MANCHESTER 1824

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ATOPY:
Not All Or None

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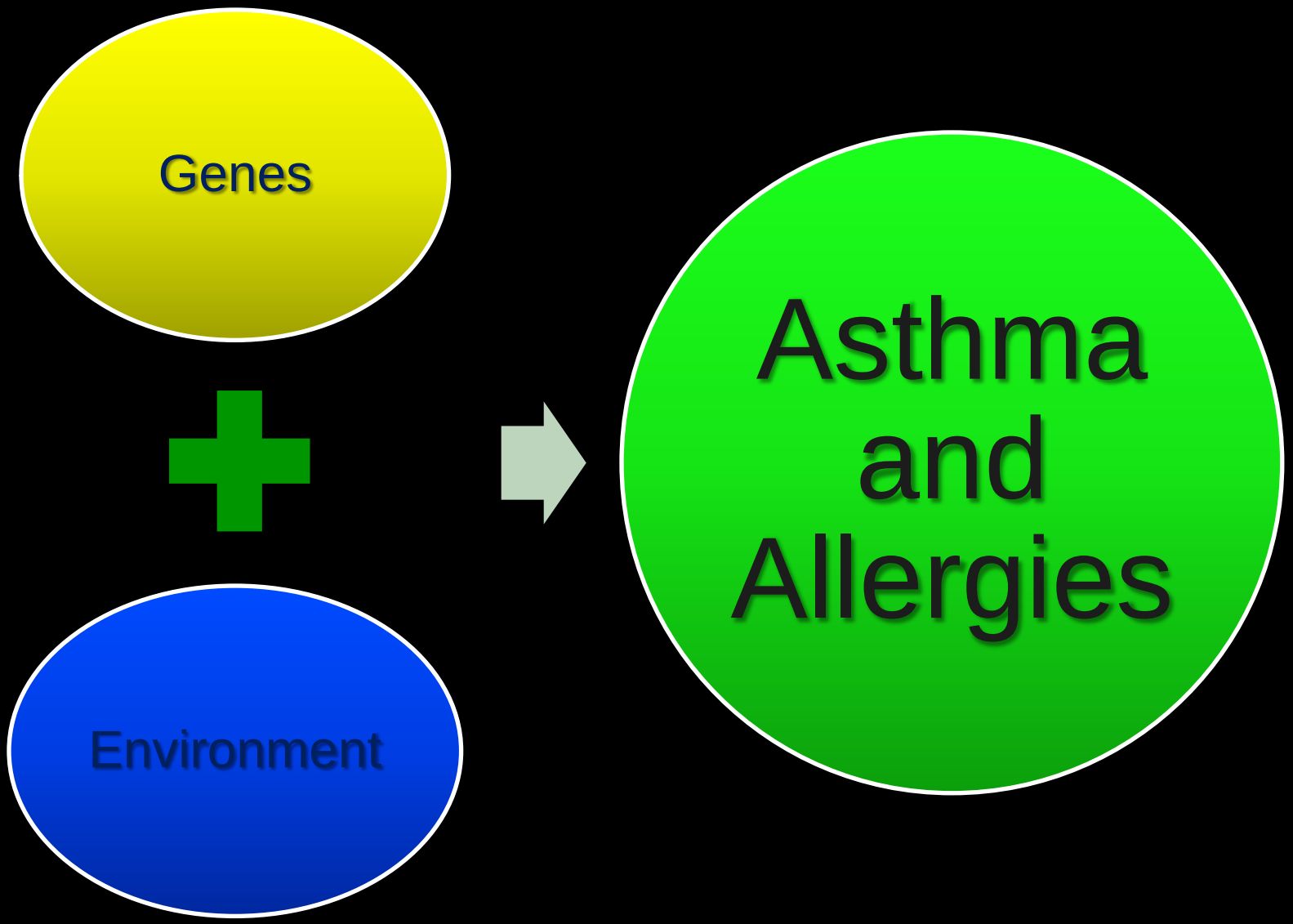
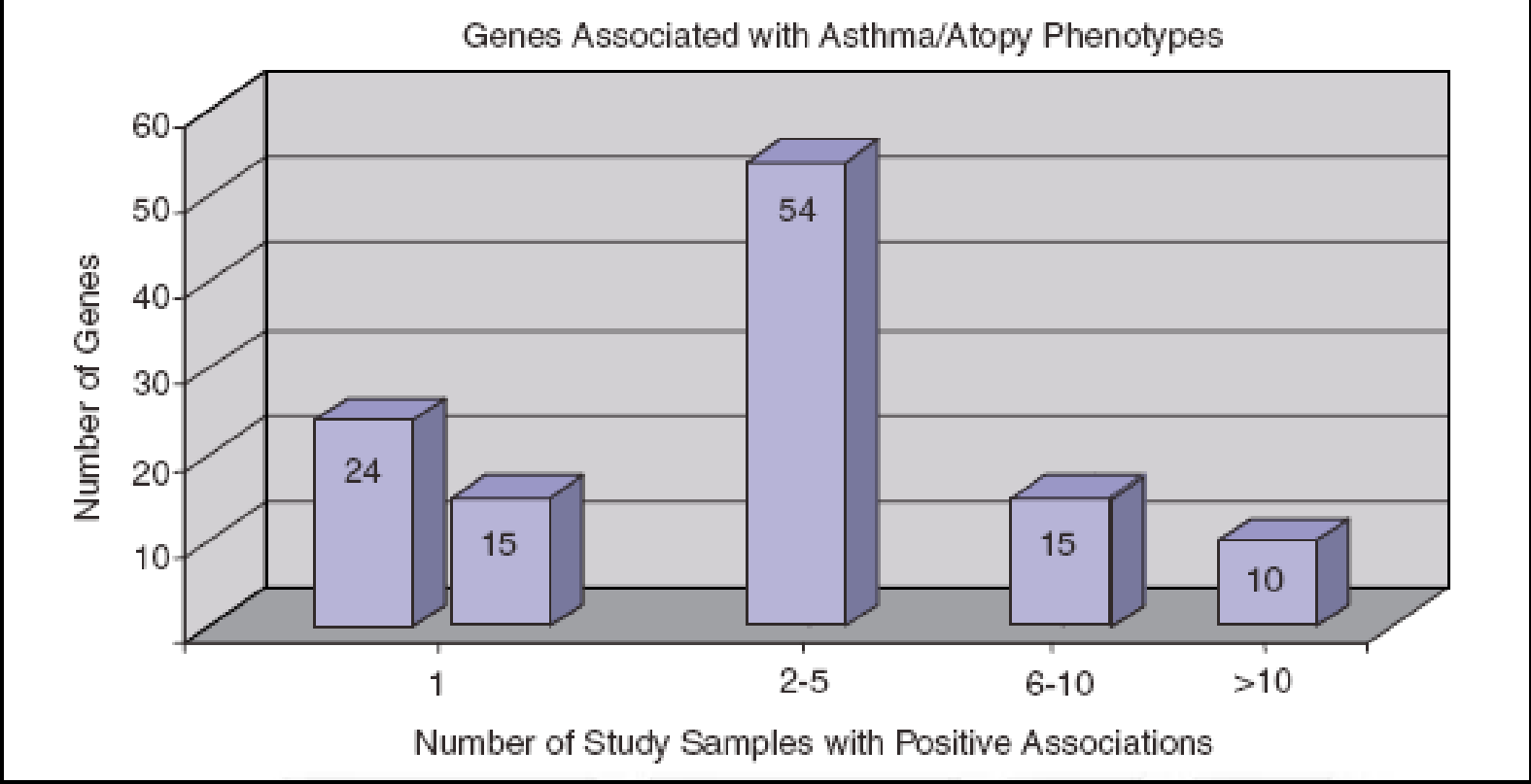

Genes
Environment
Asthma and Allergies

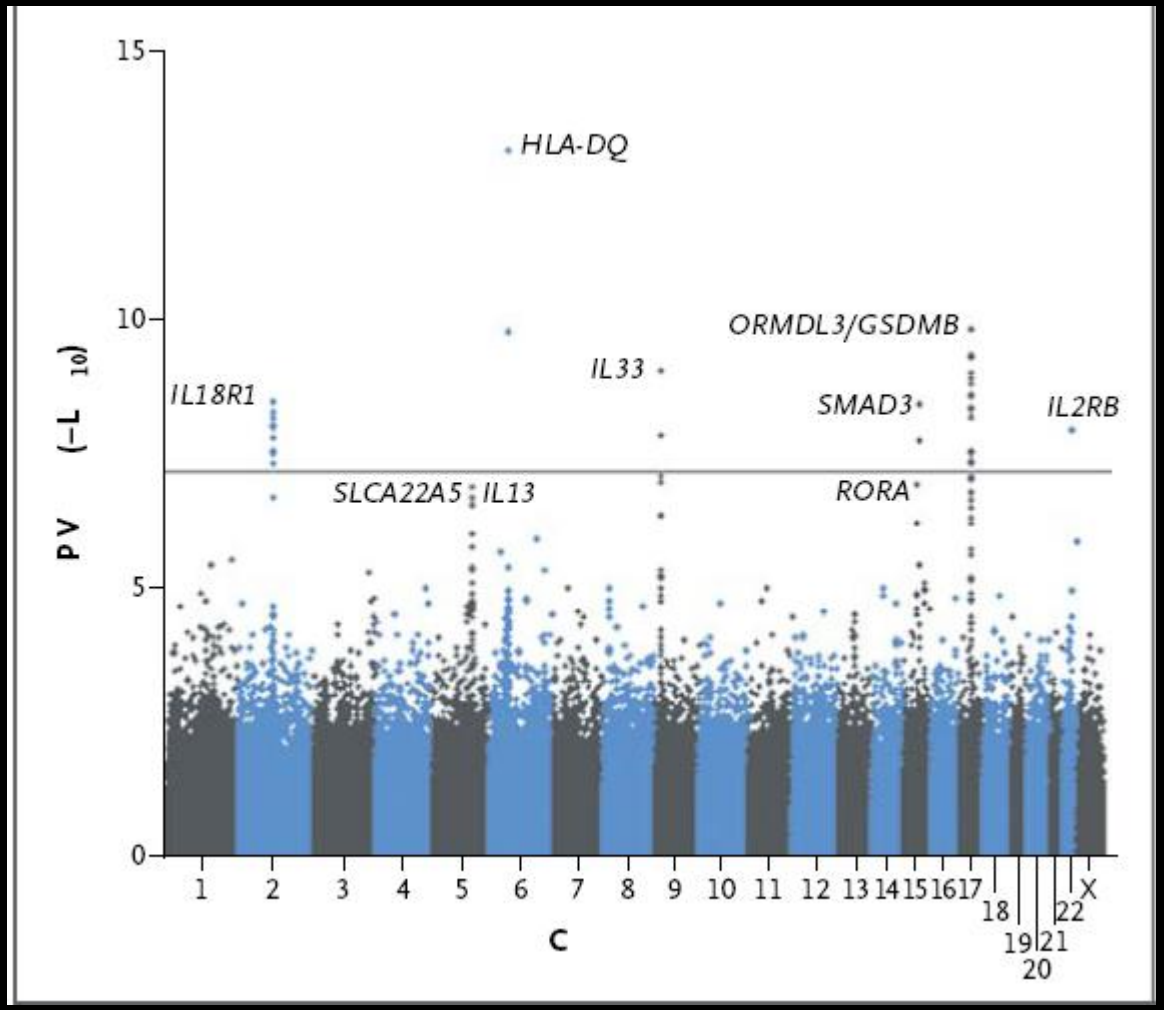
Allergy Epidemic is Environmental
but Environmental Exposures show Inconsistent Associations

- Breast Feeding
  - Protects (Kull et al, JACI 2005;116:657-61)
  - Increases the risk (Sears et al, Lancet 2002;360:901-7)
  - Does not matter (Burgess et al, Pediatrics 2006;117:e787-92)
- Cat ownership
  - Good (Hesselmar et al, CEA 1999;29:611-7)
  - Bad (Noertjojo et al, JACI 1999;103:60-65)
  - Does not matter (Rhodes et al, JACI 2001;108:720-5)

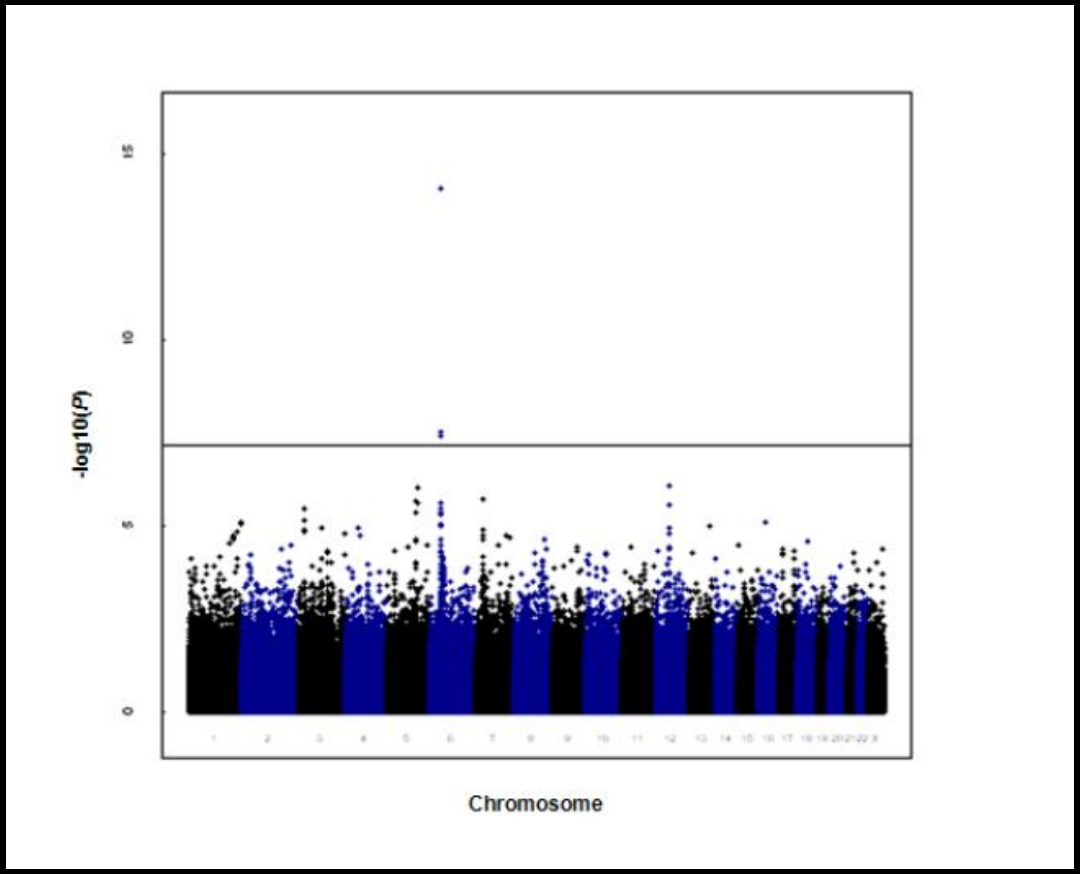
Allergic disease – inconsistent associations



Manhattan plot of Gabriel Study GWAS – asthma



Manhattan plot of Gabriel Study GWAS – total IgE



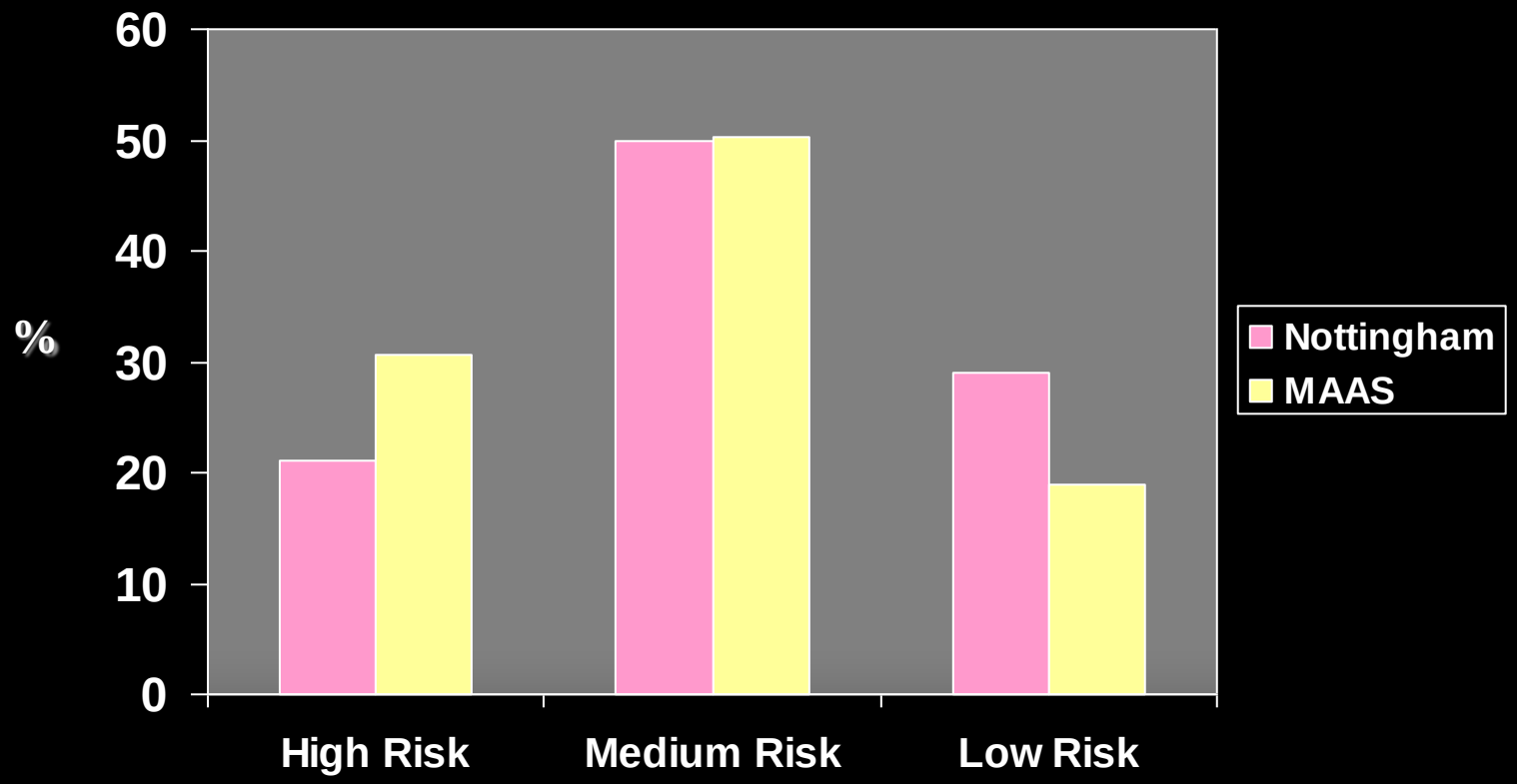
Association studies of Asthma and Allergic Diseases are inconsistent because

- We fail to consider both genetic and environmental factors
- We use simple definition of disease
  - Doctor diagnosed asthma
  - Total IgE
  - Atopy (sensitisation to any allergen)

Manchester Asthma and Allergy Study

- Unselected birth cohort
- N~1000
- Recruited *in utero* 1995-7
- Clinical follow up at age 1, 3, 5, 8 and 11 years

How Representative of the General Population is MAAS Sample at Age 5



Based on Broadfield et al, J Allergy Clin Immunol 2002; 109: 969-74

Clinical Outcomes

- Subjective outcomes, age 1, 3 , 5, 8 and 11 years
  - Validated questionnaires,
    - symptoms of asthma, eczema and rhinitis
    - physician-diagnosed illness
    - medication use
- Atopic status, age 1, 3, 5, 8 and 11 years
  - Skin tests to inhalant and food allergens
  - Total and specific IgE

Lung Function

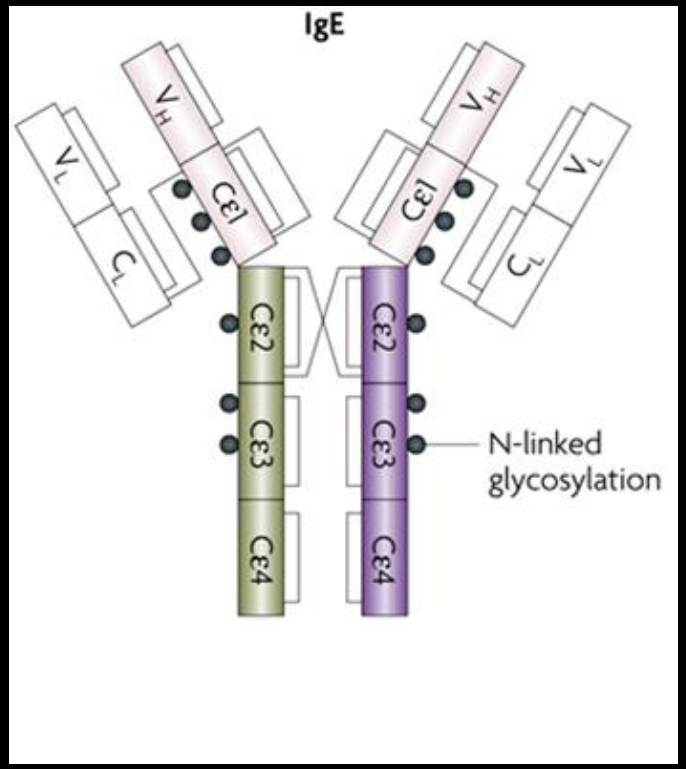
- Baseline lung function
  - Specific airways resistance (sRaw) from 3 years
  - Spirometry, age 5, 8 and 11
- Post-bronchodilator lung function, age 5, 11
- Airway responsiveness
  - Dry air challenge, age 5
  - Methacholine challenge, age 8, 11
- Exhaled breath condensate (EBC), age 8
- Exhaled Nitric Oxide (eNO), age 8, 11

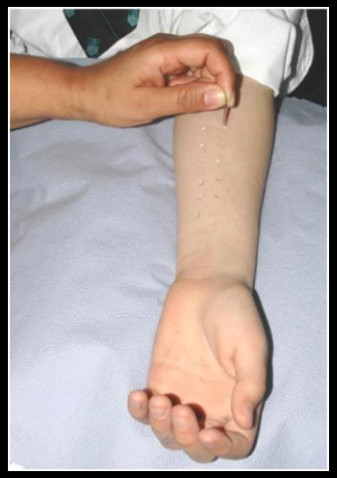
Environmental Exposures

- Allergen levels (mite, cat and dog)
- Endotoxin
- Pet ownership and contact
- Sibship
- Tobacco smoke exposure
- Childcare arrangements
- Vaccination uptake
- Duration of breastfeeding
- Dietary intake (Diet-Q), age 5, 8, 11
- Antibiotic and other medication usage (from primary care records)

Atopic Sensitisation

The presence of specific IgE



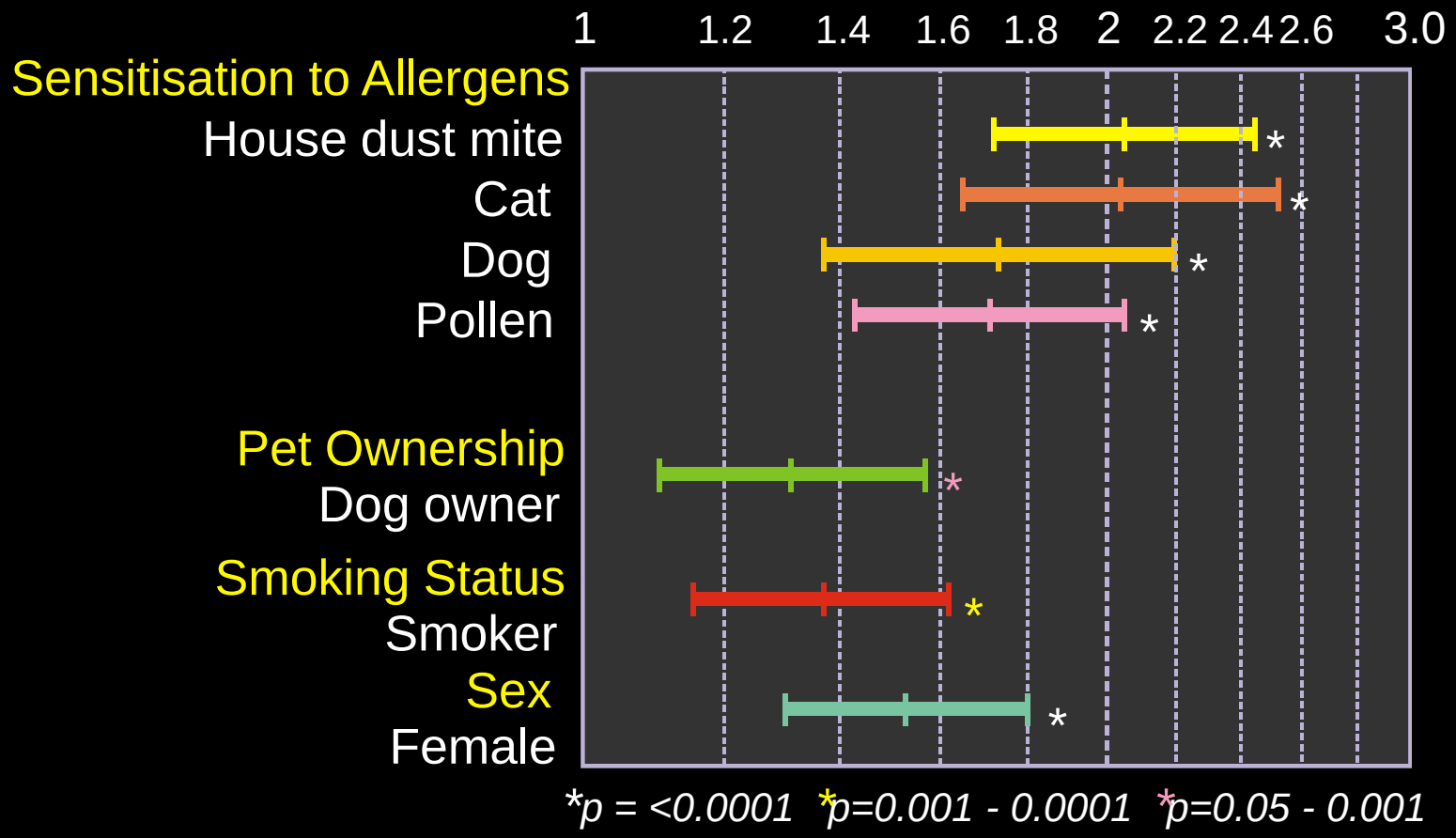


Gould and Sutton Nature Reviews Immunology 2008

Allergen-specific IgE sensitisation

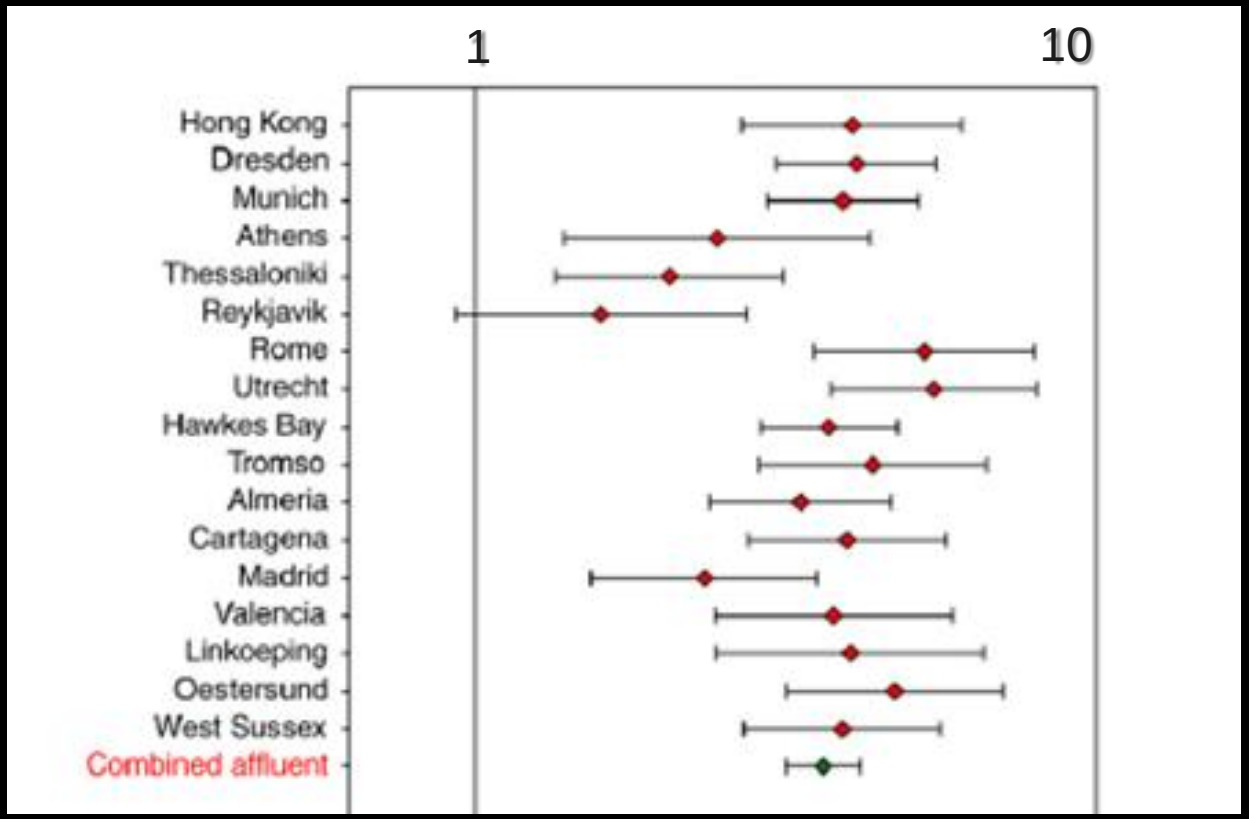
- Allergic sensitization
  - a positive allergen-specific serum IgE (sIgE>0.35 kU_A/L) test or
  - skin prick test (MWD≥3mm)
  - to any common food or inhalant allergen

Sensitisation - Risk Factors for Asthma



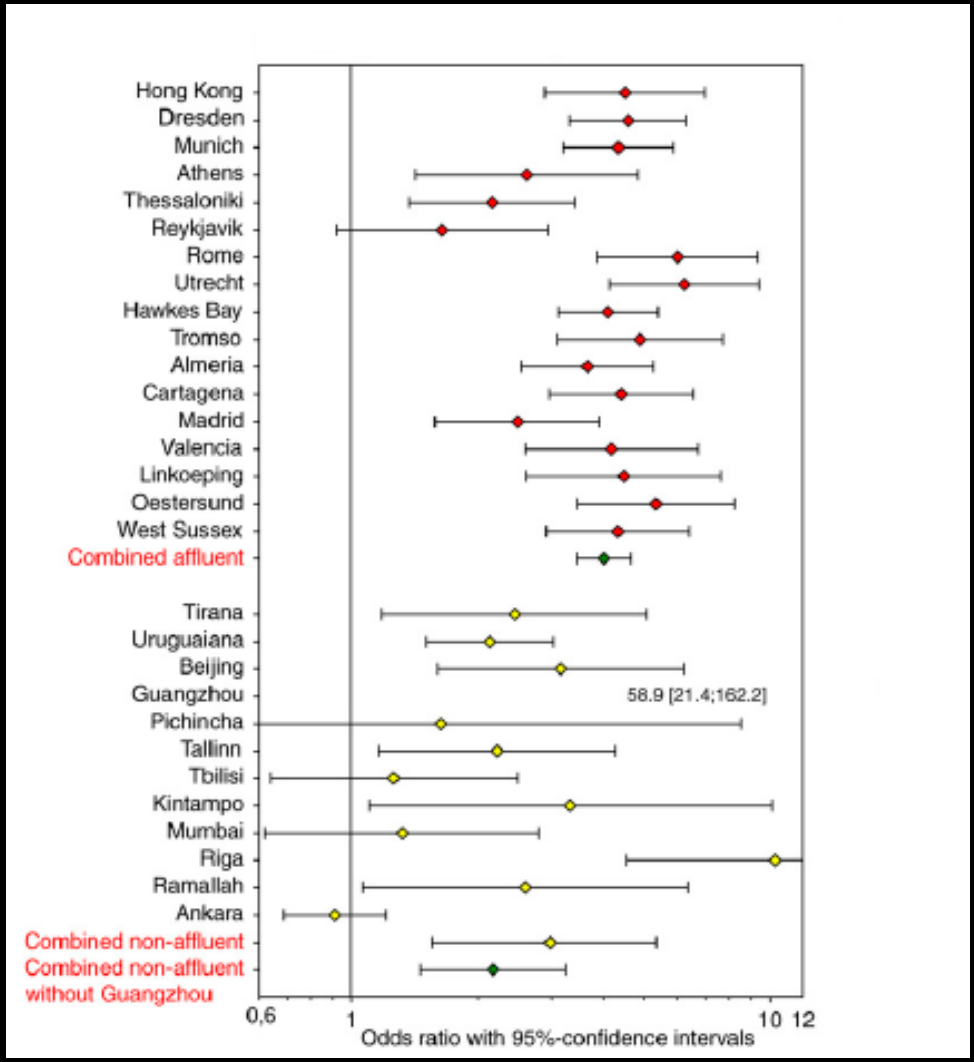
Simpson, Custovic et al, Clin Exp Allergy 2001; 31:391-399

Combined odds ratio for asthma in those with atopy was ~ 4.0 (in affluent countries)



Weinmayr 2007

Odds ratio for the association of current wheeze with skin test reactivity – the effect of affluence



Weinmayr 2007

Atopic sensitisation

- Is
  - Easy to quantify
  - Risk factor for asthma
- But
  - is neither necessary nor sufficient for disease
  - Relationship to asthma complex

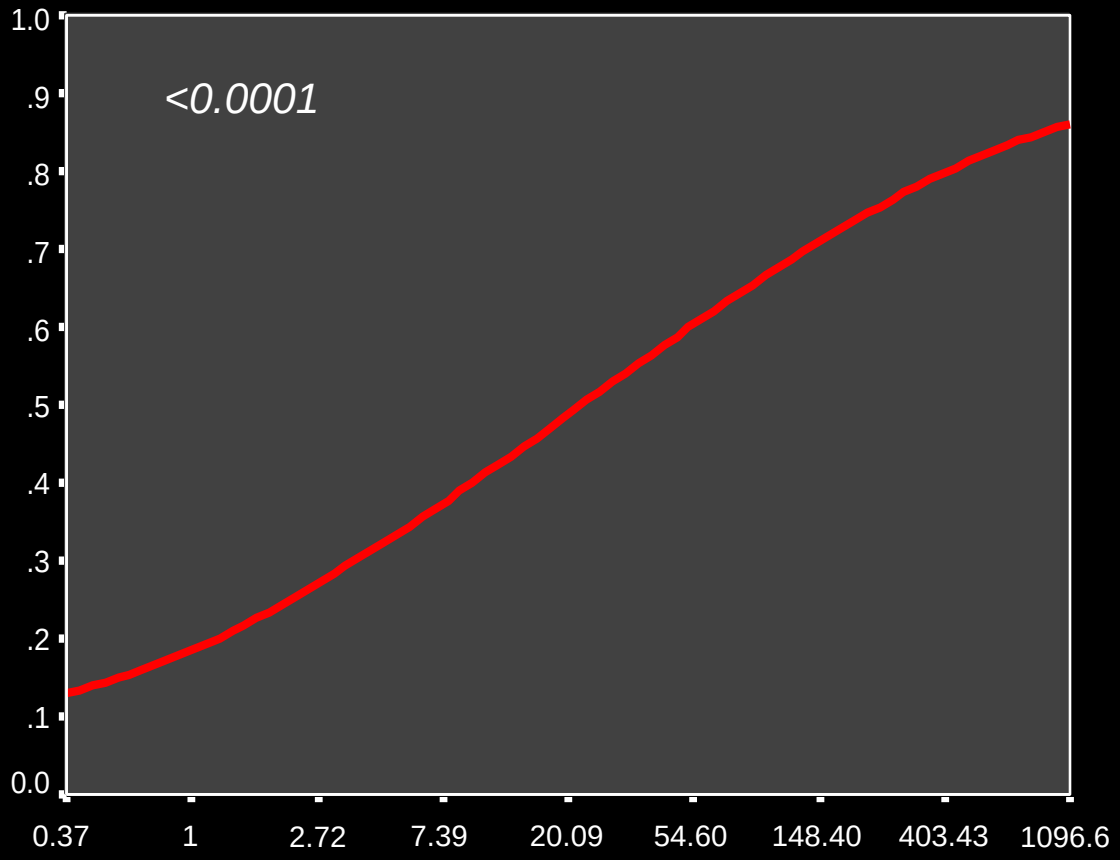
Food allergy

- negative predictive accuracy is high
  - For skin test some extracts are less good
- Positive test is suggestive, but not diagnostic

	95% Predictive Level	
Allergen	**[kU_A/L]**	**PPV**
Egg	7	98
- Infants ≤ 2 yrs	2	95
Milk	15	95
- Infants ≤ 2 yrs	5	95
Peanut	14	100
Fish	20	100
Tree nuts	~15	~95
Soybean	30	73
Wheat	26	74

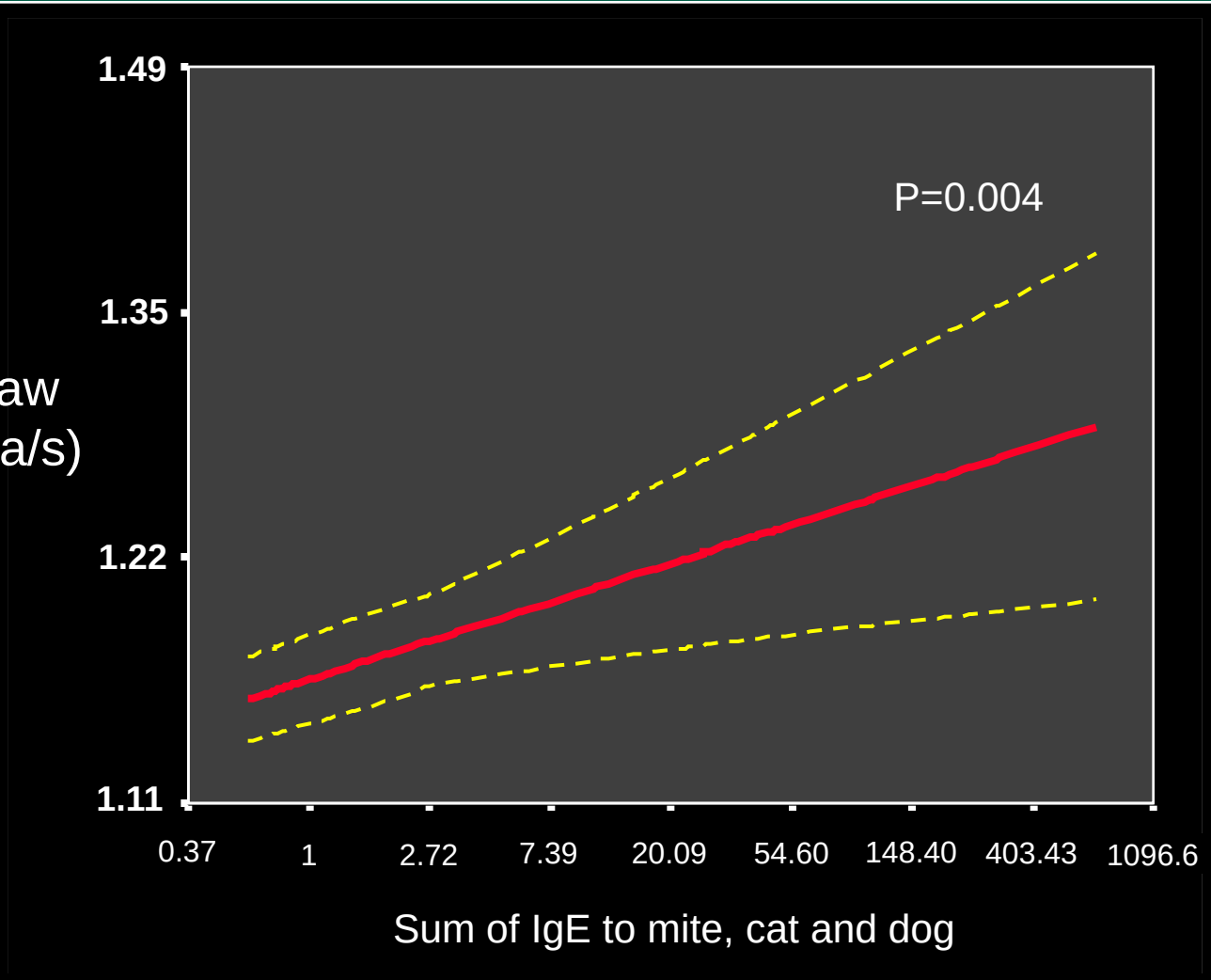
Sampson JACI 2004

Probability for Persistent Wheeze Increases With Increasing Specific IgE Antibody Levels



Simpson et al, J Allergy Clin Immunol 2005; 116: 744-749

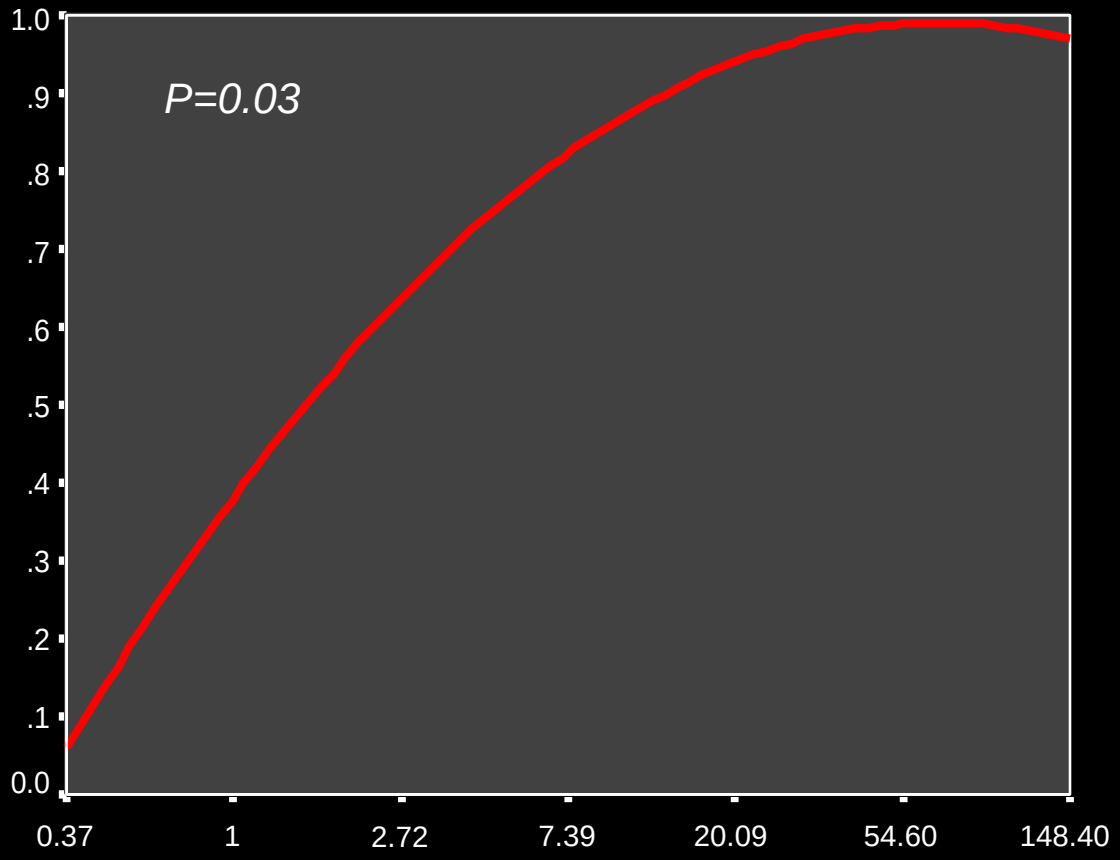
Decrement in Lung Function With Increasing Specific IgE at Age 5 Years



Simpson et al, J Allergy Clin Immunol 2005; 116: 744-749

Monitoring of Atopy and Prediction of Persistence of Wheezing

Specific IgE Levels at Age 3 Predict the Subsequent Persistence of Wheeze



Simpson et al, J Allergy Clin Immunol 2005; 116: 744-749

IgE to Mite, Cat and Dog and the Prediction of Childhood Wheezing

In a 3 year-old child presenting to a physician with wheezing, will the wheeze continue in years to come?

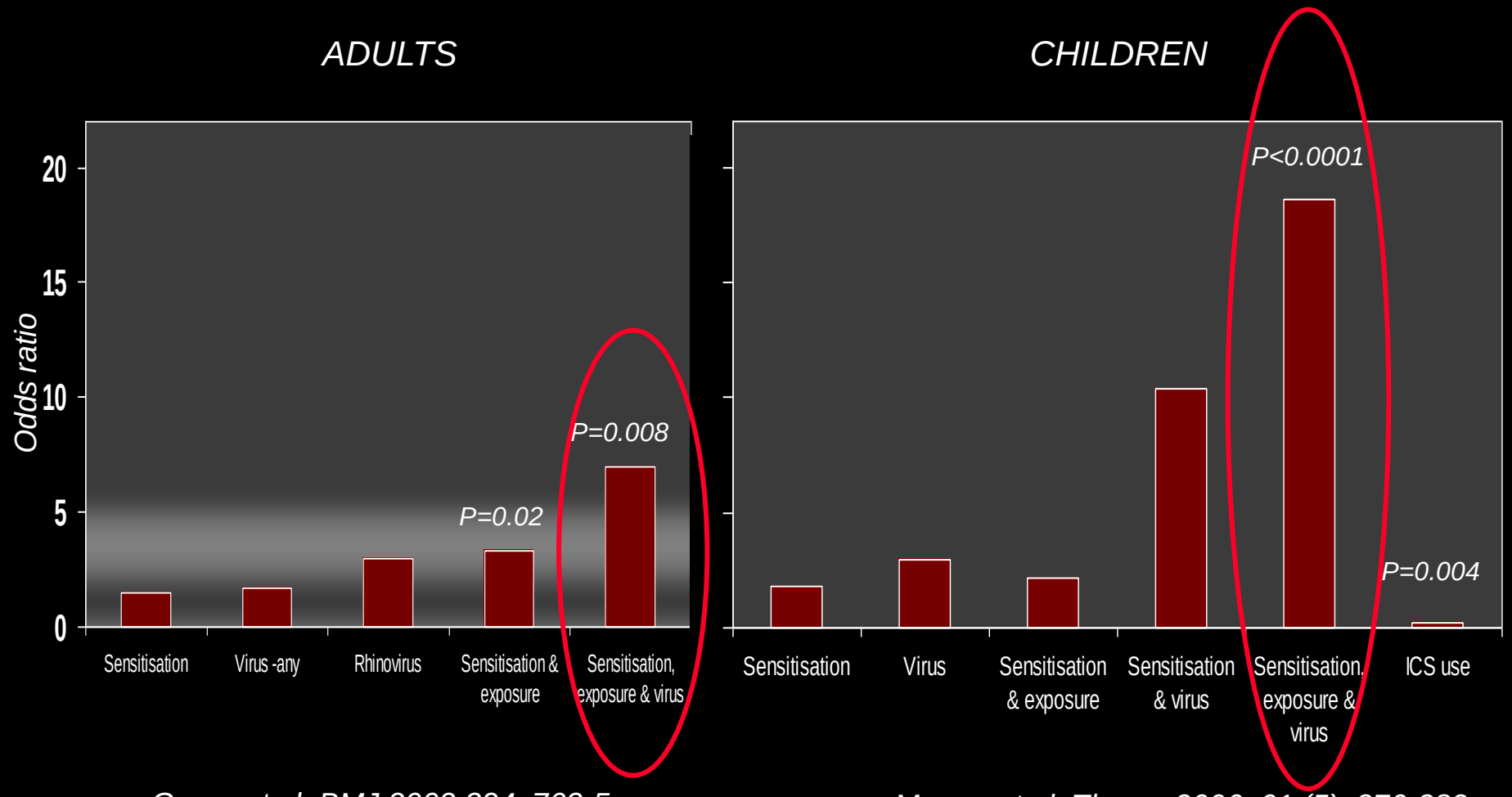
- **0.5 kUA/L: 18%** probability of persistence of wheezing
- **10 kUA/L: 50%** probability of persistence of wheezing
- **30 kUA/L: 90%** probability of persistence of wheezing

Ahlstedt S et al. Diagnosis of allergy. In: Custovic A, Platts Mills TAE eds. Managing Allergy, 2009

Gender, Age, Exposures

Atopy and Asthma Exacerbations

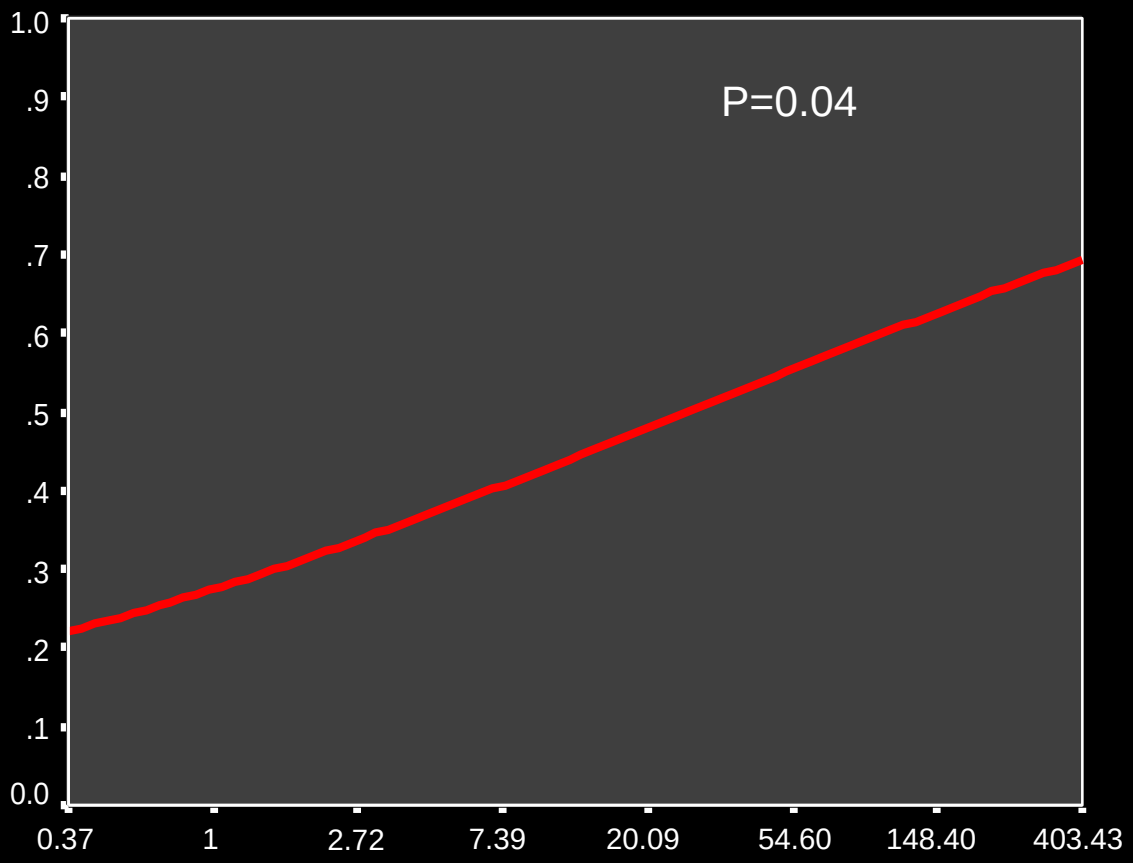
Sensitisation, Exposure and Respiratory Virus Infection Increase the Risk of Hospital Admission



Green et al, BMJ 2002;324: 763-5

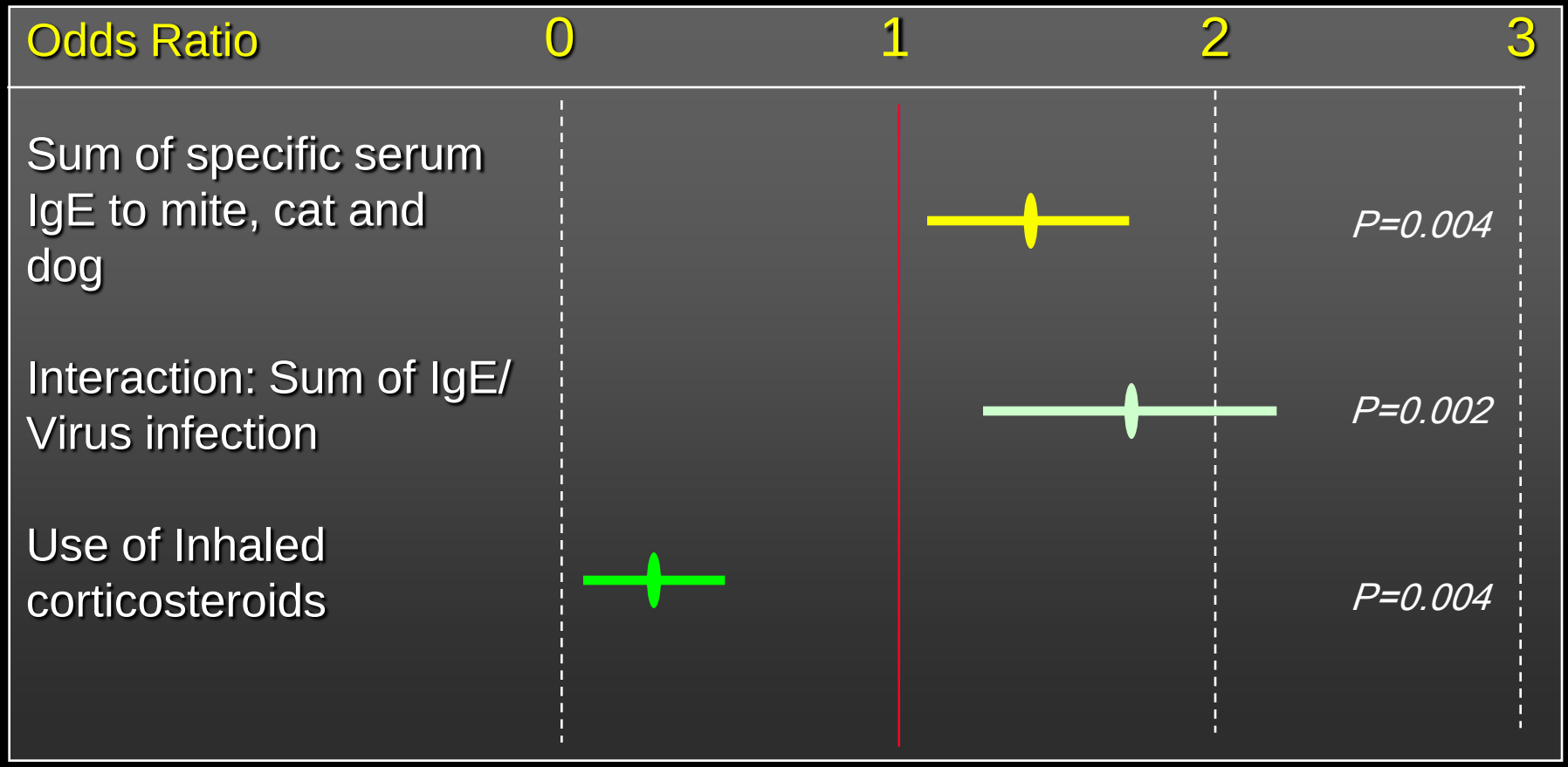
Murray et al, Thorax 2006; 61 (5): 376-382

Amongst Atopic Children, the Risk of Hospital Admission Increases With Increasing IgE



Murray et al, Allergy Clin Immunol Int 2007; Suppl 2: 270-3

Interaction Between Specific IgE Levels and Virus Infection in Increasing the Risk of Hospital Admission in Asthmatic Children



Murray et al, Allergy Clin Immunol Int 2007; Suppl 2: 270-3

IgE-antibody Quantification and Clinical Expression of Asthma

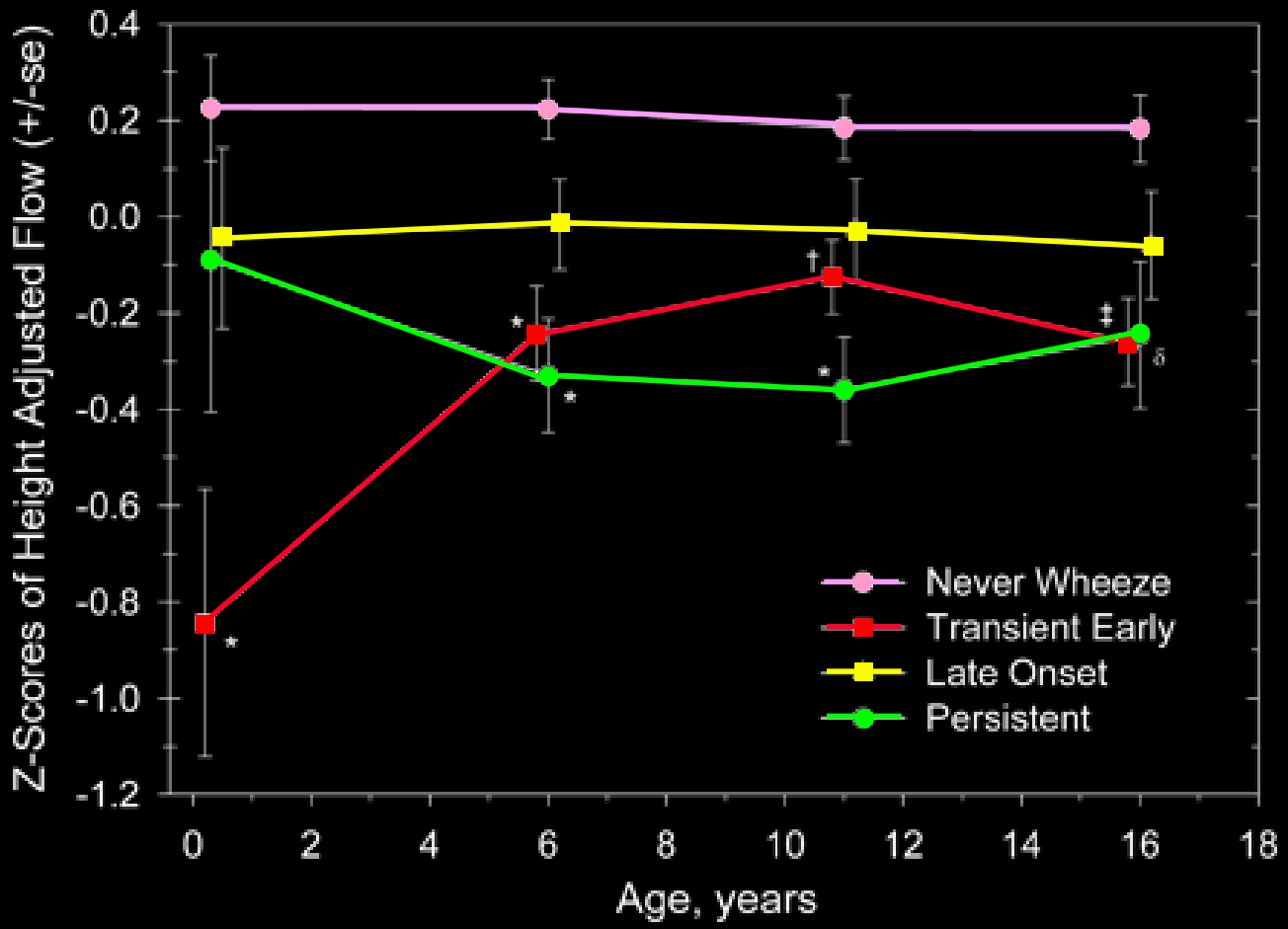
- IgE-antibody quantification
  - Increases the confidence that “atopic sensitization” contributes to the expression of asthma
  - May help identify young children at risk of persistent symptoms
  - May help identify asthmatics at risk of exacerbations
  - May help treatment decision-making process
- Different sensitization profiles are associated with different clinical phenotypes

Simpson et al, JACI 2005; 116: 744-749
Marinho et al, Allergy 2007; 62: 1379-86
Murray et al, Allergy Clin Immunol Int 2007; Suppl 2: 270-3

We propose

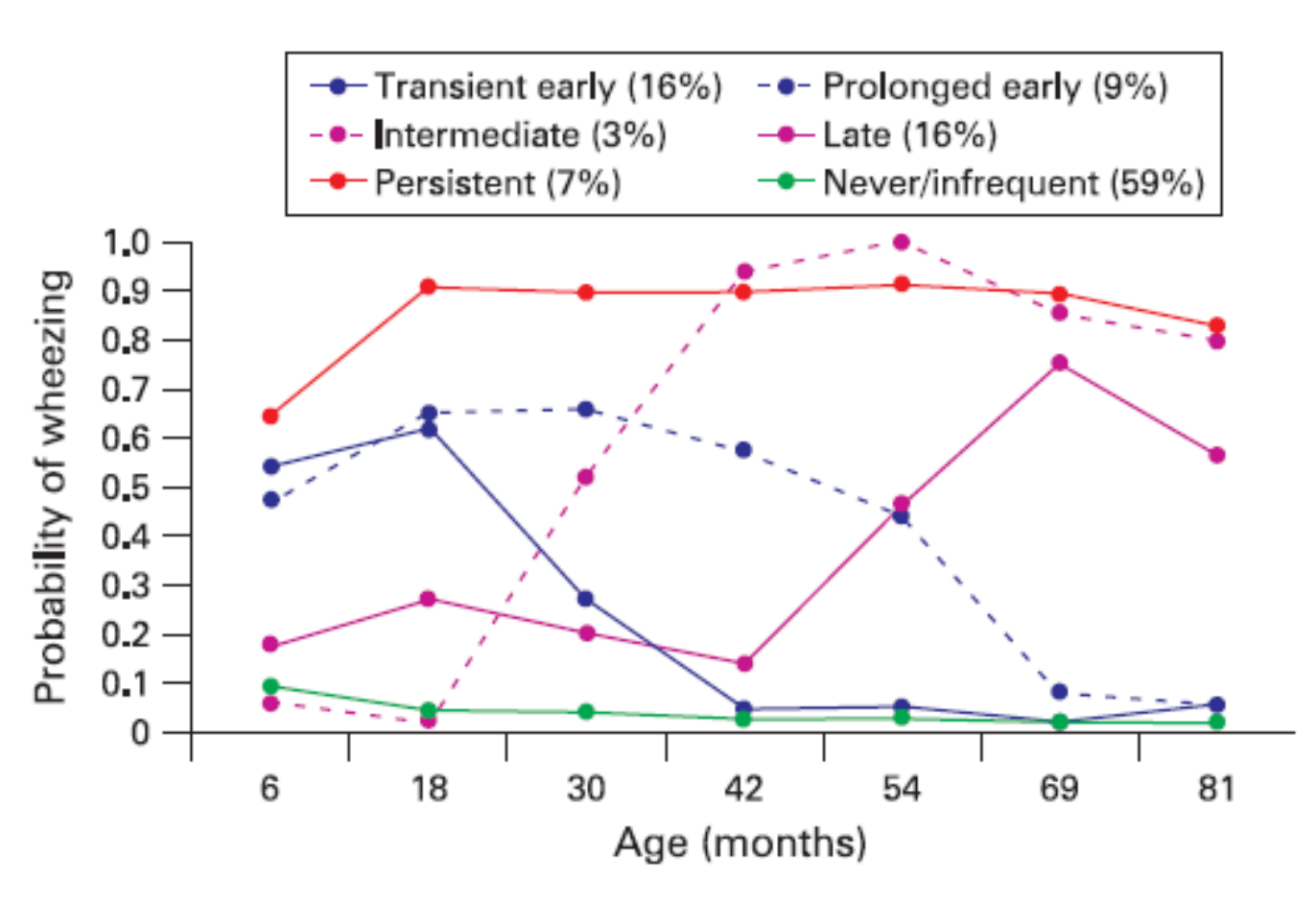
- The diagnostic label of atopy encompasses
  - multiple different phenotypes
  - with different aetiologies
  - not all of which are associated with disease
- More useful information may be obtained by identifying common underlying clusters that are characterized by IgE responses

Phenotype definition – lessons from asthma



Morgan et al, AJRCCM 2005;172):1253-8

Wheeze phenotypes in the population – latent classes



Henderson et al Thorax 2008

Beyond Atopy

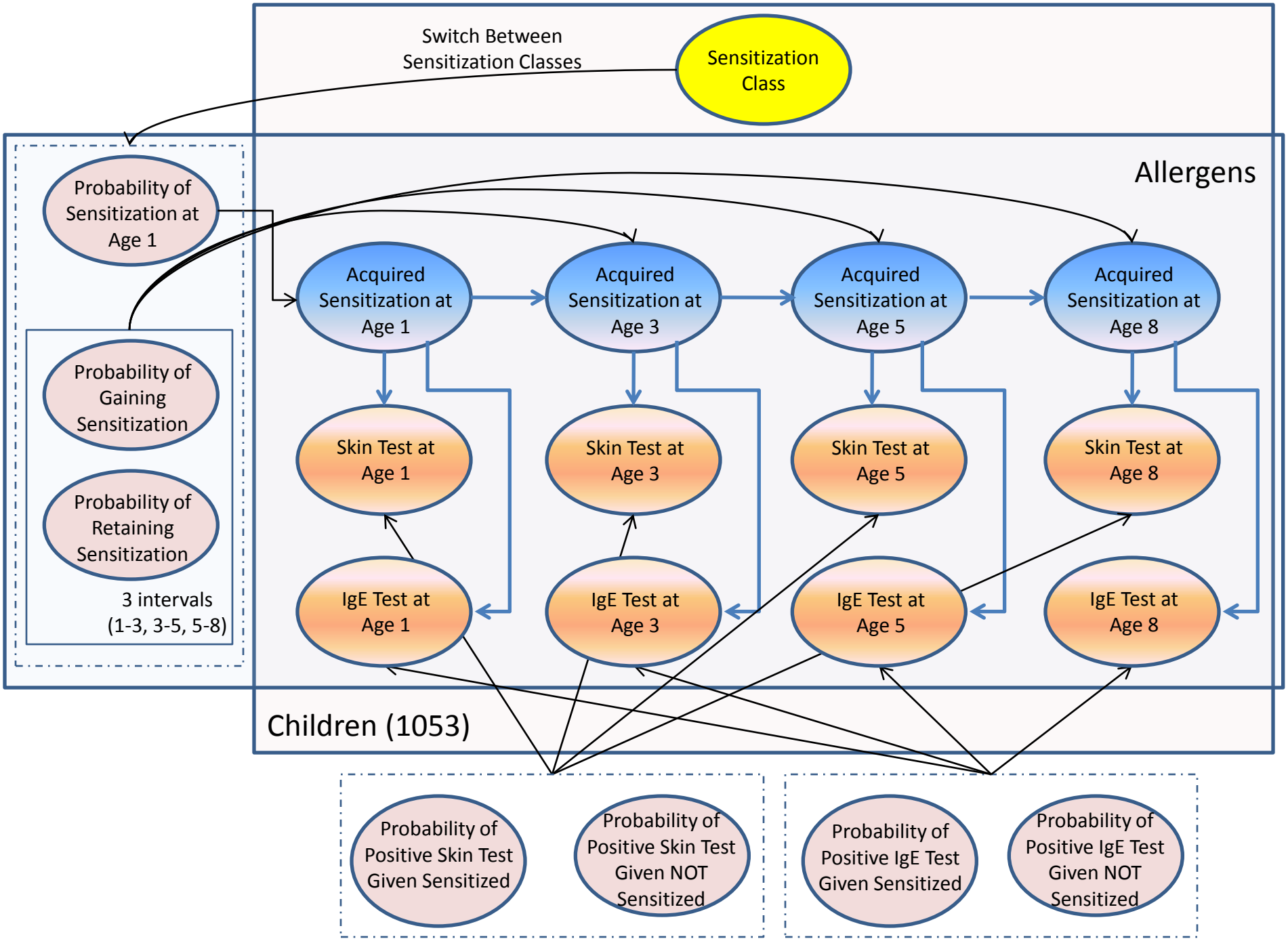
Multiple Patterns of Sensitization in Relation to Asthma in a Birth Cohort Study

Angela Simpson[1]*, Vincent Y. F. Tan[2]*, John Winn[3], Markus Svensén[3], Christopher M. Bishop[3], David E. Heckerman[4], Iain Buchan[5], and Adnan Custovic[1]

How to Avoid the Constraints of the Investigator-imposed Classifications?

A Machine Learning Approach using Bayesian inference for unsupervised learning of latent variables to identify structure within the data:

- Allows one to model data with complex structure
- Model can be tailored to dataset
- Prior knowledge can be more precisely encoded in the dataset
  - Not just a “black box” approach
- Can scale to large models (millions of records)


Switch Between Sensitization Classes
Sensitization Class
Allergens
Probability of Sensitization at Age 1
Probability of Gaining Sensitization
Probability of Retaining Sensitization
3 intervals (1-3, 3-5, 5-8)
Acquired Sensitization at Age 1
Acquired Sensitization at Age 3
Acquired Sensitization at Age 5
Acquired Sensitization at Age 8
Skin Test at Age 1
Skin Test at Age 3
Skin Test at Age 5
Skin Test at Age 8
IgE Test at Age 1
IgE Test at Age 3
IgE Test at Age 5
IgE Test at Age 8
Children (1053)
Probability of Positive Skin Test Given Sensitized
Probability of Positive Skin Test Given NOT Sensitized
Probability of Positive IgE Test Given Sensitized
Probability of Positive IgE Test Given NOT Sensitized

Outcome: Sensitization Class

- A single multinomial latent variable
- Each child was then assigned to its highest probability class
- No assumptions about the number or the nature of the classes
- The unsupervised learning algorithm automatically discovered the latent structure
  - Assumption: data missing at random
  - Missing data: inferred using Variational Message Passing - VMP

Simpson et al, Am J Respir Crit Care Med 2010; 181(11):1200-6

Results: Sensitisation Class

- "No latent vulnerability" (623/1053, 59.2%)

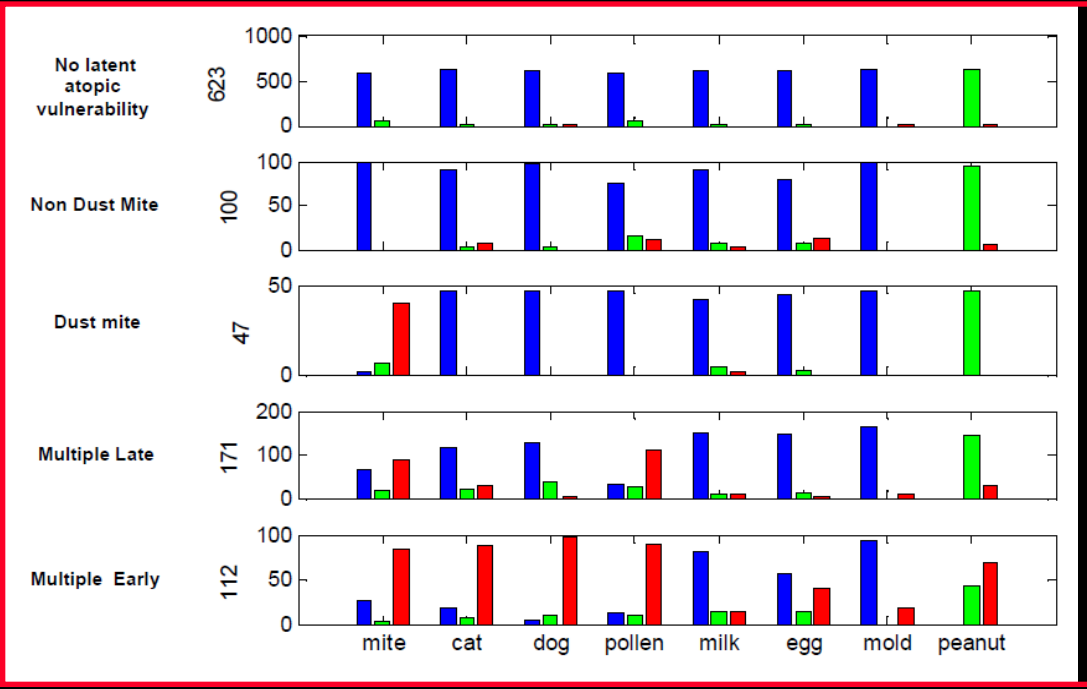
  Children With Latent Atopic Vulnerability Cluster Into Four Distinct Sensitisation Classes

- (1) *Non-dust Mite Atopic Vulnerability* (9.5%)
- (2) *Dust Mite Atopic Vulnerability* (4.5%)
- (3) *Multiple Late Atopic Vulnerability* (16.2%)
- (4) *Multiple Early Atopic Vulnerability* (10.6%)

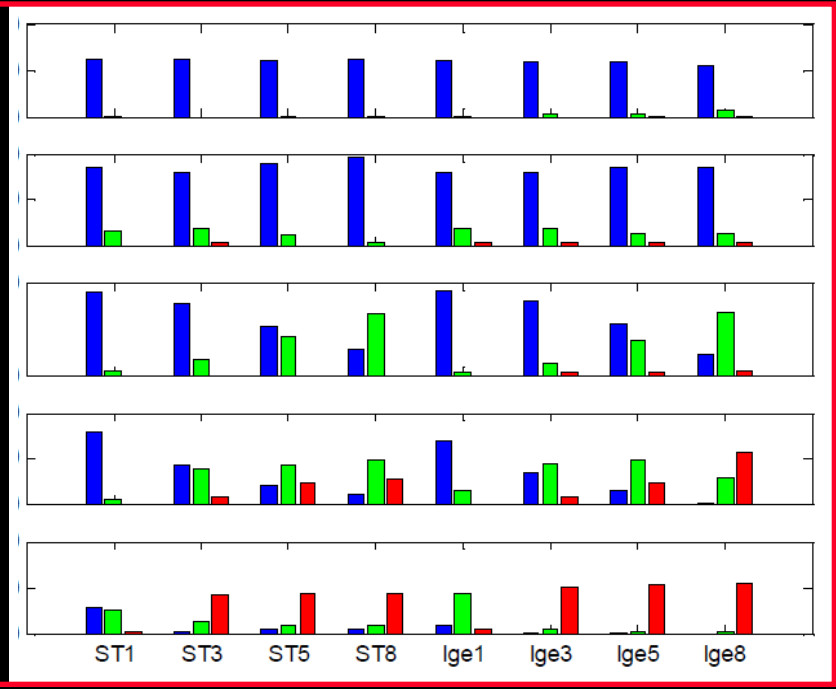
Simpson et al, Am J Respir Crit Care Med 2010; 181(11):1200-6

The Structure Of The Five Classes:

Number of sensitizations to each allergen and at each time point



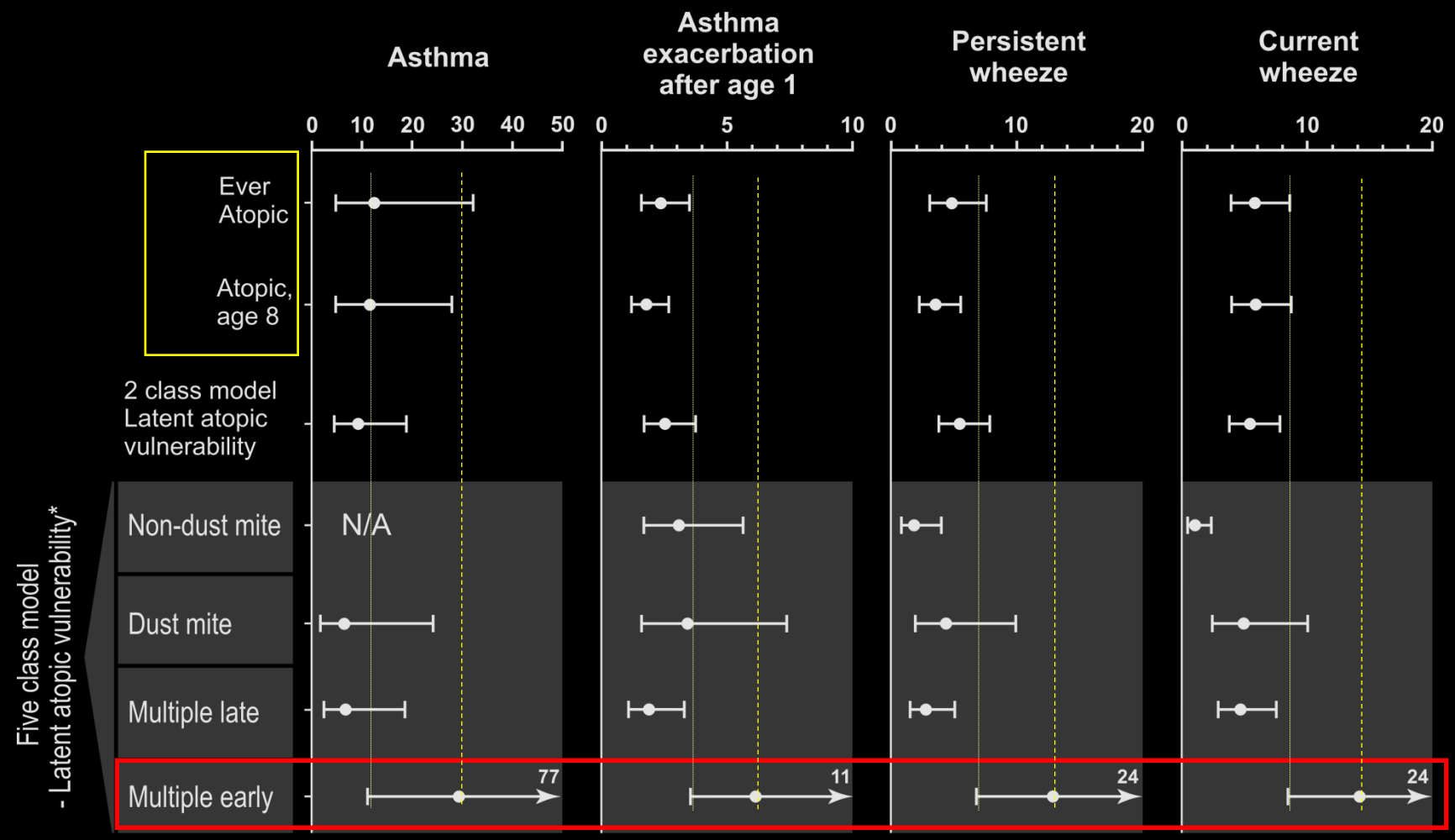
Number of sensitizations to each allergen



Number of sensitizations at each time point

Simpson et al, Am J Respir Crit Care Med 2010; 181(11):1200-6

Latent Atopic Vulnerability Classes and Asthma

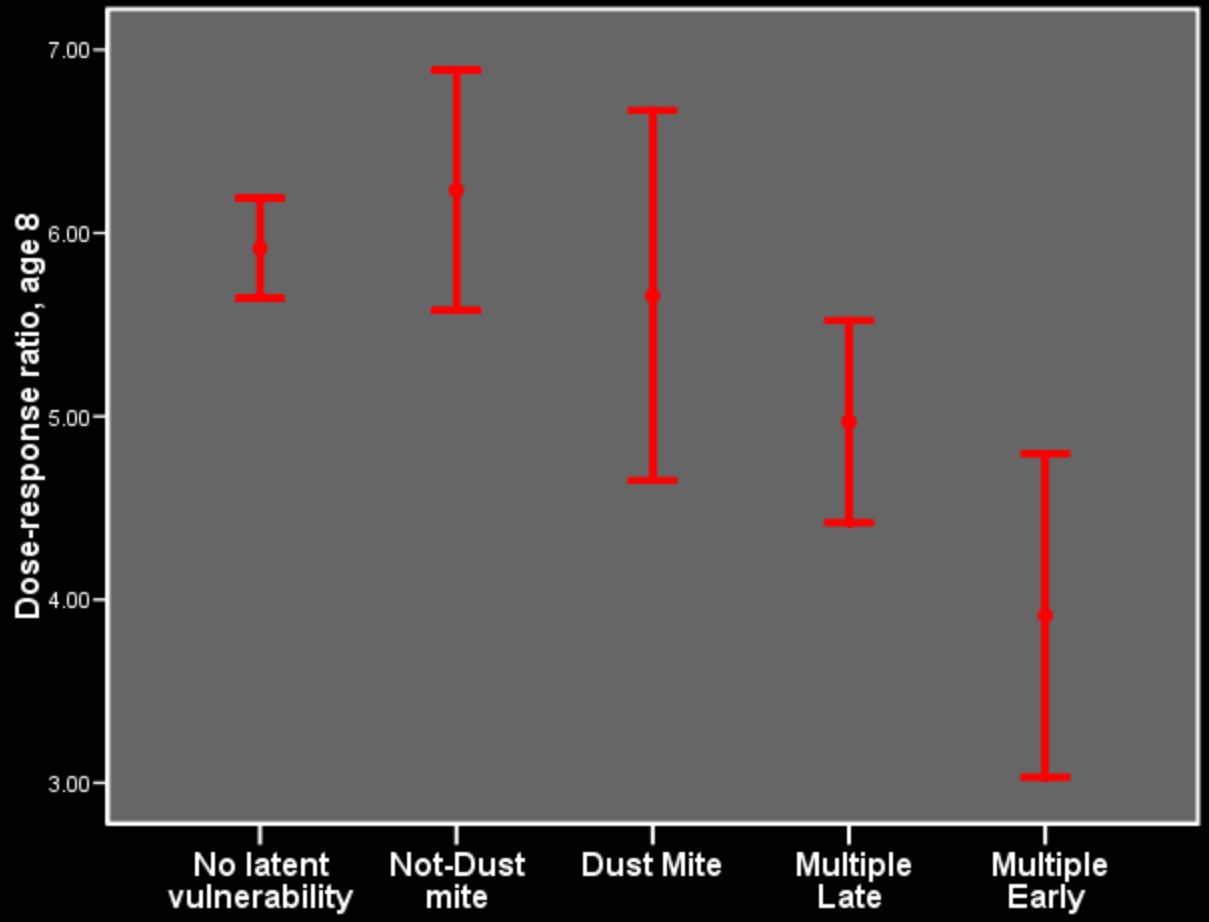


Simpson et al, Am J Respir Crit Care Med 2010; 181(11):1200-6

Multiple Early Latent Class:
Significantly Poorer Lung Function

Simpson et al, Am J Respir Crit Care Med 2010; 181(11):1200-6

Multiple Early Latent Class:
Significantly More Hyper-reactive



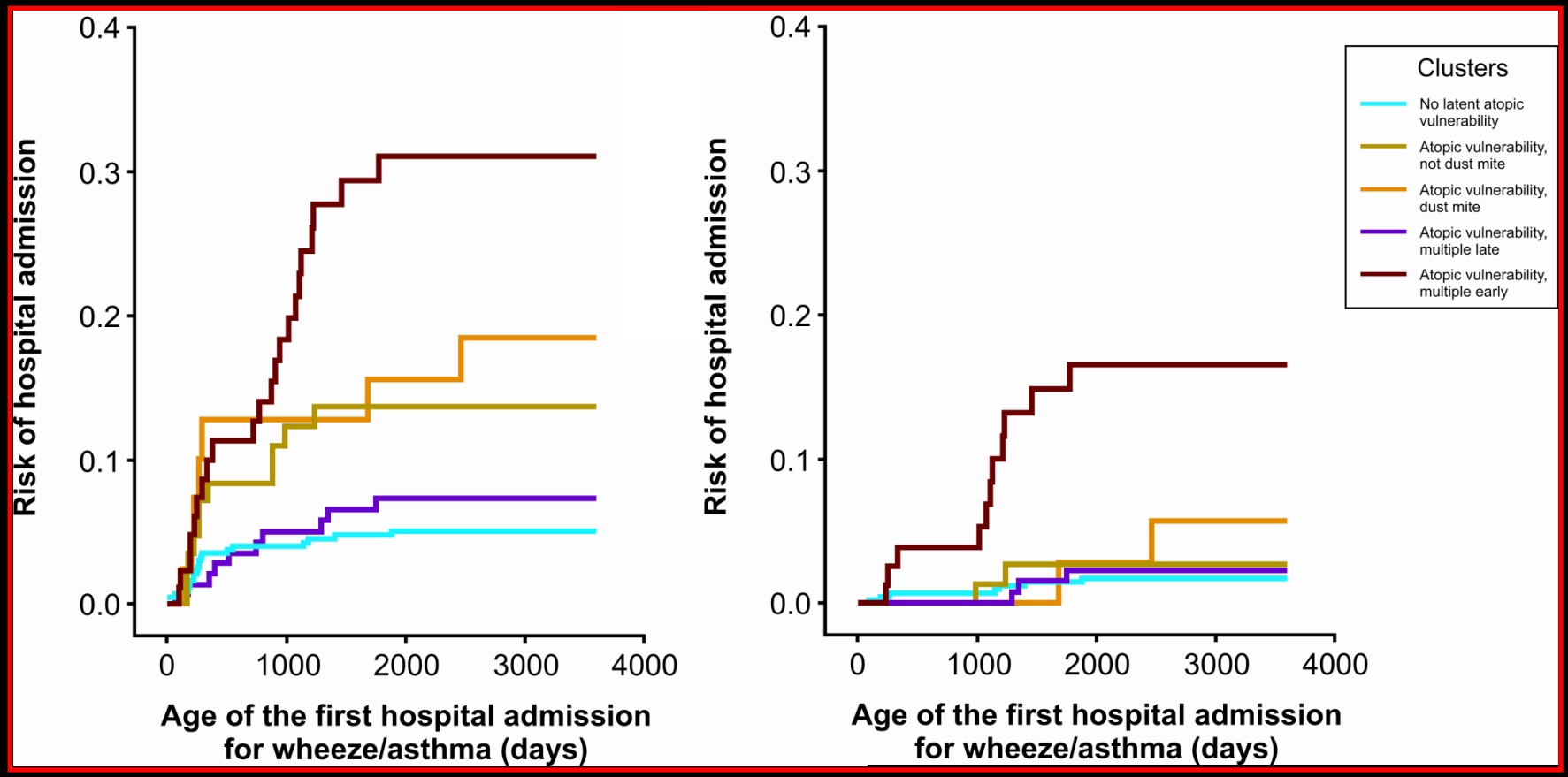
Simpson et al, Am J Respir Crit Care Med 2010; 181(11):1200-6

Multiple Early Latent Class:

Significantly More and Earlier Hospitalisations

Hospitalization with wheeze/asthma (any age)

Hospitalization with wheeze/asthma (after age 3 yr)

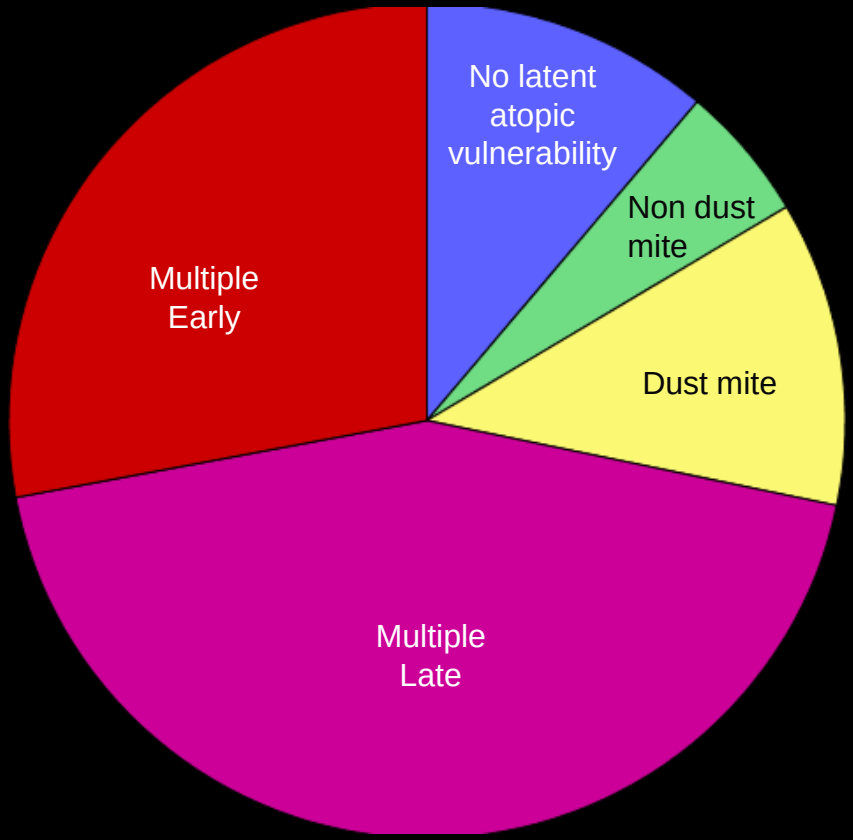


Simpson et al, Am J Respir Crit Care Med 2010; 181(11):1200-6

$$\text{ATOPY} = \sum_{i=1}^{n} \text{ATOPY}_i$$

Simpson et al, Am J Respir Crit Care Med 2010; 181(11):1200-6

How Does Atopic Sensitisation Defined Conventionally At Age 8 Years Relate To The 5-class Model?



Simpson et al, Am J Respir Crit Care Med 2010; 181(11):1200-6

What have we learnt?

- Viewing atopic sensitisation as a dichotomous trait is an oversimplification
- IgE antibody responses do not reflect a single phenotype of atopy, but multiple different atopic vulnerabilities
- Need to
  - confirm model in different datasets
  - Identify a simple diagnostic test

What is the Marker of the Different Types of Sensitisation?

Can Component-resolved Diagnostics Help?

Allergy or tolerance in children sensitized to peanut: Prevalence and differentiation using component-resolved diagnostics

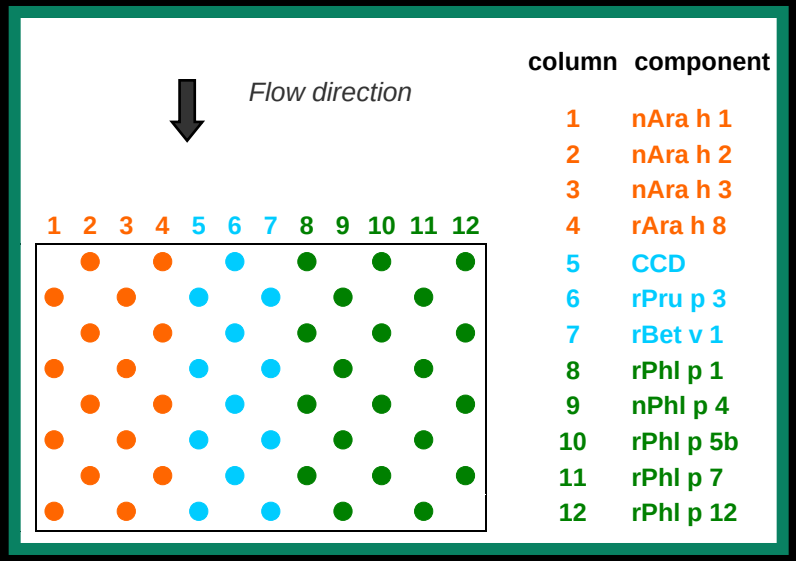
Nicolaos Nicolaou, MD, MPhil,[a] Maryam Poorafshar, PhD,[b] Clare Murray, MD,[a] Angela Simpson, MD,[a] Henric Winell, MSc,[b] Gina Kerry, RN,[a] Annika Härlin, MSc,[b] Ashley Woodcock, MD, FMedSci,[a] Staffan Ahlstedt, PhD,[c] and Adnan Custovic, MD, PhD, FRCP[a] *Manchester, United Kingdom, and Uppsala and Stockholm, Sweden*

Peanut Allergy And Tolerance Amongst Peanut–sensitized Children

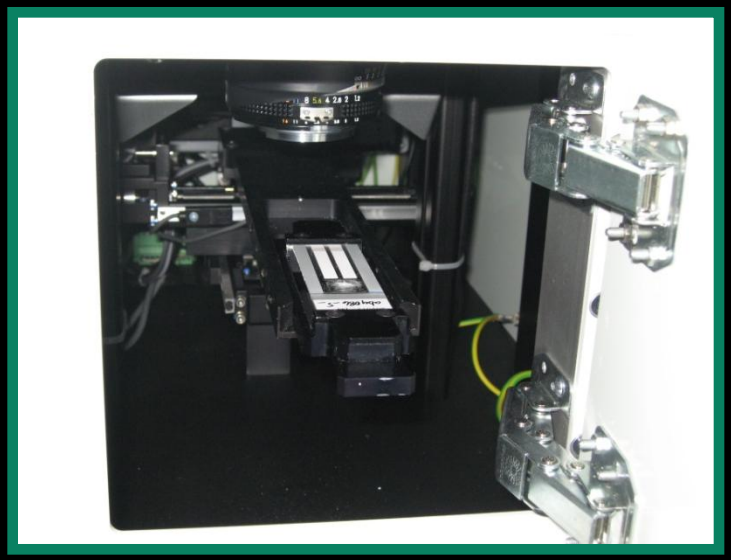
- 11.8% of children at age 8 years are peanut-sensitized
- Majority of these children are peanut-tolerant (i.e. do not have peanut allergy)
- The proportion of children with peanut allergy amongst those sensitized to peanut is only 22.4% (95% CI 14.8%–32.3%)

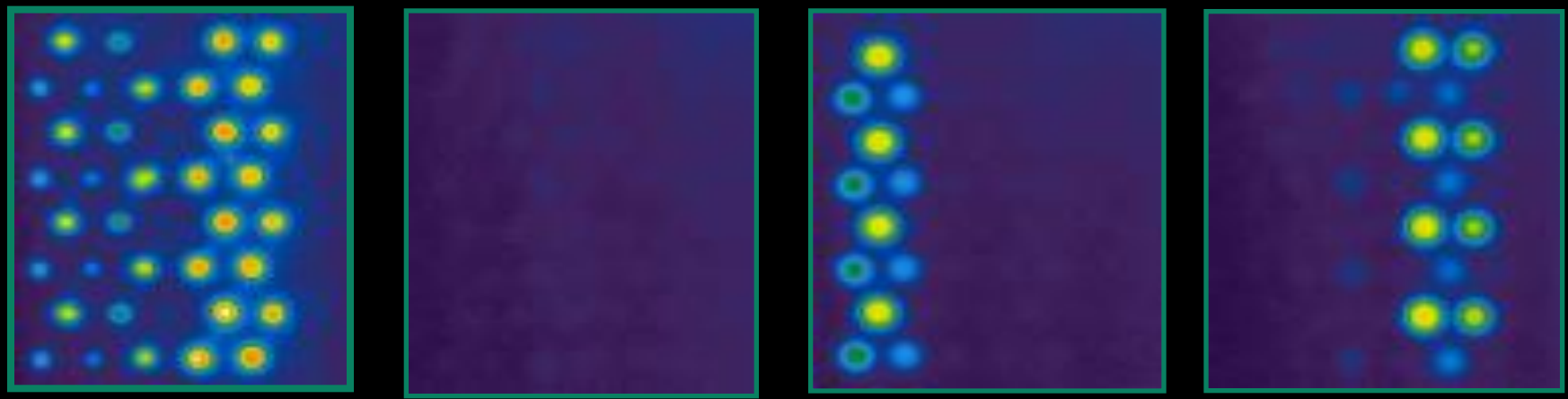
Nicolaou et al, J Allergy Clin Immunol 2010; 125(1): 191-7

Microarray: Component Detection

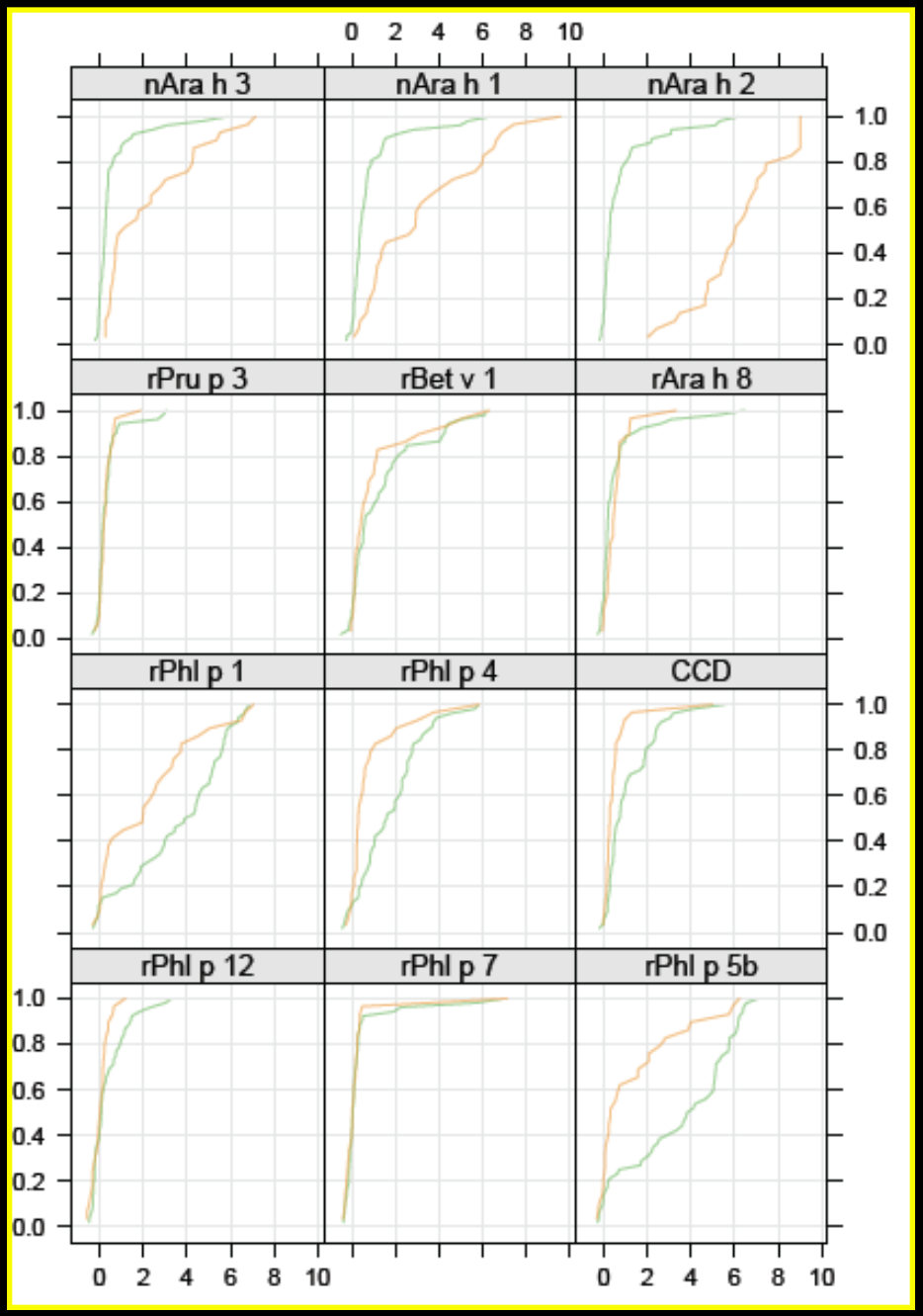


column	component
1	nAra h 1
2	nAra h 2
3	nAra h 3
4	rAra h 8
5	CCD
6	rPru p 3
7	rBet v 1
8	rPhl p 1
9	nPhl p 4
10	rPhl p 5b
11	rPhl p 7
12	rPhl p 12





Nicolaou et al, J Allergy Clin Immunol 2010; 125(1): 191-7



Nicolaou et al, J Allergy Clin Immunol 2010; 125(1): 191-7

Discriminating Peanut Allergy From tolerance: Random Forests Classifier

- When all components were used:
  - Only 7.7% peanut-tolerant subjects were misclassified as peanut-allergic
  - Only 6.9% peanut-allergic subjects were wrongly classified as peanut-tolerant
- Ara h 2 - the most important predictor of peanut allergy amongst all components investigated
- Predictive accuracy of Random Forests analysis *identical* when only Ara h 2 was used compared to all component

Nicolaou et al, J Allergy Clin Immunol 2010; 125(1): 191-7

Conclusions

- Identification of a child at high risk of asthma is not possible with absolute certainty (as yet)
- sIgE quantification in early life in conjunction with clinical history can help identify early wheezers at high risk of developing persistent asthma
  - Individual benefit – best practice management
  - Appropriate selection for intervention studies

Sly PD et al, Lancet 2008; 372: 1100-06

Conclusions

- Within each clinical phenotype, the information on the specific IgE antibody levels needs to be put into the context of:
  - Gender and age
  - Patient's personal allergen exposure and other environmental exposures
  - Presence of respiratory virus infection
  - Genetics
- Future – IgE measurement will have much more to offer to clinicians