

# Lessons from Cross-Sectional and Longitudinal Studies in Infants and Children



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The International Study of Asthma  
and Allergies in Childhood

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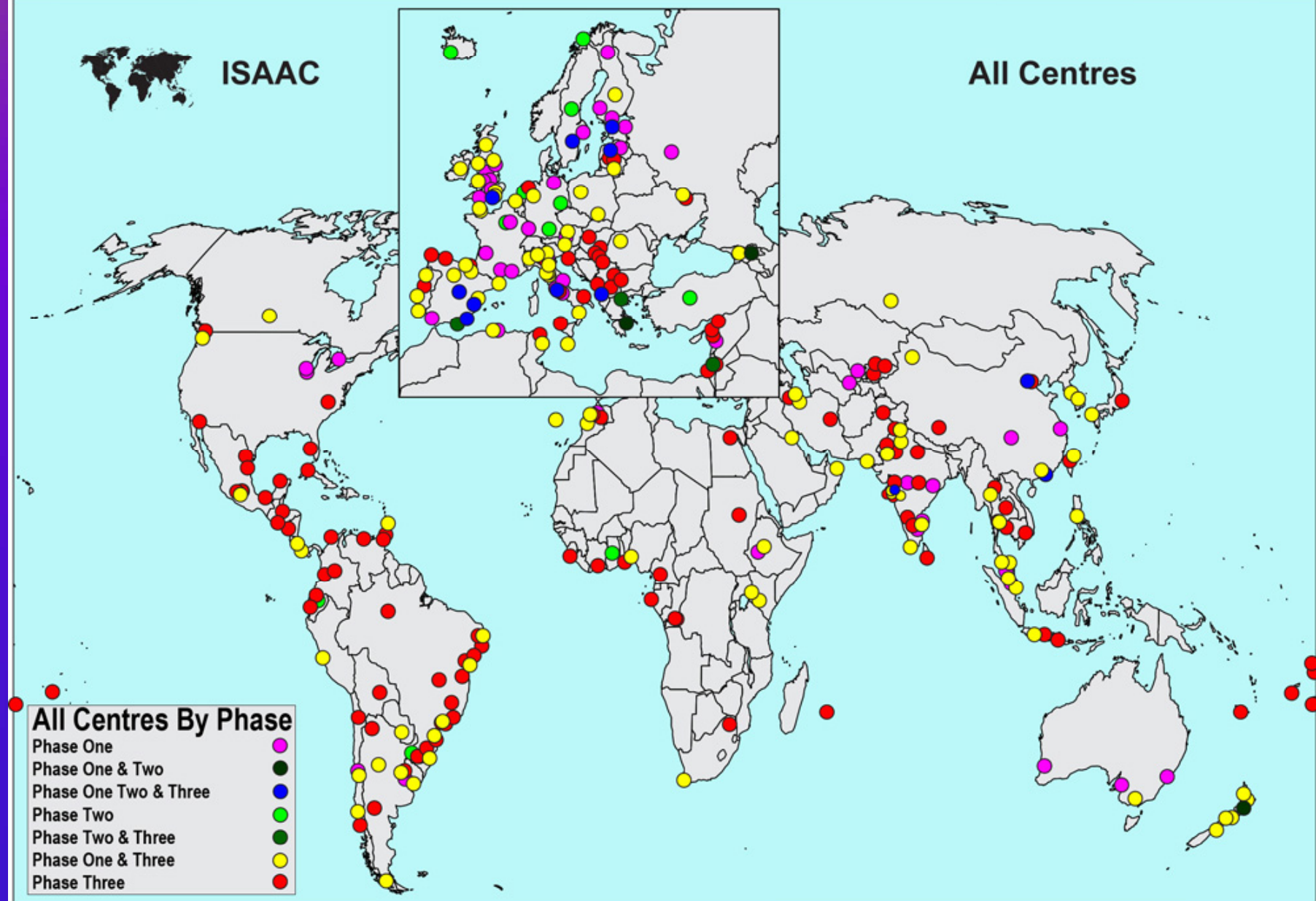
# Lessons from data

- **Global variations of asthma prevalence**
- **Time trend of asthma prevalence**
- **Environmental risk factors**
  - Ecological level
  - Individual level



ISAAC

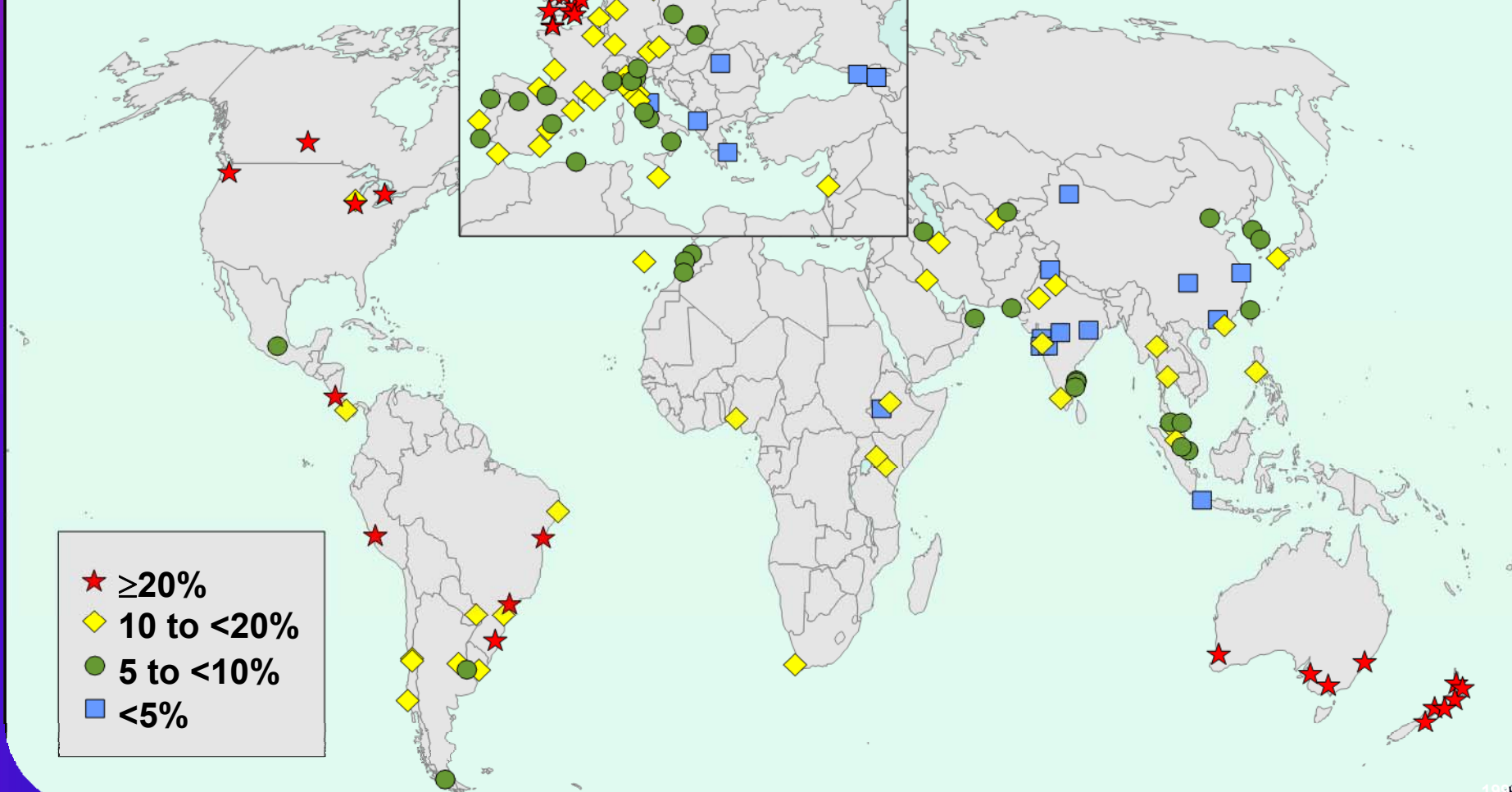
All Centres



# Global variations

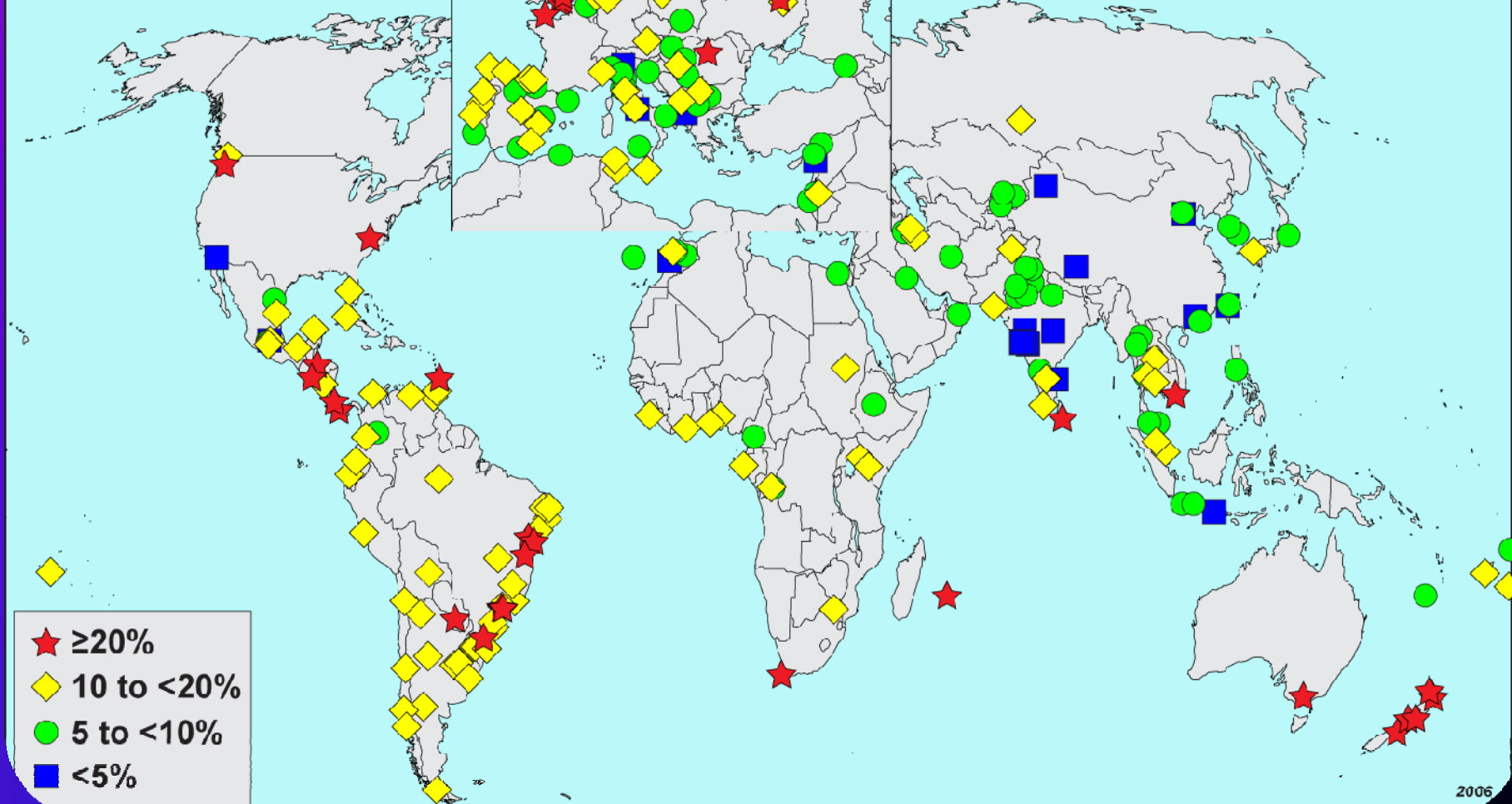
 **ISAAC**  
**Phase One**

**Wheeze in last 12 mths**  
**13-14 yr age grp**



 **ISAAC**  
**Phase Three**

**Wheeze in the Past 12 Months**  
**13-14 Year Age Group**

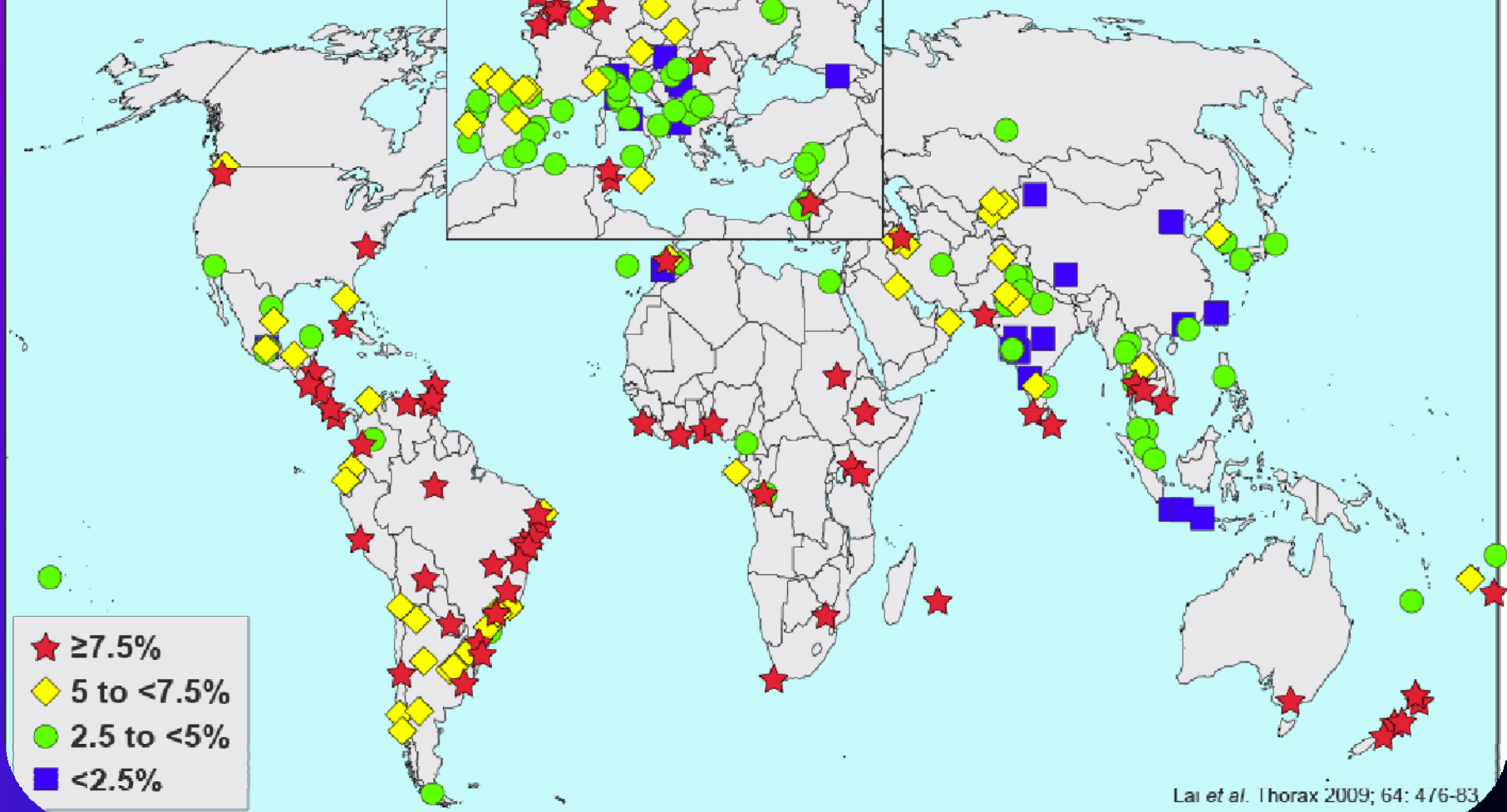


2006



ISAAC  
Phase Three

Symptoms of Severe Asthma  
13-14 Year Age Group



Lai *et al.* Thorax 2009; 64: 476-83.

# Some lesson from global variations

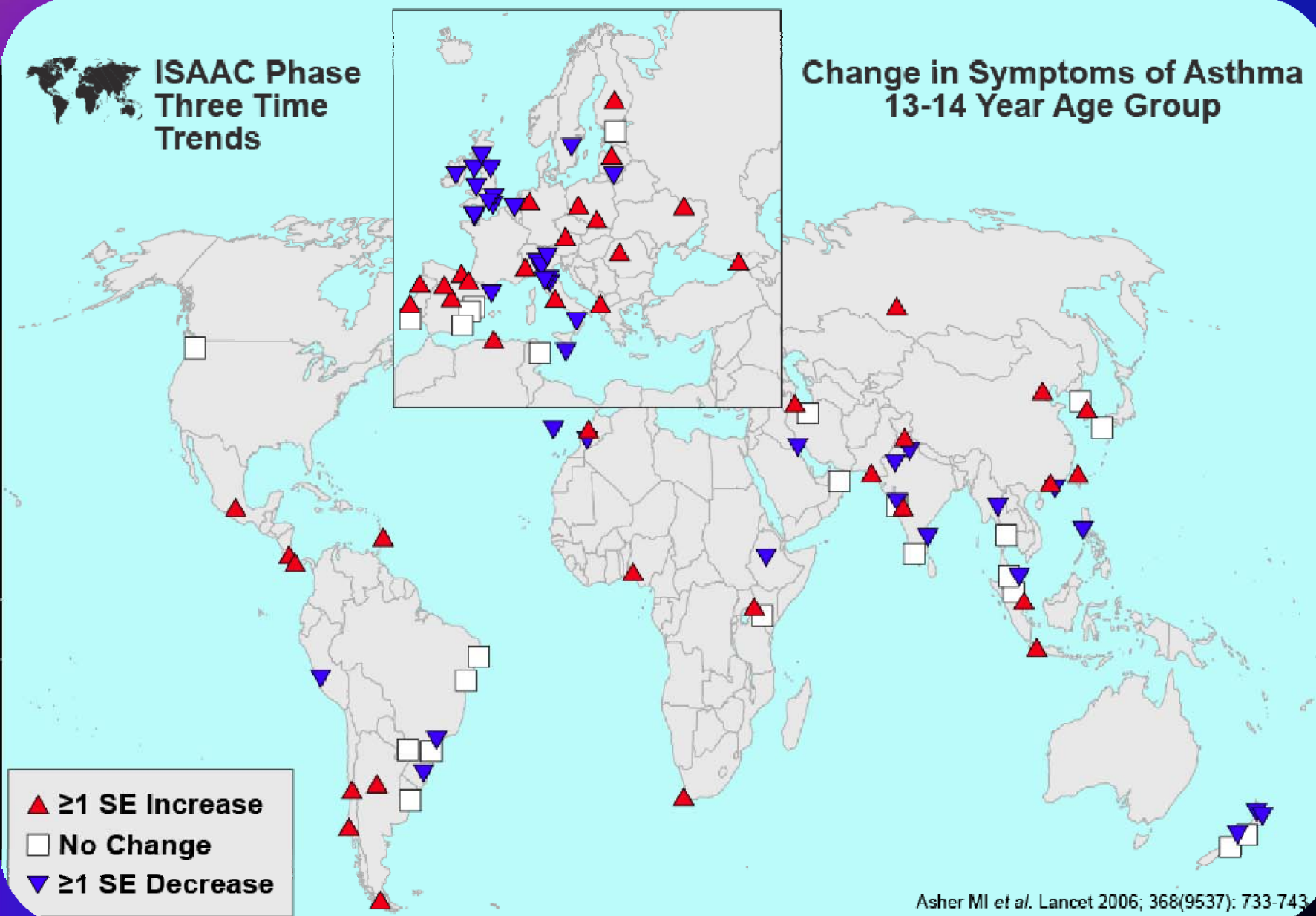
- Asthma is not less prevalent in low-income countries
- More severe asthma is more frequent in areas with higher prevalence
- Hygiene hypothesis does not work everywhere
- Prevalence is highly variable in genetically similar areas
- Environmental local factors probably exert a key role in asthma inception

# Temporal trends



## ISAAC Phase Three Time Trends

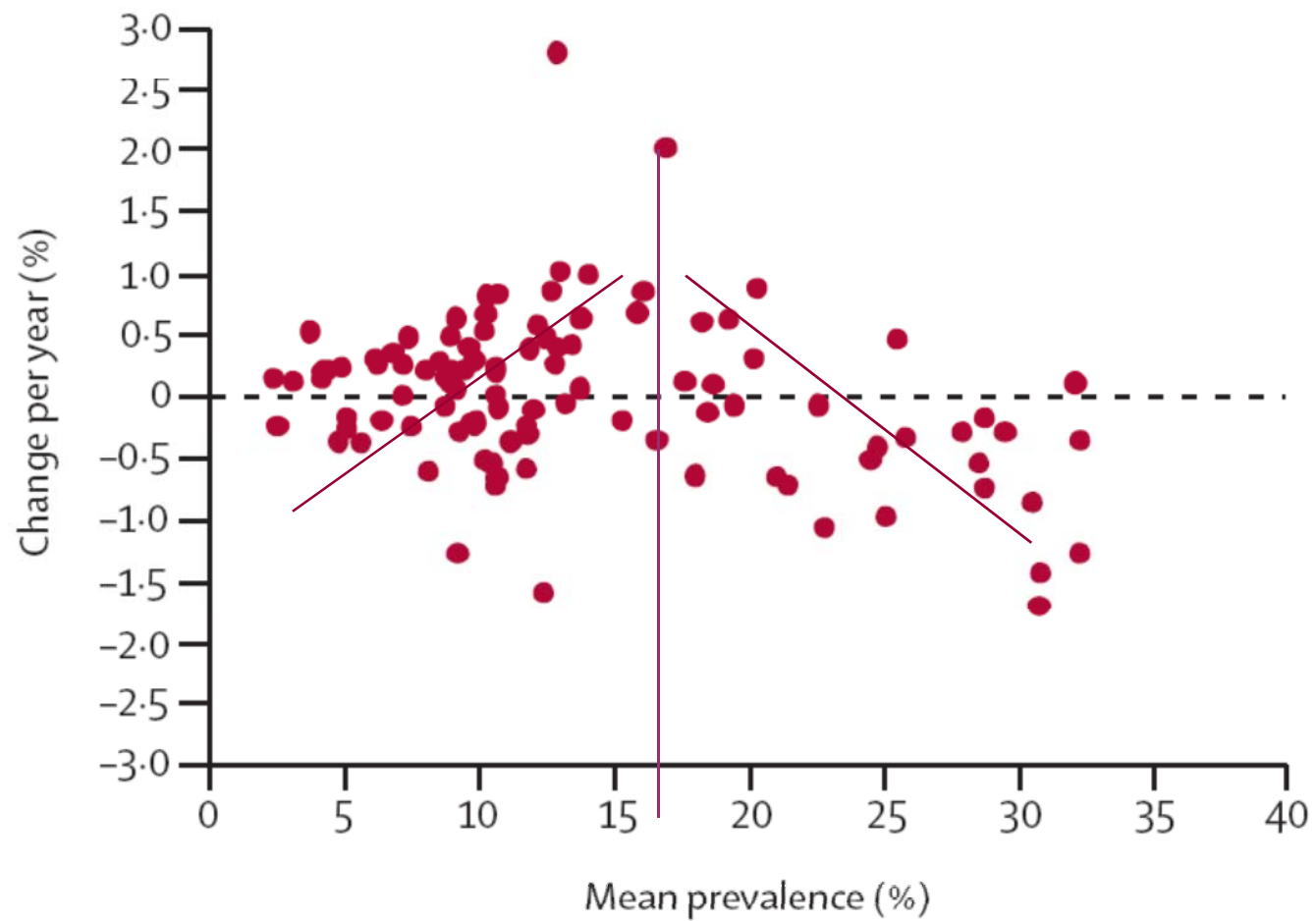
## Change in Symptoms of Asthma 13-14 Year Age Group



Asher MI *et al.* Lancet 2006; 368(9537): 733-743

### 13-14 year age-group

#### Asthma

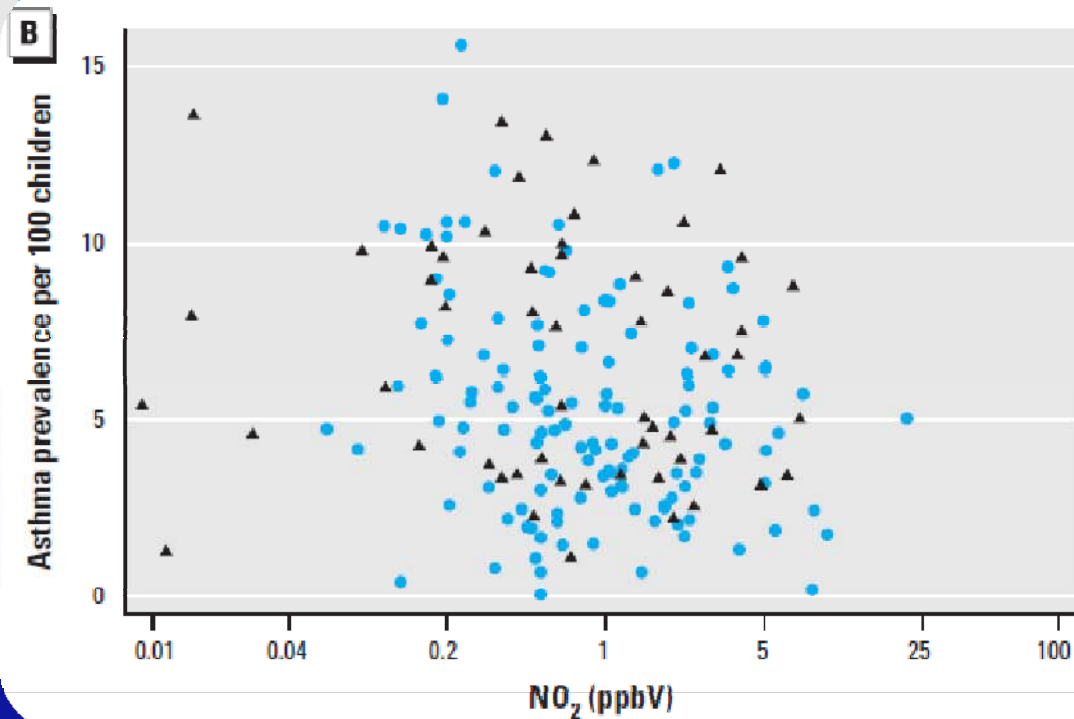
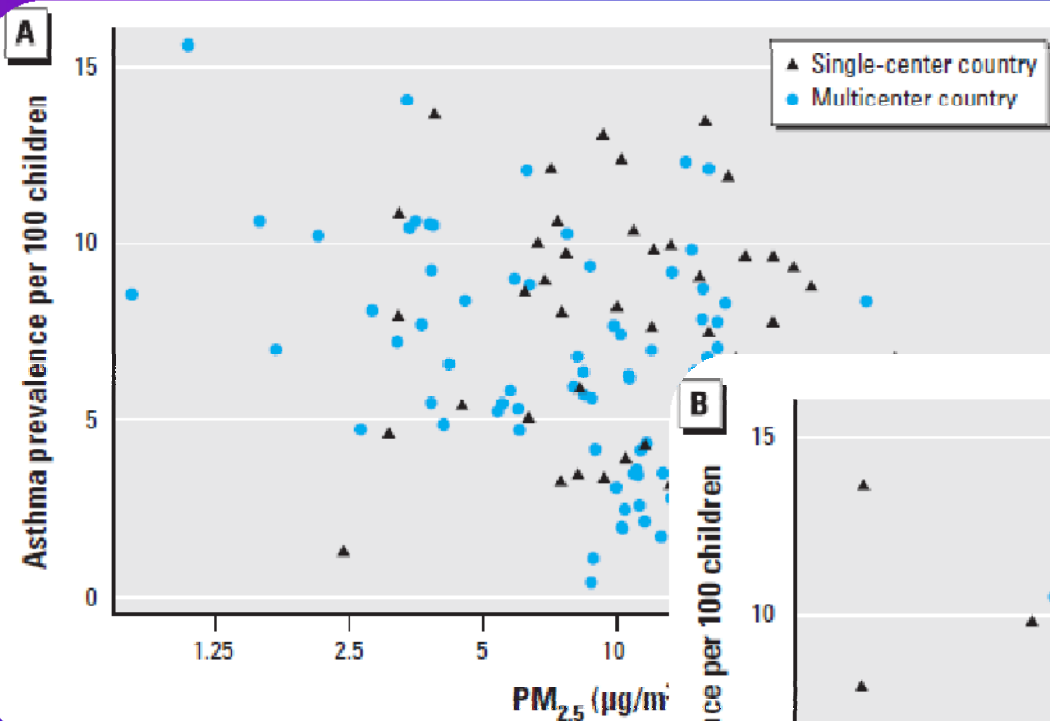


# Some lessons on time trends

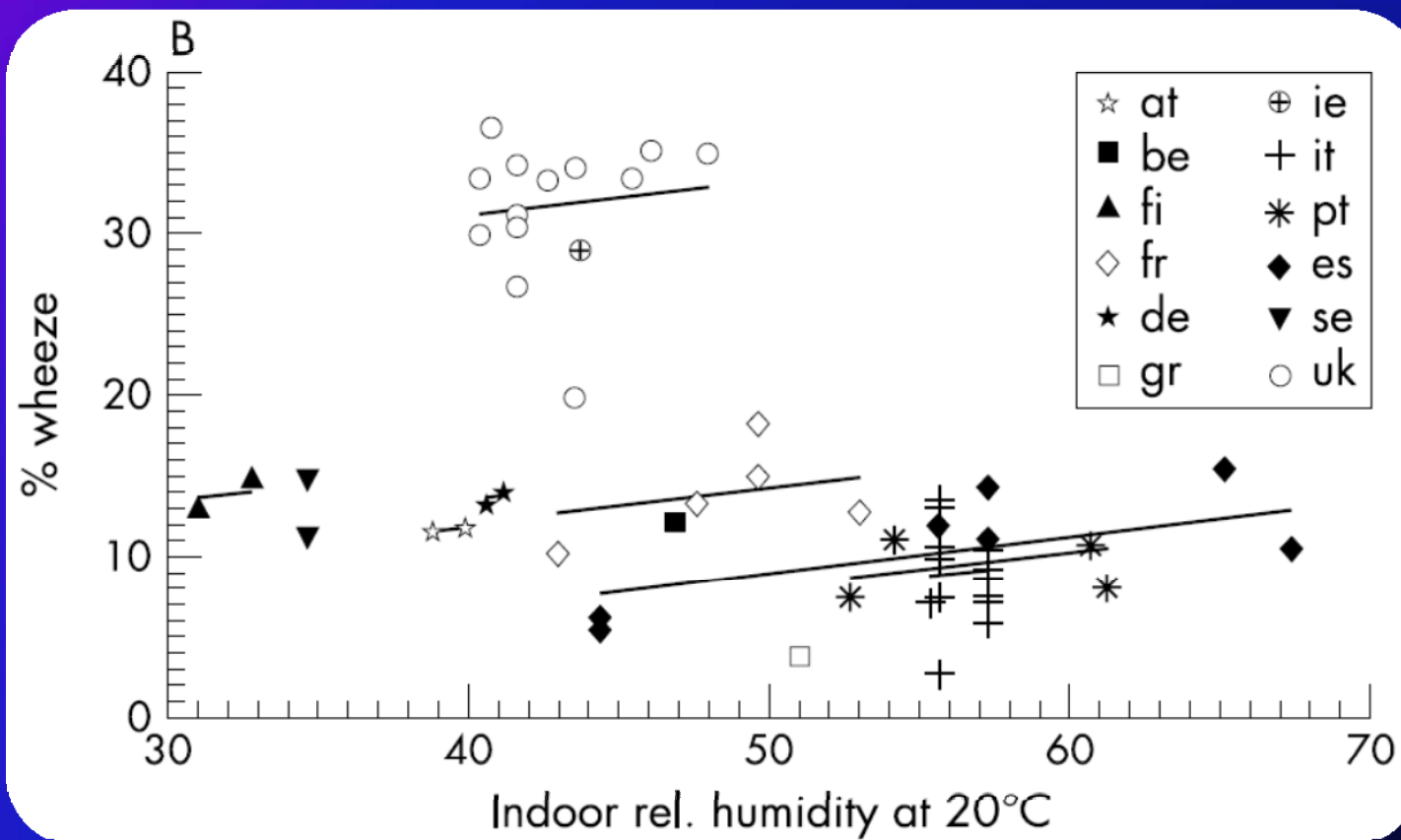
- In areas with high prevalence 20 years ago, it tends to decrease or maintain
- In areas with low prevalence by that time, asthma prevalence tends to increase
- There might be a cohort effect in some areas by which new generations suffer from more frequent asthma

# **Environmental factors (ecological level)**

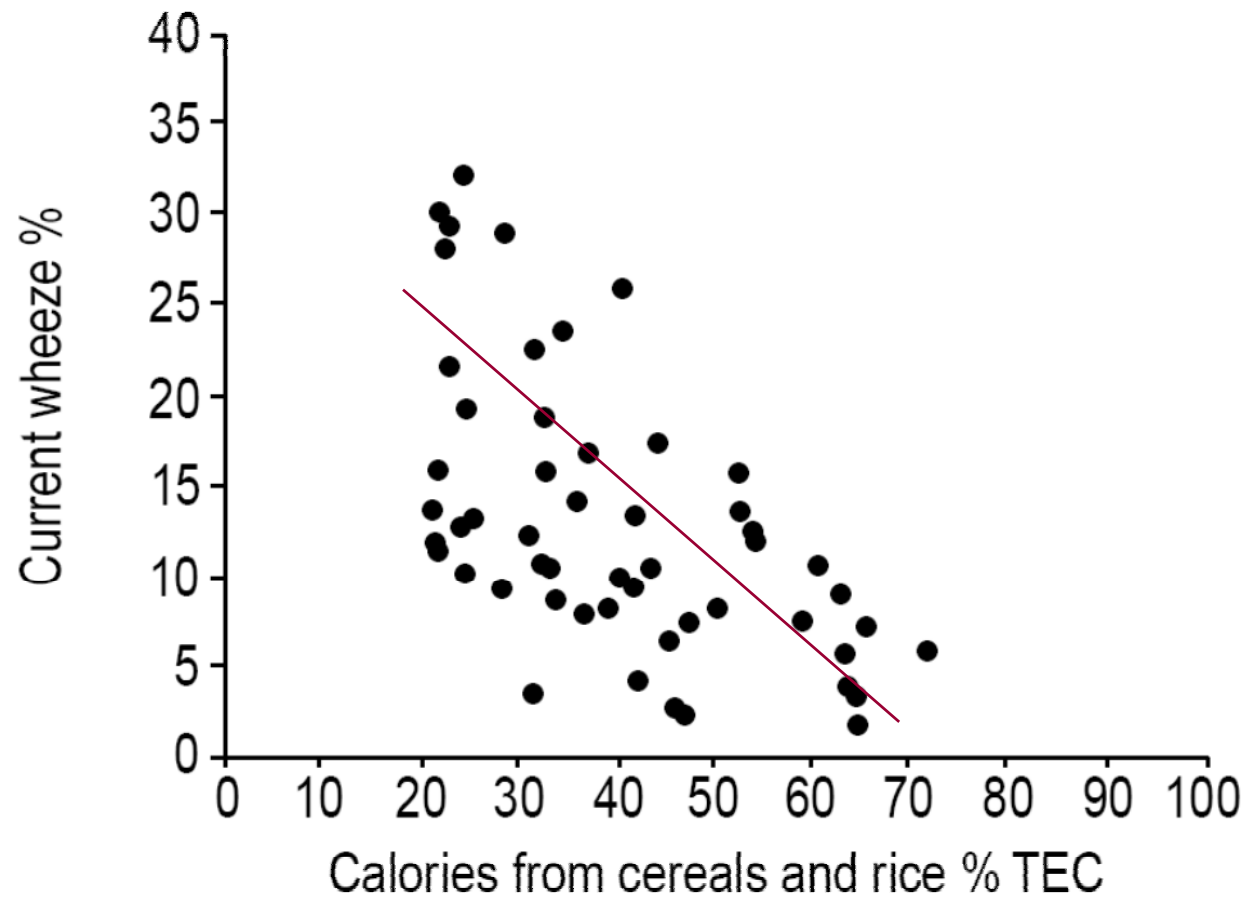
# Air pollution



# Climate



# Diet: cereals



# Some lessons from environmental factors (ecological level)

- It does not seem that pollution or pollen counts explain much of the difference between centres.
- Diet and climate (relative humidity) are good candidates for explaining those differences.

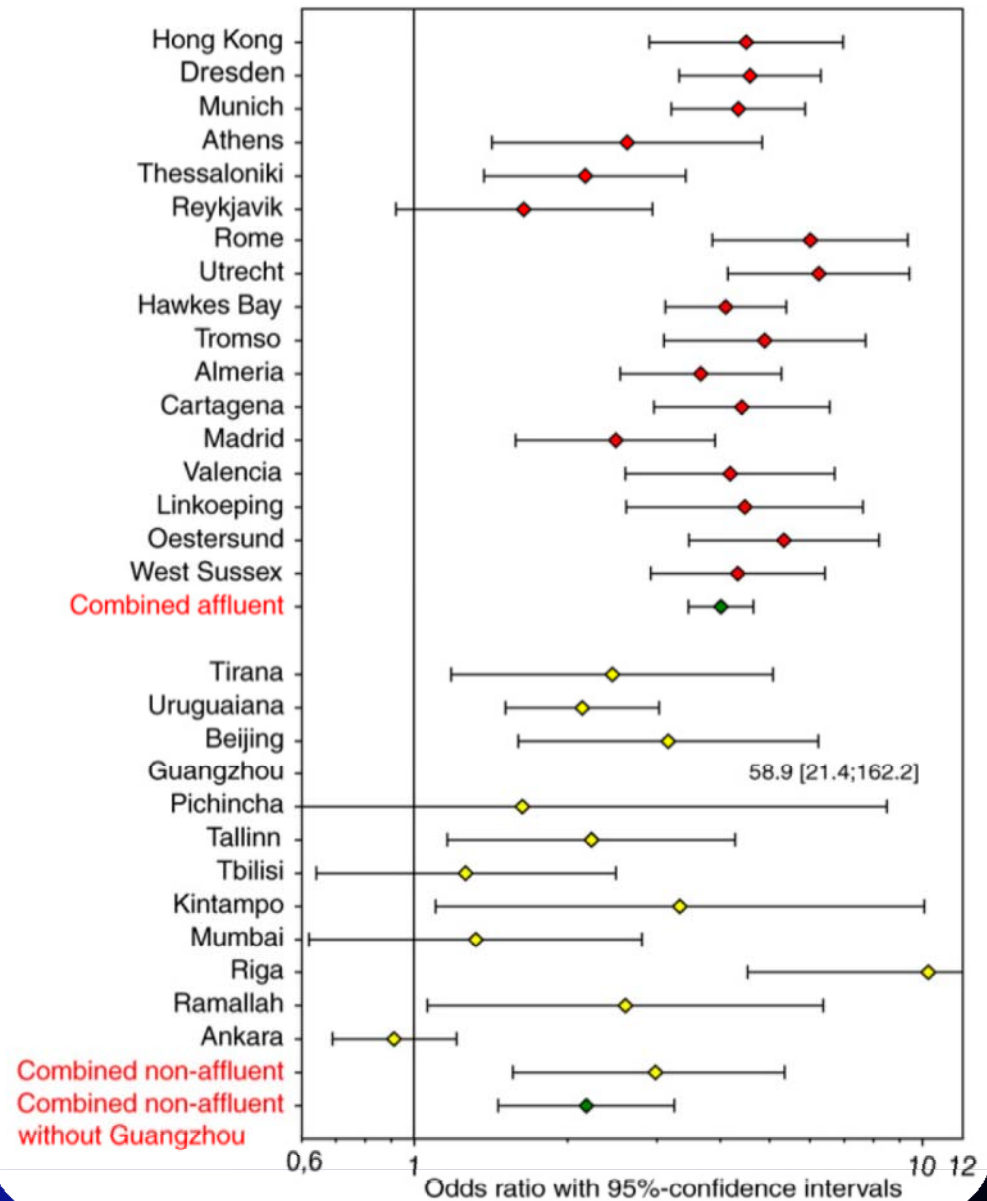
# **Environmental factors (individual level)**

# Atopy



**a**

OR for the association of current wheeze with skin prick test reactivity



# Truck traffic

Group/symptom	OR (95% confidence interval)		
	High vs. never	Medium vs. never	Low vs. never
Current wheeze	1.35 (1.23–1.49)	1.24 (1.13–1.35)	1.07 (0.98–1.16)
Asthma ever	1.18 (1.08–1.28)	1.08 (1.00–1.17)	1.01 (0.94–1.09)
Current wheeze–video	1.44 (1.26–1.64)	1.28 (1.14–1.44)	1.11 (0.99–1.23)
Severe asthma symptoms	1.53 (1.36–1.72)	1.26 (1.13–1.41)	1.07 (0.97–1.18)
Rhinoconjunctivitis	1.39 (1.27–1.52)	1.21 (1.12–1.32)	1.06 (0.98–1.14)
Eczema	1.54 (1.37–1.73)	1.30 (1.17–1.45)	1.08 (0.97–1.19)



# Breast feeding

	Affluent countries <sup>+</sup>		Nonaffluent countries <sup>§</sup>	
	Adjusted <sup>f</sup>		Adjusted <sup>f</sup>	
	OR	95% CI	OR	95% CI
<b>Atopic wheeze</b>				
Duration of breastfeeding <sup>¶¶</sup>				
Not breastfed	1	Reference	1	Reference
<6 months	0.89	0.70–1.13	1.01	0.64–1.57
≥6 months	0.87	0.68–1.11	0.78	0.46–1.33
<b>Nonatopic wheeze</b>				
Duration of breastfeeding <sup>ff</sup>				
Not breastfed	1	Reference	1	Reference
<6 months	0.88	0.69–1.11	0.82	0.61–1.11
≥6 months	1.00	0.79–1.26	0.64	0.49–0.85

# Paracetamol

	Adjusted* (all children) N=194 555	Adjusted† (children with complete covariate data) N=105 041	Multivariate analysis‡ (children with complete covariate data) N=105 041
Asthma	1.76 (1.68–1.85)	1.77 (1.66–1.89)	1.46 (1.36–1.56)
Rhinoconjunctivitis	1.78 (1.69–1.86)	1.74 (1.62–1.87)	1.48 (1.38–1.60)
Eczema	1.54 (1.47–1.61)	1.54 (1.44–1.64)	1.35 (1.26–1.45)

Data are OR (95% CI). \*Adjusted for sex, region of the world, language, and gross national income. A total of 194 555 children were included from 69 centres in 29 countries, except in the analysis of eczema (191 915 children from 68 centres in 28 countries). †Adjusted for sex, region of the world, language, and gross national income. ‡Multivariate analysis included centres with at least 70% data available for all covariates. Children who had a missing value for any of the covariates were removed.

**Table 1:** Association between paracetamol use for fever in the first year of life and symptoms of asthma, rhinoconjunctivitis, and eczema at 6–7 years of age

## Some lessons from environmental factors (individual level)

- The association between asthma and atopy varies between areas, and is much weaker in low income countries.
- Breast feeding seems to protect against asthma only in non-atopic children and only in low income countries.
- Certain drugs are associated to asthma prevalence further to a mere indication bias.
- Oxidative stress might be of more importance in asthma inception that it has been thought until now (paracetamol, diesel, diet).

# Some other lessons from environmental factors (individual level)

- **Other positive associations include:**
  - Open fire cooking & tobacco smoke exposure
  - Farm animals
  - Dampness in homes
  - Burger/fast food intake
  - Obesity
  - Migration to higher prevalence country
  - Greater family size (severe asthma)
- **Other negative associations include:**
  - Fresh fruits and vegetables
  - Mediterranean diet



# I The International S Study of A Asthma and A Allergies in C Childhood

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Make ISAAC your  
Homepage

Set as homepage

You are here: Home

**ISAAC**, The International Study of Asthma and Allergies in Childhood, is a unique worldwide epidemiological research programme established in 1991 to investigate asthma, rhinitis and eczema in children due to considerable concern that these conditions were increasing in western and developing countries.

ISAAC has become the largest worldwide collaborative research project ever undertaken, involving more than 100 countries and nearly 2 million children and its aim is to develop environmental measures and disease monitoring in order to form the basis for future interventions to reduce the burden of allergic and non-allergic diseases, especially in children in developing countries.

The ISAAC findings have shown that these diseases are increasing in developing countries and that they have little to do with allergy, especially in the developing world. Further population studies are urgently needed to discover more about the underlying mechanisms of non-allergic causes of asthma, rhinitis and eczema and the burden of these conditions.

## New network to continue ISAAC's work in asthma

The ISAAC Programme formally finished in December 2012. The [Global Asthma Network](#) was founded in 2012 and will extend the work of ISAAC in the asthma field.

## The ISAAC Story

The ISAAC Steering Committee is proud to announce that **the ISAAC Story**, a 20 year history of ISAAC, is available on the website. This fascinating account contains details from the [how ISAAC was first conceived](#) through to the [findings of the very latest papers](#). [Recollections of founding members](#), full descriptions of all aspects of the [methodology](#) and [tools](#), all [publications graphs and maps](#) are available as well as pages for each of the [9 regions](#), [105 countries](#) and [306 centres](#) containing centre information, collaborators and personal

## News

[In Memoriam of Tadd Clayton](#)  
[19 August 1965 - 11 February 2015](#)

### ISAAC collaborator awarded best poster prize

ISAAC collaborator Elaine Fuenes was awarded the prize for the best poster at the International Society for Environmental Epidemiology meeting in Basel. [read more](#)

### ISAAC links damp homes and asthma

The latest ISAAC paper shows a link between dampness in the home and impaired respiratory health in children and is a further ISAAC paper to attract editorial comment. [View Editorial](#), [View article](#)

### ISAAC Cooking Fuels paper published

This ISAAC Phase Three EQ paper, ISAAC Cooking Fuels, has once again attracted editorial comment in its publishing journal, Lancet Respiratory Medicine [View Editorial](#). Wong GWK, Brunekreef B, Ellwood P, Anderson HR, Asher MI, Crane J, Lai CKW, for the ISAAC Phase Three Study Group. *Cooking fuels and prevalence of asthma: a global analysis of phase three of the International Study of Asthma and Allergies in Childhood (ISAAC)*. Lancet Resp Med 2013; Epub ahead of Print [View abstract](#)

### ISAAC Diet paper published

Fast food diet linked to asthma and eczema severity in kids

<http://isaac.auckland.ac.nz/>



Health professionals in all countries should regard frequent or severe recurrent wheezing in infancy as part of the spectrum of asthma

[www.globalasthmareport.org](http://www.globalasthmareport.org)

**People die of asthma every day - it's time to take control**

[Read more](#)

**Global Asthma Report 2014**



[Professor Innes Asher launches the Global Asthma Report 2014 at the Union's 45th World Conference on Lung Health in Barcelona](#)

## Surveillance



**Short Surveys**  
Gathering information on important aspects of asthma management

## Management



**Management Guidelines**  
Promoting the use of standardised asthma management guidelines

## Advocacy



**Global Events**  
A list of important conferences and meetings.

## Our Network

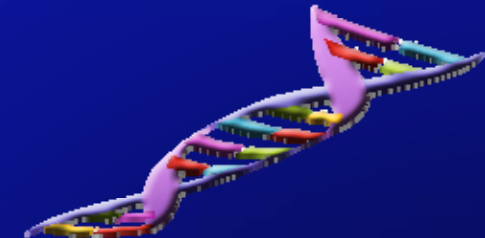




**Environmental factors**



**Epigenetics**  
(can be modified after conception)



**Genetic polymorphisms**  
(born with)



**Inter-individual variability**

# Asthma Birth Cohorts Database

[About](#)[Cohorts](#)[Help](#)[Useful Links](#)

## Welcome to the Asthma Birth Cohorts Database

Asthma and allergy birth cohorts increasingly provide new insights into the development and natural history of the diseases. Over 130 birth cohorts focusing on asthma and allergy have been initiated in the last 30 years. A NIAID (National Institute of Allergy and Infectious Diseases), NHLBI (National Heart Lung and Blood Institute), MeDALL (Mechanisms of the Development of Allergy, FP7) joint workshop was held in Bethesda, Maryland September 11-12, 2012 with three objectives: (1) documenting the knowledge that asthma/allergy birth cohorts have provided; (2) identifying the knowledge gaps and inconsistencies; and (3) developing strategies for moving forward, including potential new study designs and the harmonization of existing asthma birth cohort data. The meeting was organized around the presentations of five distinct workgroups: (1) clinical phenotypes; (2) mechanisms and risk factors; (3) immune development of asthma and allergy; (4) pulmonary development; and (5) harmonization of existing birth cohorts. The report of the workshop is published and is available at the following link: [Asthma Birth Cohorts Workshop Report](#). The database was created as a result of the workshop to encourage sharing of information among birth cohorts.

The website contains tables which: (1) describes the characteristics (contact point, location, sample size, retention, population, etc.) of the birth cohort; (2) details data collection (spirometry, skin testing, home allergens, DNA, etc.) at differing ages; (3) provides a selected bibliography of key publications provided by the participating birth cohorts; and (4) includes a search function which allows you to search across birth cohorts.

An explanation of how to navigate the site and use the search and export features is included in the Help section: [Help](#)

[Search the list of cohorts](#)

[View/print the total list of cohorts](#)

Over 130 birth cohorts focusing on asthma and allergy have been initiated in the last 30 years

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National Institute of  
Allergy and  
Infectious Diseases



National Heart, Lung,  
and Blood Institute

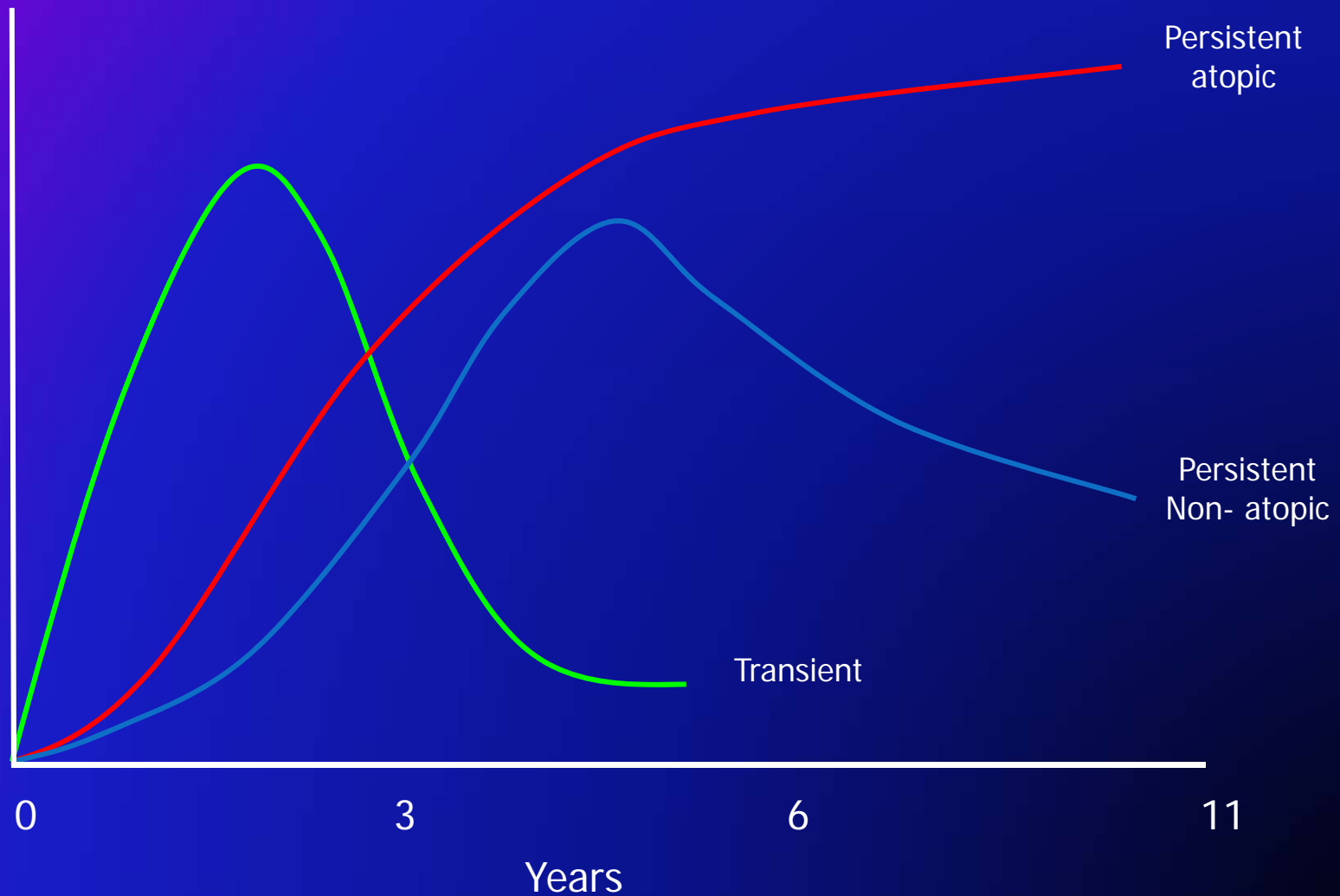


U. S. Department of Health and Human Services  
National Institutes of Health

NIAID

<http://asthmabirthcohorts.niaid.nih.gov>

# Phenotypes



# Endotypes

## The Asthma Syndrome

Symptoms of asthma, variable airflow obstruction

## Asthma phenotype characteristics

Observable characteristic with no direct relationship to a disease process. Includes physiology, triggers, inflammatory parameters

## Asthma Endotypes

Distinct disease entities which may be present in clusters of phenotypes, but each defined by a specific biological mechanism

Endotype 1

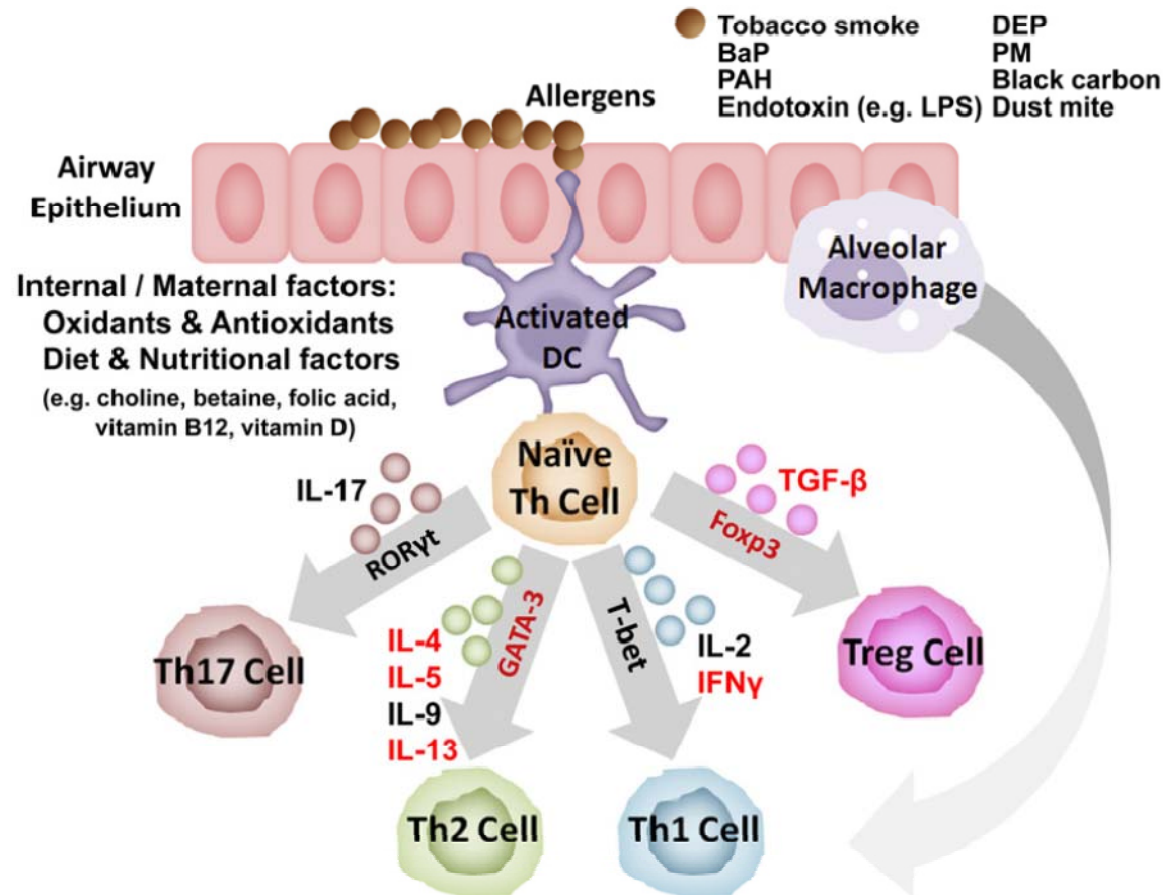
Endotype 2

Endotype 3

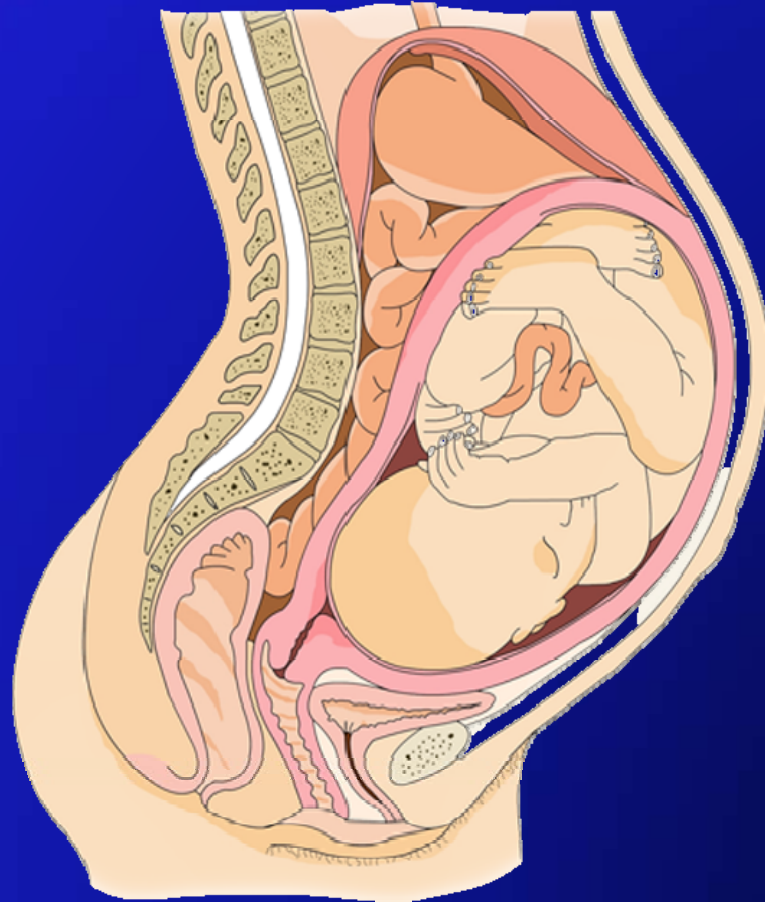
Endotype 4

Endotype 5

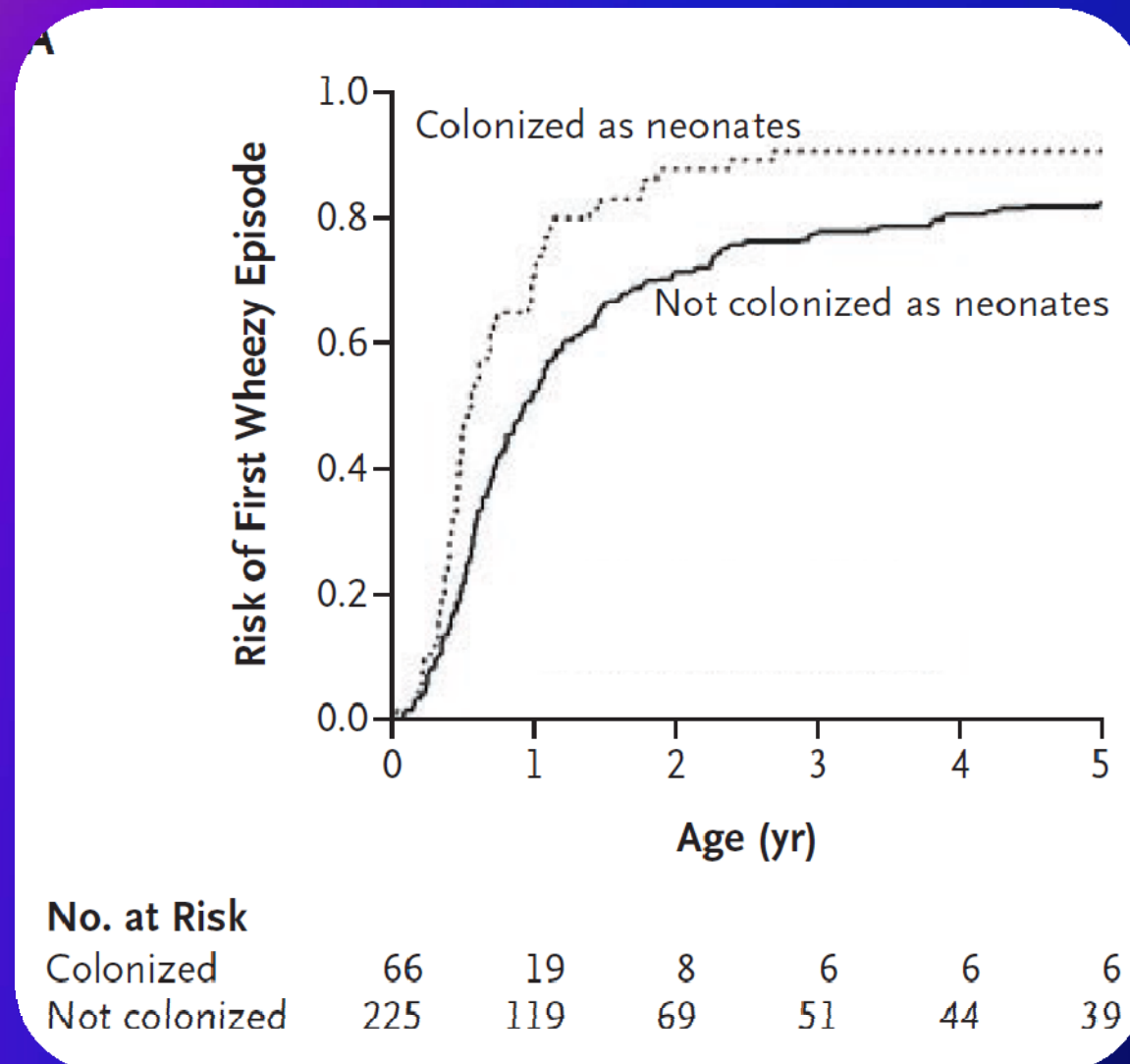
# Epi / genotypes?



# Window of opportunity & Foetal programming



# New (?) infections



H. Bisgaard et al. NEJM 2007

# CONCLUSIONS

- Cross-sectional studies have identified a considerable number of factors associated to higher asthma prevalence, but fewer associated to lower prevalence.
- However, no cause-effect relationship can be concluded from cross-sectional studies.
- Birth and prenatal cohort studies add (and will add) important insights on the natural history and mechanisms (including genetic and epigenetic) of asthma.
- Cohort studies can identify cause-effect relationship which could be the starting point for primary prevention.