002;347:869-79

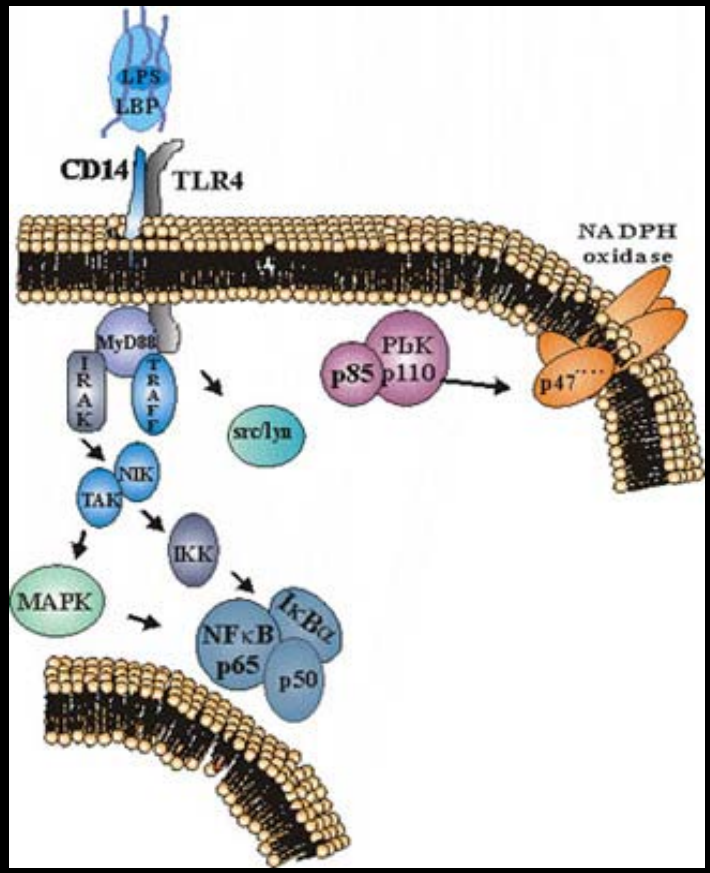


Endotoxin and allergy – Associated in Sweden, but not Estonia

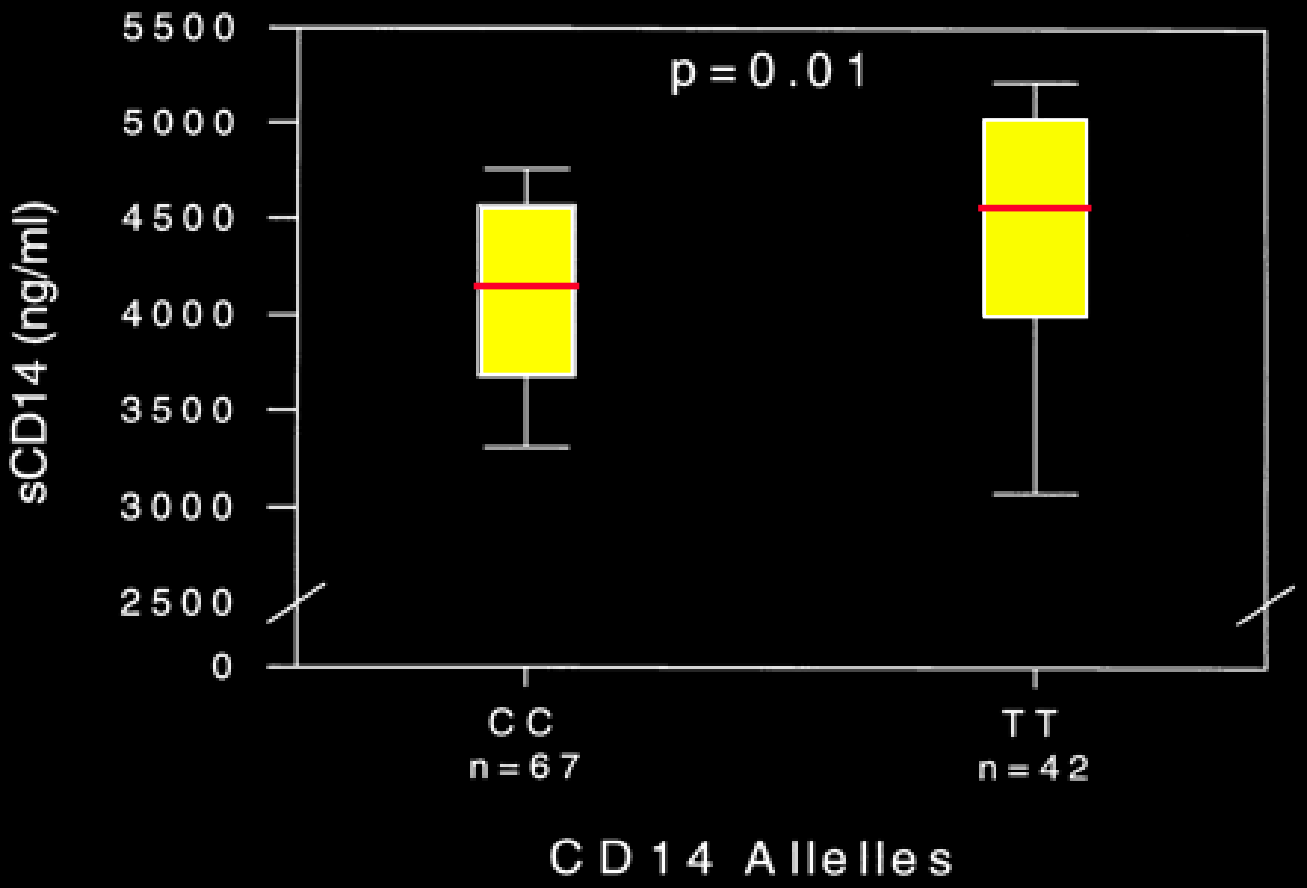
Bottcher et al CEA 2003; 33: 295

CD14

- Pattern recognition receptor
- Part of receptor complex for LPS (endotoxin)
- Soluble or membrane bound CD14
- Maps to 5q32 - region of linkage to asthma

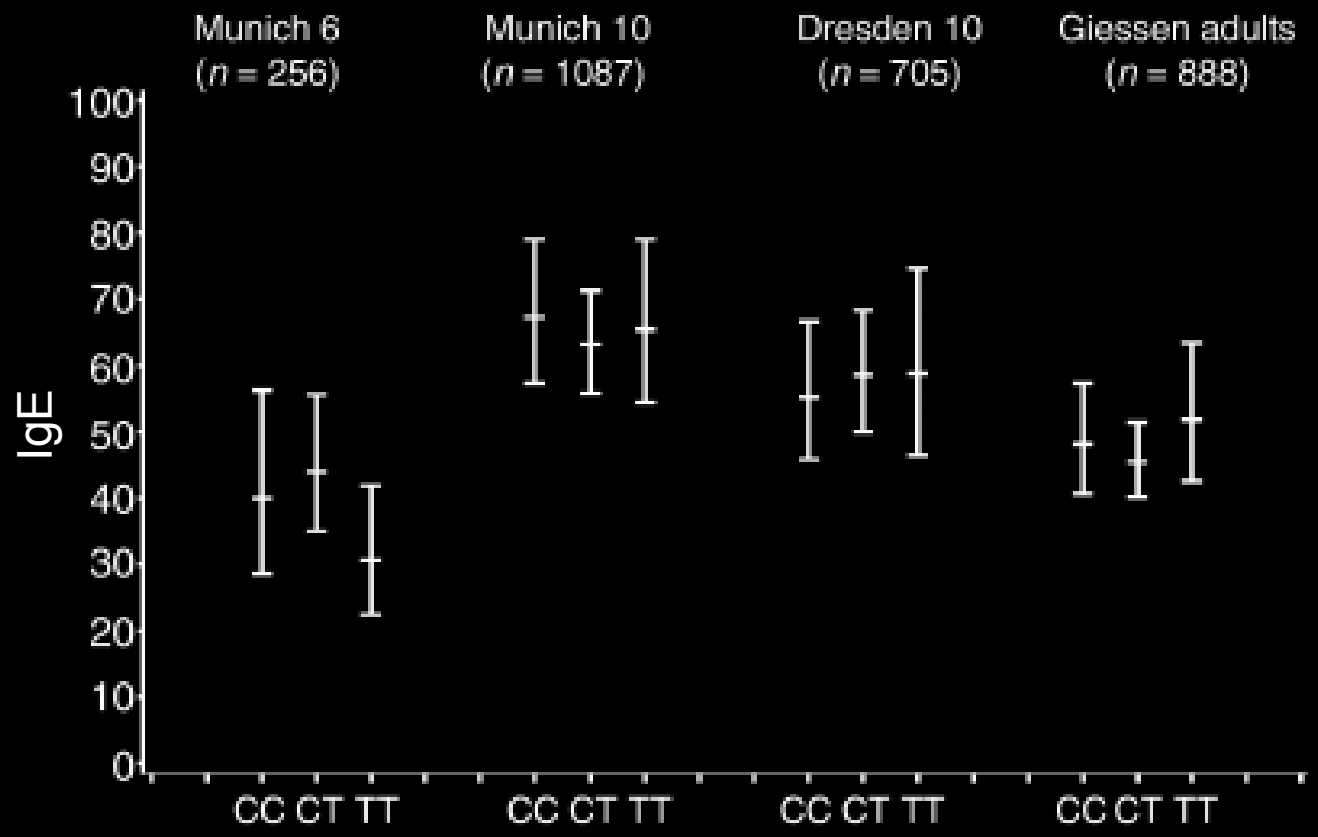


sCD14 varies with *CD14* genotype



Baldini et al, AJRCMB 1999; 20: 976

No association between CD14 and IgE in German children

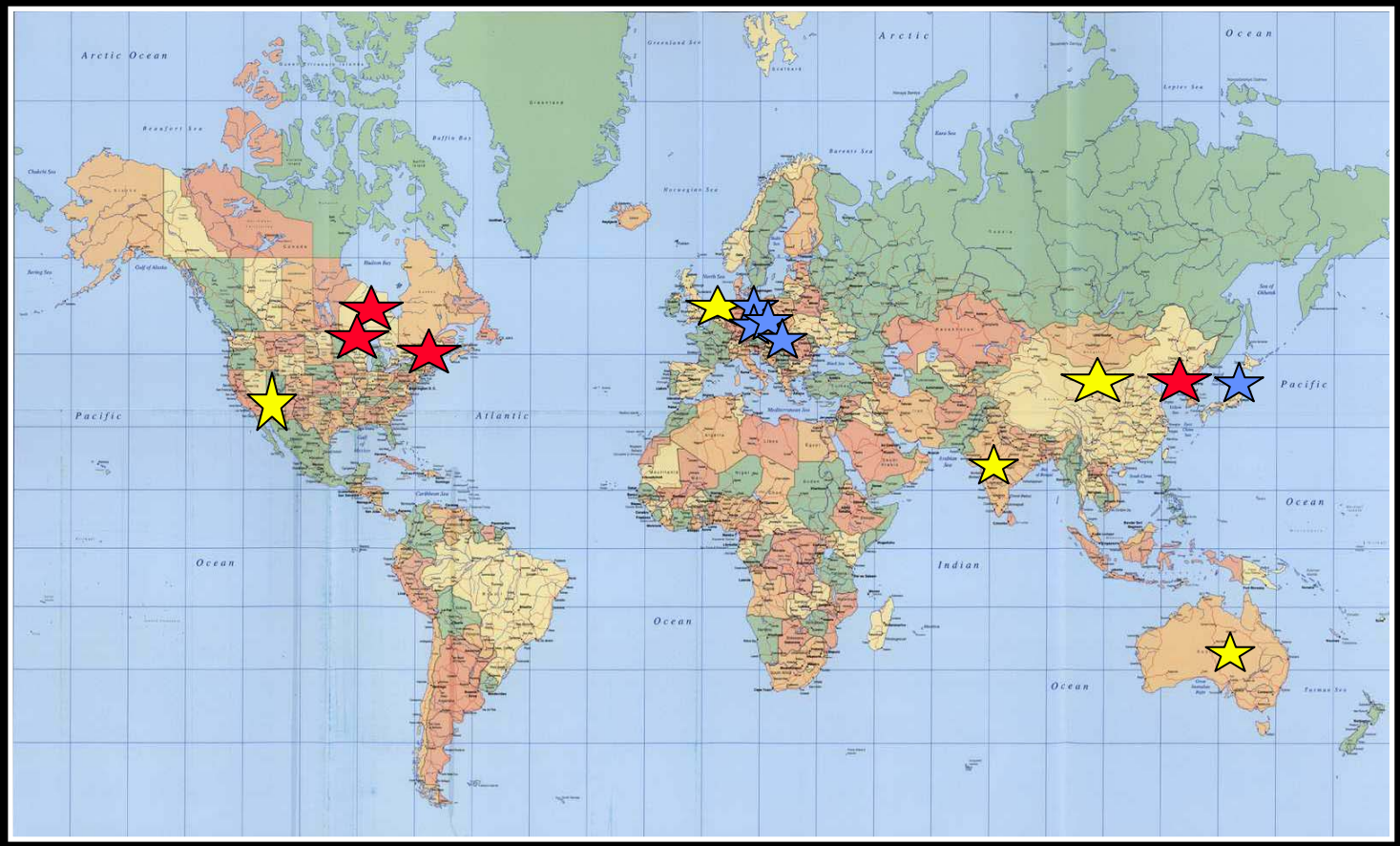


Kabesch et al, Allergy 2004; 59: 520

CD14/-159 in the Hutterites

- Founder population South Dakota
- Descended from 64 founders (1700s)
- Communal agrarian lifestyle
- Asthma very common
- T allele associated with positive skin tests ($p<0.001$)

Studies of CD14/-159 Genotype



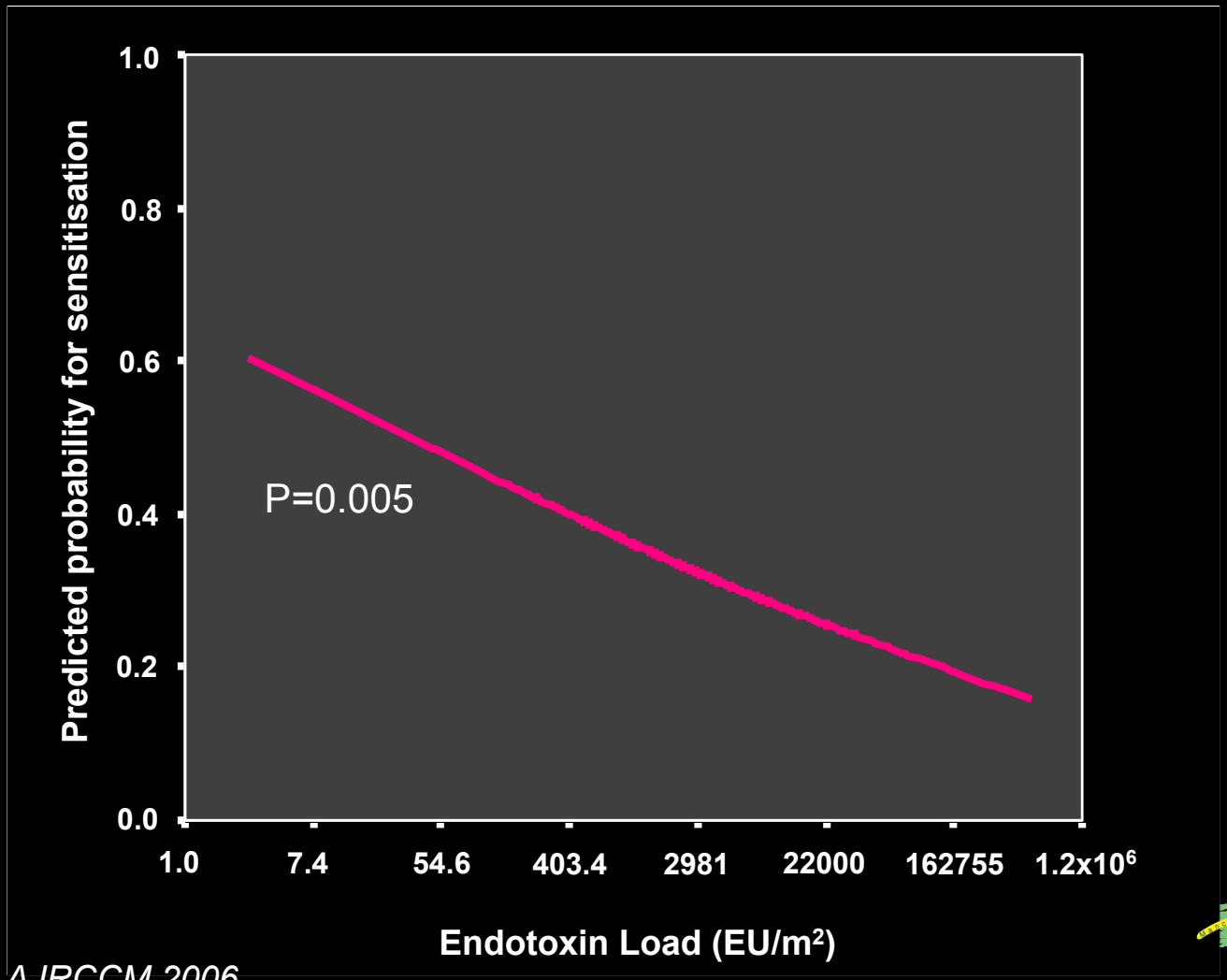
★ C allele associated ★ T allele associated ★ No association

Inconsistencies in results for CD14 and endotoxin

- CD14 polymorphisms associated with allergic sensitisation in some populations but not other
  - Risk allele different in different populations
- Endotoxin protective in some populations but not others

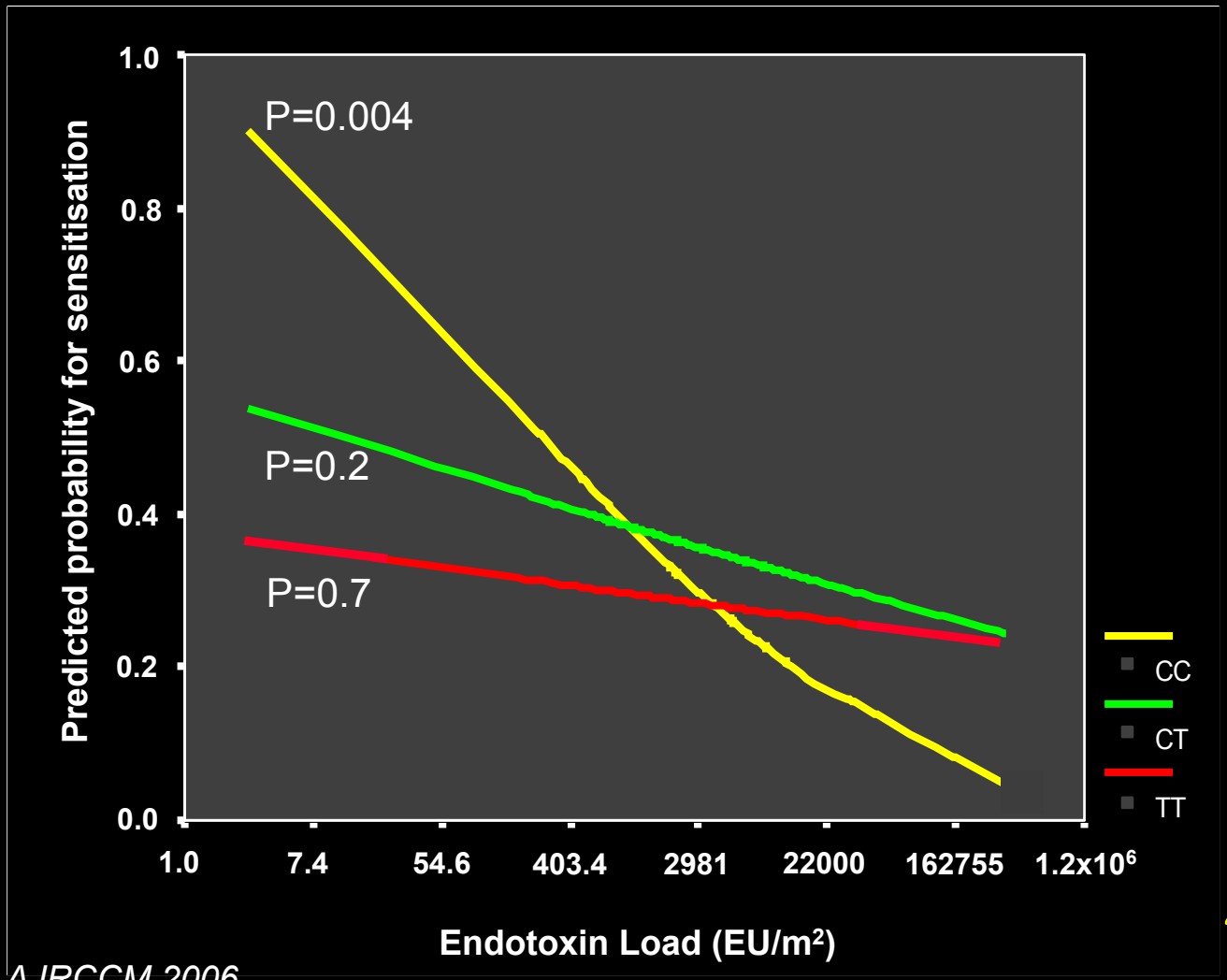
Baldini et al: Am J Res Cell Mol Biol 1999 20 (5) 976-83
Koppelman et al: Am J Res Crit Care Med 2001 163 965-969
Sengler et al Clin Exp Allergy 2003 33 166 -169
Goa et al : Clin Genetic 1999 56 (2) 164-5
Ober et al: Am J Hum Genet 2000 67 1154-62

Endotoxin Exposure and IgE Mediated Sensitisation



Simpson et al, AJRCCM 2006

CD 14 Promoter Polymorphism, Endotoxin Exposure and Sensitization



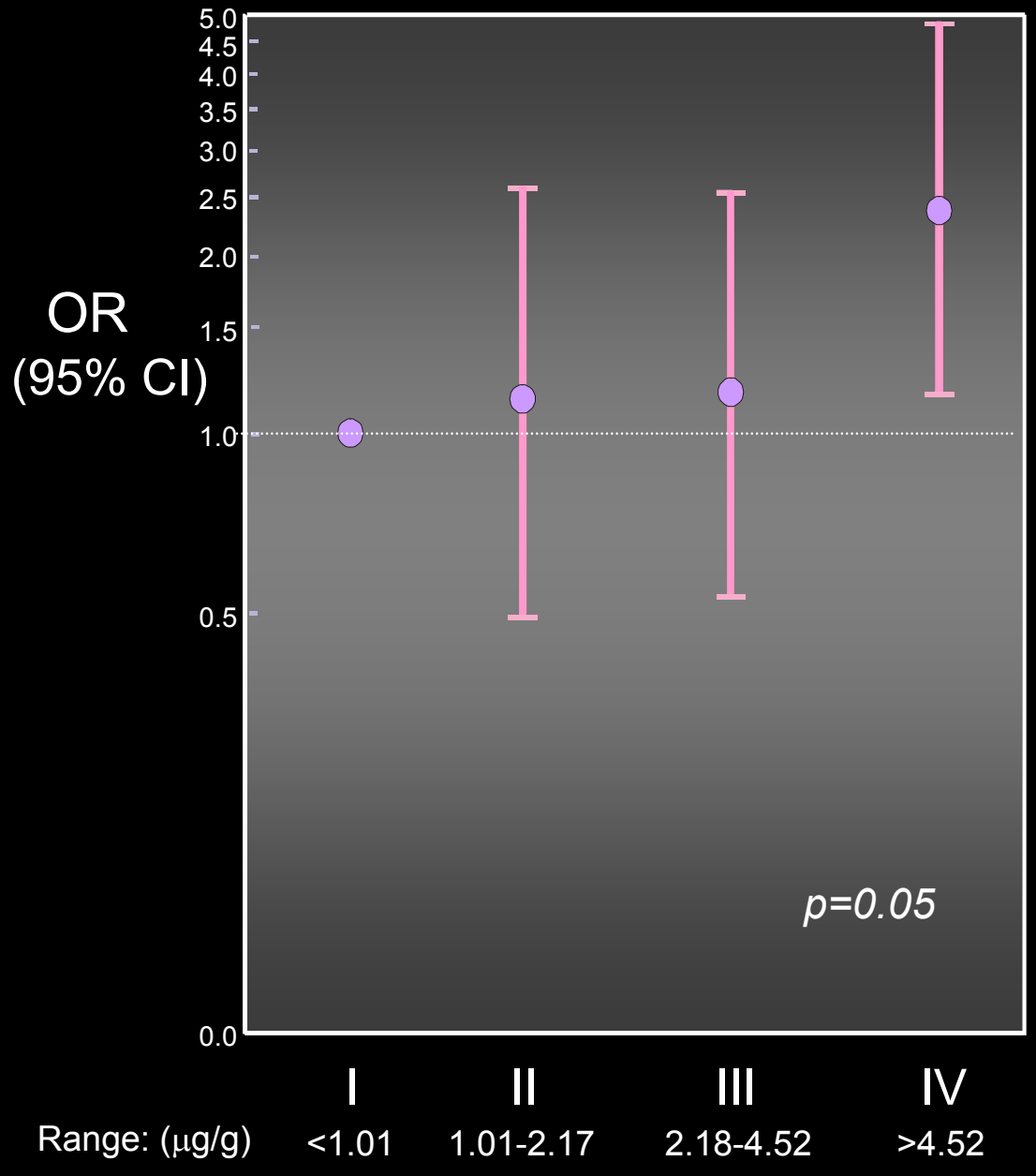
Simpson et al, AJRCCM 2006

Relationship Between Allergen Exposure and the Development of Sensitization, Wheeze & Lung Function

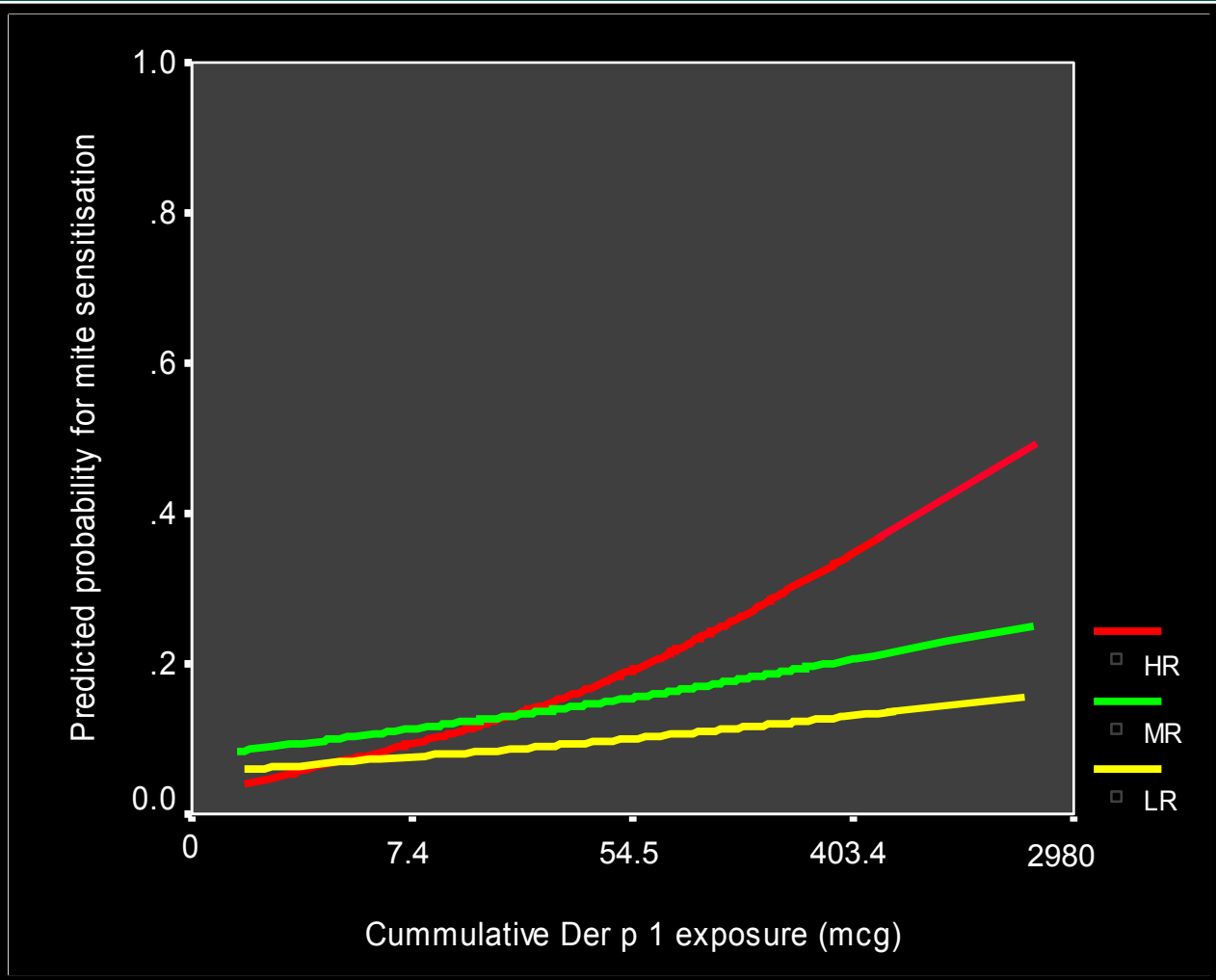
Odds Ratios for Wheeze and Der p 1 Quartiles

Scrivener et al

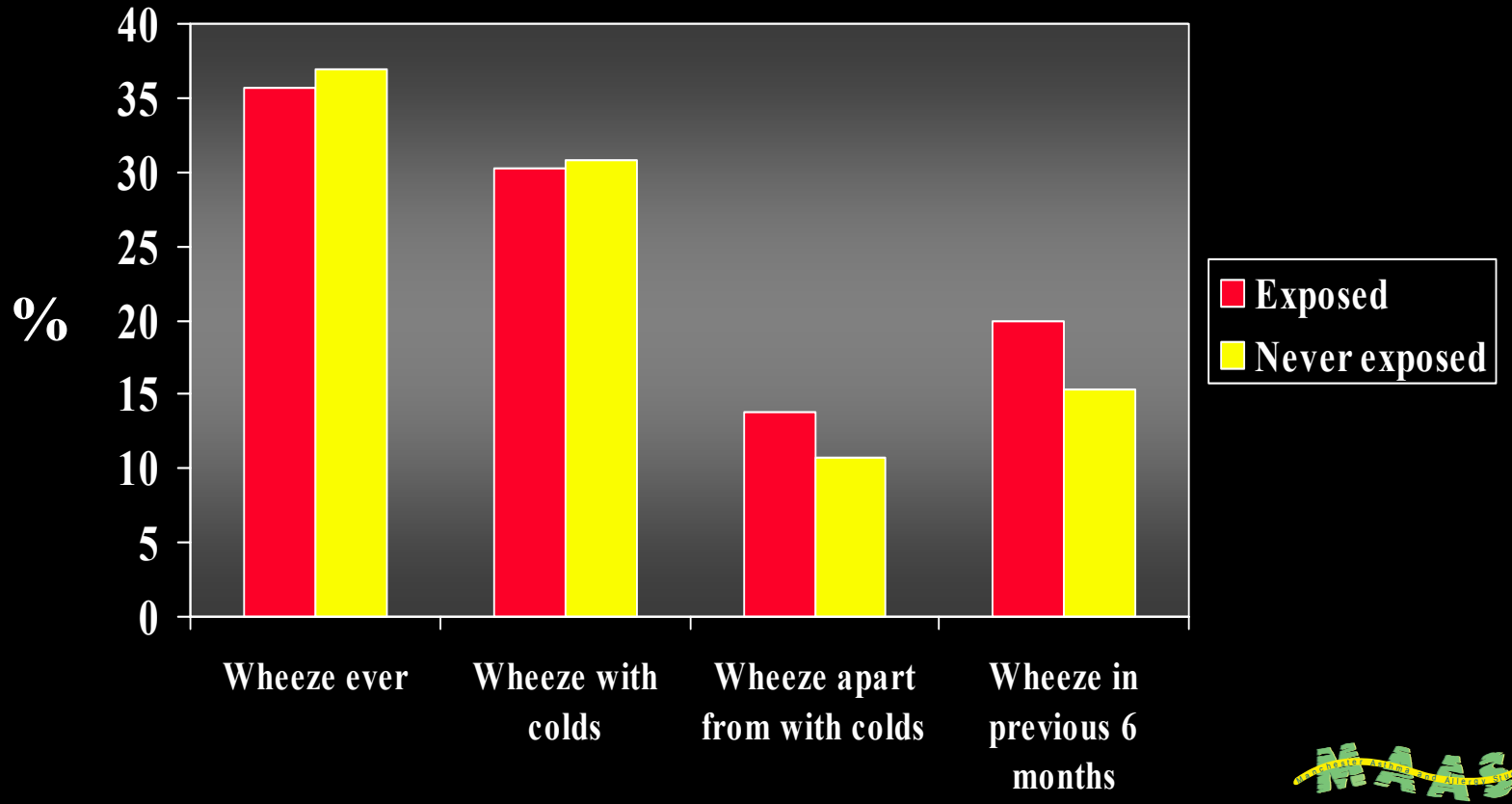
Lancet 2001; 358: 1493-1499



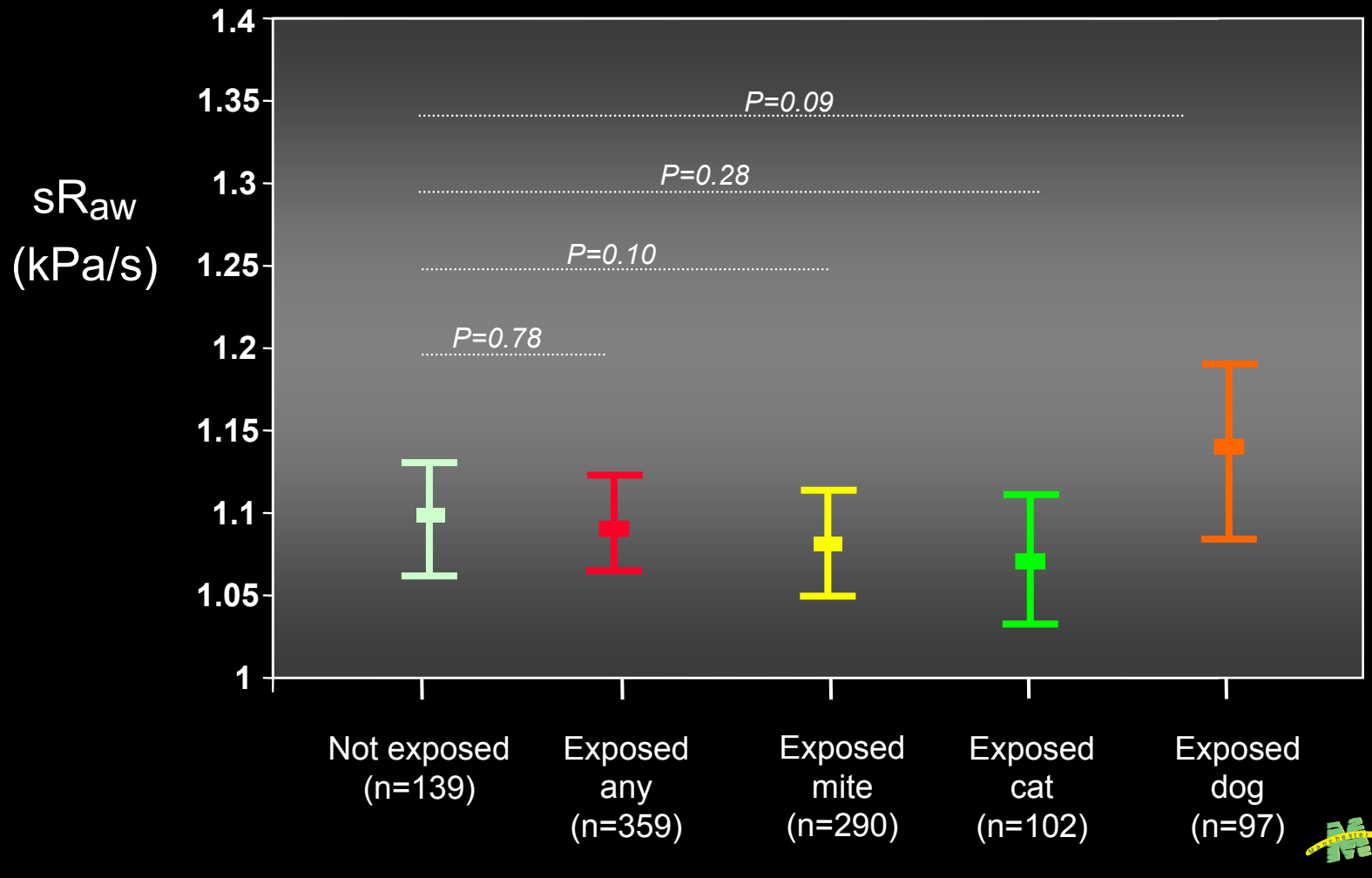
Mite Allergen Exposure Increases the Risk of Specific Sensitisation



No Association Between Exposure to Dust Mite and Wheeze at Age 3 Years



No Effect of Allergen Exposure on Lung Function at Age 3 Years



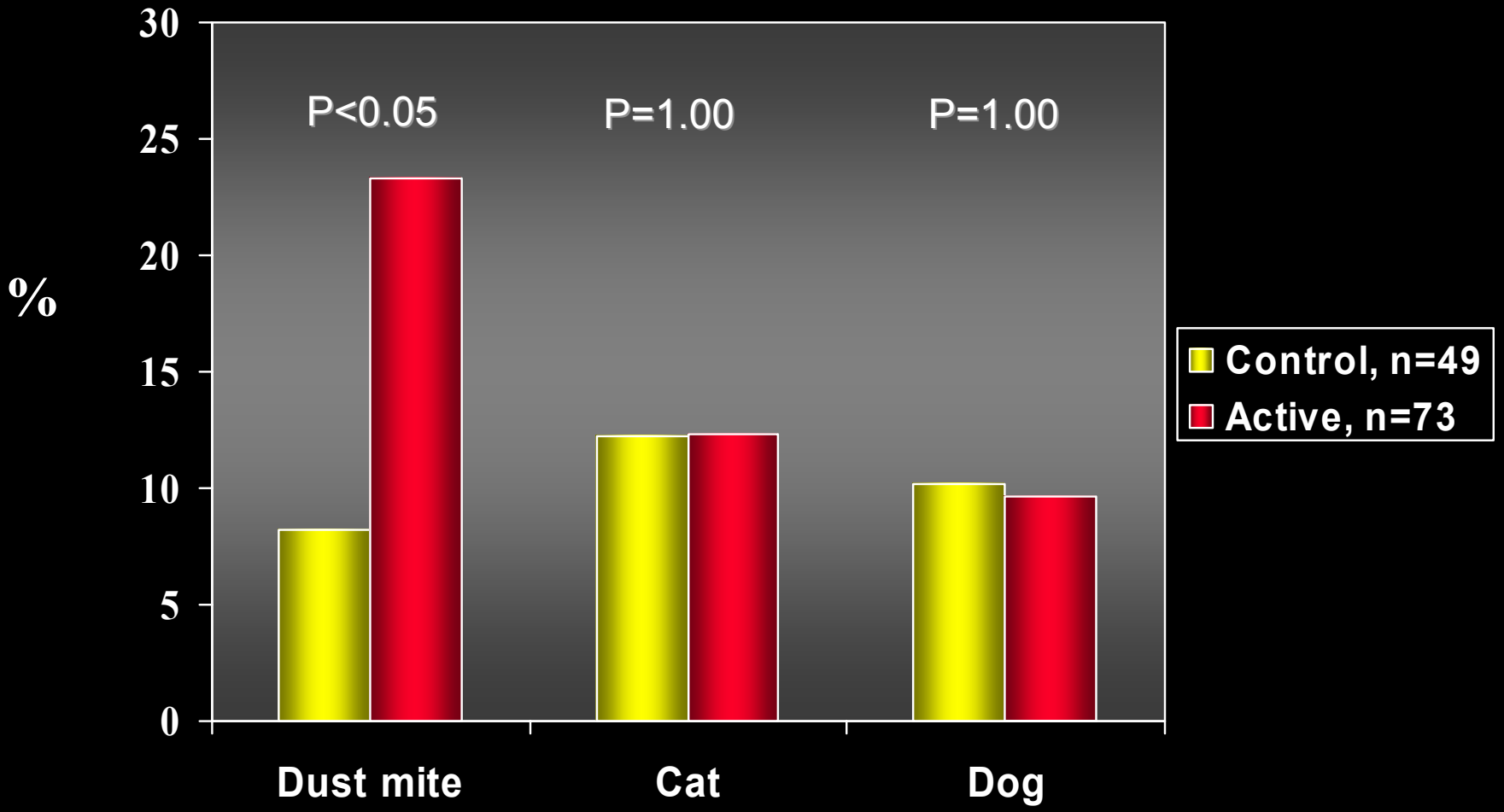
Lowe at al. Arch Ped Adolesc Med. 2004; 158: 996-1001

- Allergen exposure increases the risk of IgE-mediated sensitisation
- No effect of allergen exposure on wheeze or lung function

- Successful allergen avoidance should:
  - Reduce sensitisation
  - Have no effect on wheeze
  - Have no effect on lung function

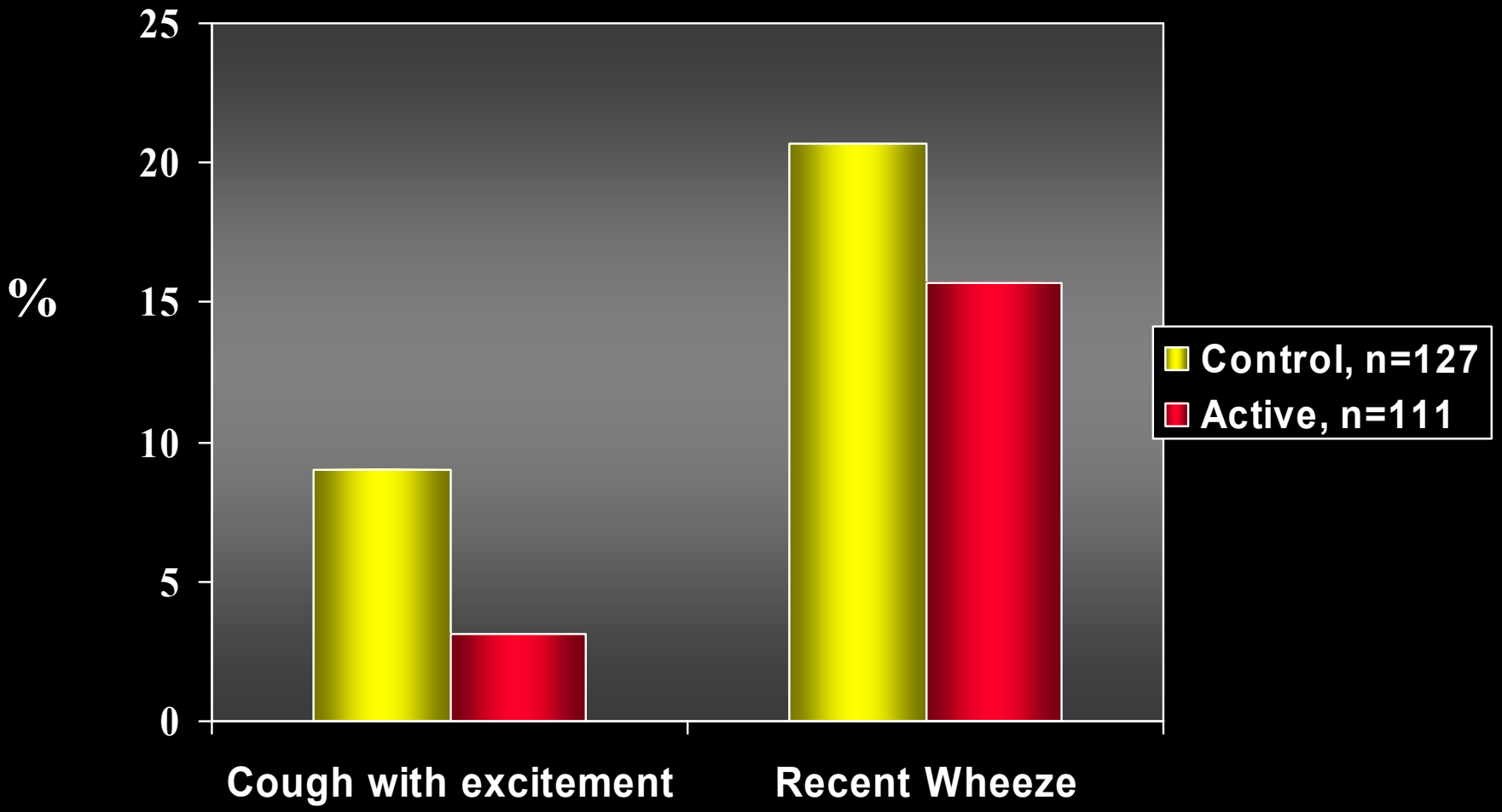
INTERVENTION STUDY: CLINICAL EFFECT OF ALLERGEN AVOIDANCE

Age 3: Effect of Environmental Control on Sensitisation to Allergens (IgE)



Woodcock et al, AJRCCM 2004; 170: 433-9

Age 3: Effect of Environmental Control on Respiratory Symptoms



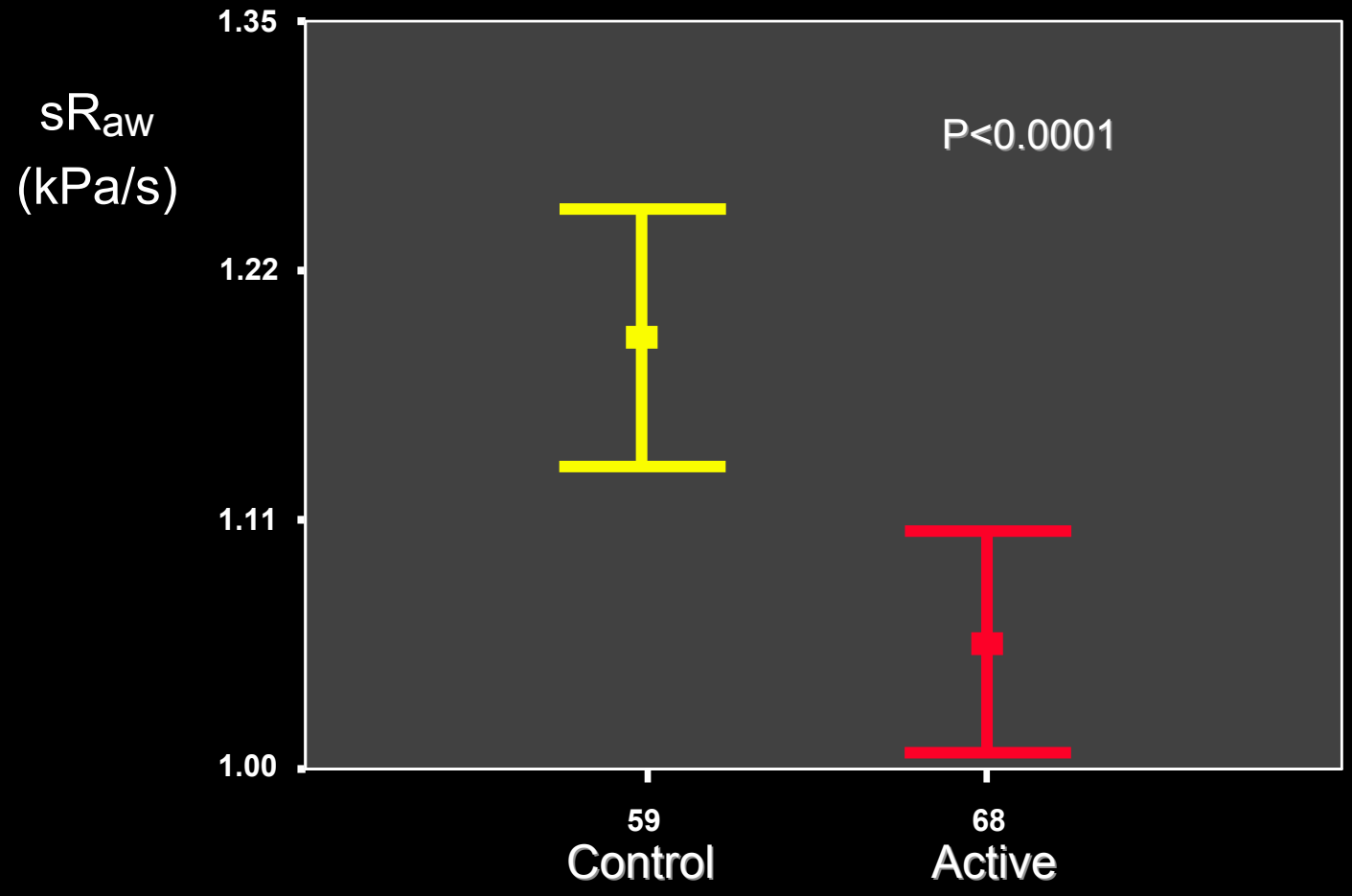
Woodcock et al, AJRCCM 2004; 170: 433-9

Lung Function in Pre-School Children

- No effect of allergen exposure on lung function[1]
- Lung function significantly worse in[2]:
  - High risk children (irrespective of the reported symptoms or atopic status)
  - Sensitized children (irrespective of the reported symptoms)

1. Lowe at al, Arch Ped Adolesc Med 2004; 158: 996-1001
2. Lowe at al, Lancet 2002; 359: 1904-8

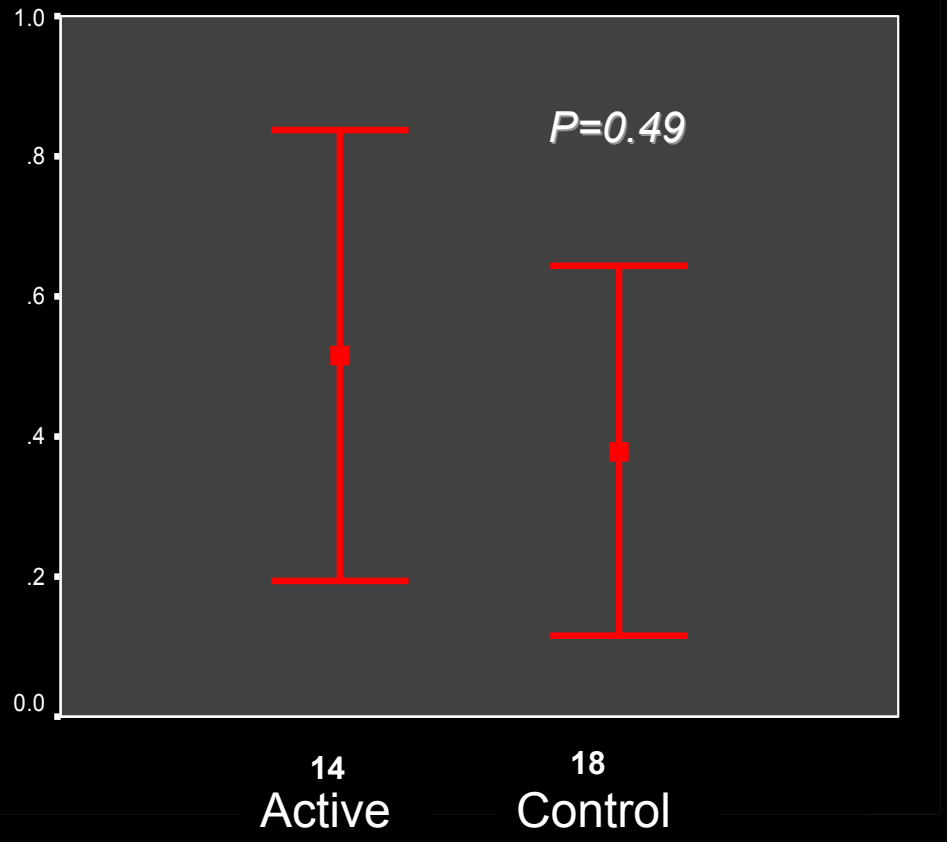
Lung Function in the Active and Control Group at Age 3 Years



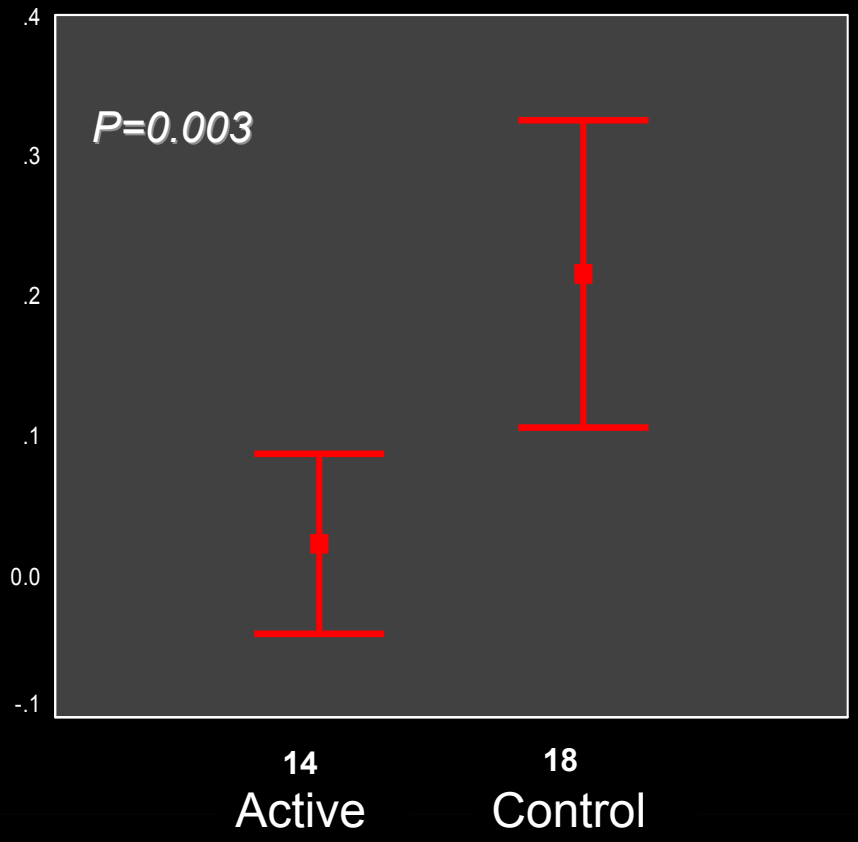
Woodcock et al, AJRCCM 2004; 170: 433-9

Lung Function in Infancy: Rapid Thoraco-Abdominal Compression (RTC) Technique

Lung Function in the Active and Control Group in Infancy and at Age 3 Years



Lung function (VmaxFRC) at age 4 weeks

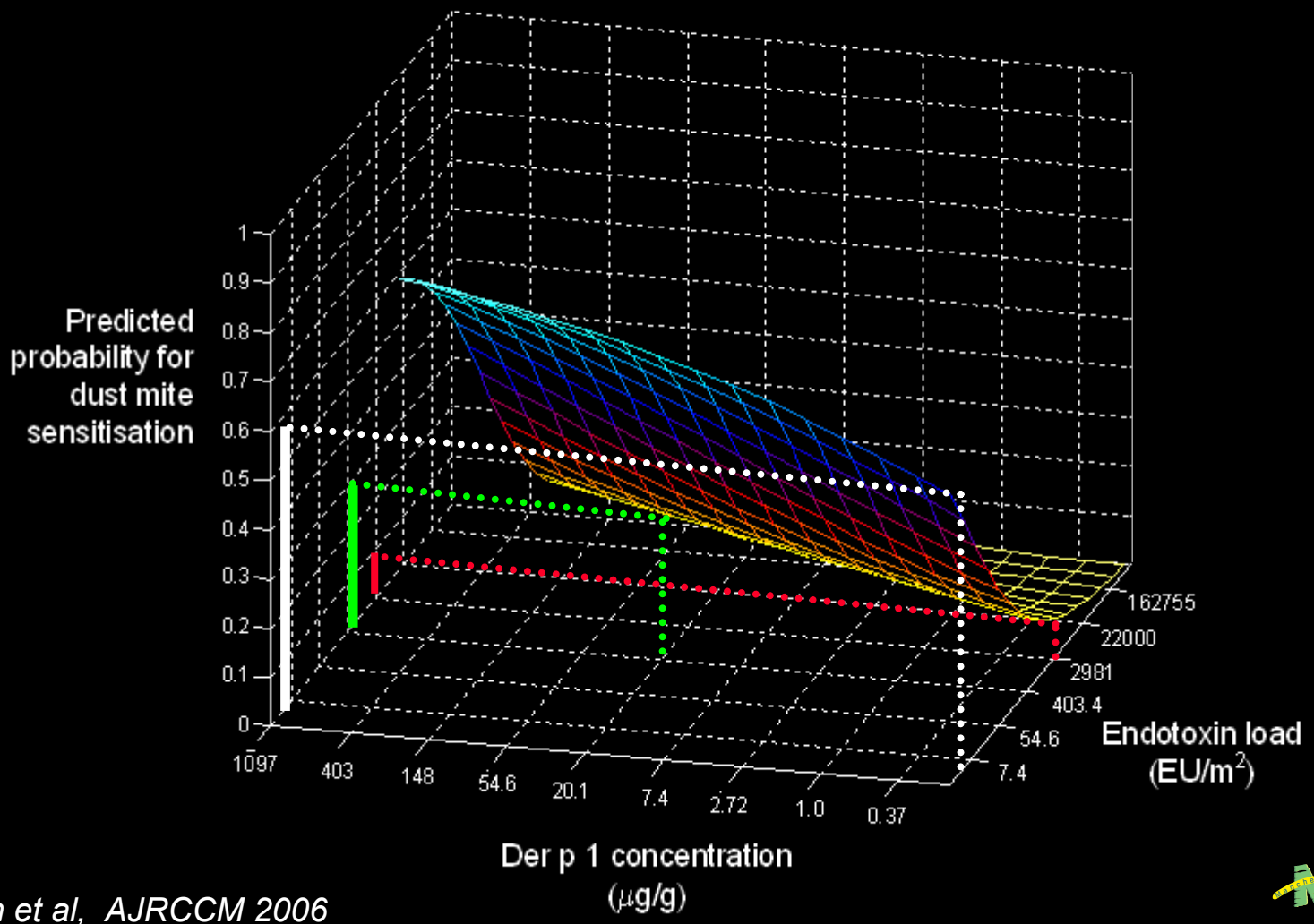


Lung function (sRaw) at age 3 years

Woodcock et al, AJRCCM 2004; 170: 433-9

Primary Prevention:
From the whole population to individuals at risk

Endotoxin and Der p 1 Exposure and Probability for Mite Sensitisation in Children With *CD14 -159* CC Genotype



Simpson et al, AJRCCM 2006

Conclusions

- Totality of evidence on risk factors remains conflicting
  - No clear indication of the types of microbes that might be “protective”
  - Relationship between allergen exposure and development of clinical phenotypes inconsistent
- Elucidate protective exposures
- Determine environmental and genetic basis for subsequent disease
- To understand risk factors for asthma and allergies, study the interaction between the inherited risk and the environment

Conclusions-Prevention

- Some of the results encouraging
  - Longer follow-up is required before we can be sure that the interventions cause no harm
  - We cannot as yet give any advice within the public health context.
- The selection of subjects needs to be refined
  - Identify particular genetic polymorphisms which confer an increase in risk
- This will results in tailor made approaches for individuals.

Custovic and Simpson, ABC of Allergies, BMJ 2006