Evolution of asthma from childhood

Carlos Nunes
Center of Allergy and Immunology of Algarve, PT
allergy@mail.telepac.pt

- Questionnaire data
  - Symptoms occurring once or several times at follow-up (wheeze, dyspnea, cough, nocturnal symptoms)
  - Self-reported asthma
  - Use of asthma treatment (eg. salbutamol use)
  - Video questionnaire
  - Doctor diagnosis

- Intermediate phenotypes of asthma
  - Airway hyper-responsiveness
    - Direct (methacoline, histamine)
    - Indirect (exercise, mannitol, cold-air challenge)
  - Reversibility on β2-agonist
  - Variability of peak expiratory flow rate (PEFR)
  - Lung function (eg. FEV1, FEF 25-75, PEF)

- Combination of questionnaires and phenotypes intermediates (asthma scores and asthma algorithm)

Global studies on allergy and asthma

- Different profiles of allergy across the world was showed throughout several authors
- Role of “westernization” is important do develop allergic disease
- Significant difference among countries and regions
- Different prevalence of self-reported asthma and current wheeze among migrant children compared with those born in native country
- Different prevalence of migrant children depend of origin country. Perhaps misdiagnosis and underdiagnosis in their countries of origin can explain the differences

- Regional differences in asthma prevalence and socio-economic factors like lifestyle and domestic exposures differences need more studies

- The greater risk of developing atopy and asthma among children with high standard of life while exposure to general urban deprivation and pollution is associated with an increase risk of respiratory symptoms and infections but a more modest increase in allergic diseases

- Allergic diseases in the setting of urban poverty may be more severe and result in greater morbidity and mortality owing to poor access to care, unavailability of medication and problems with adherence and risk avoidance

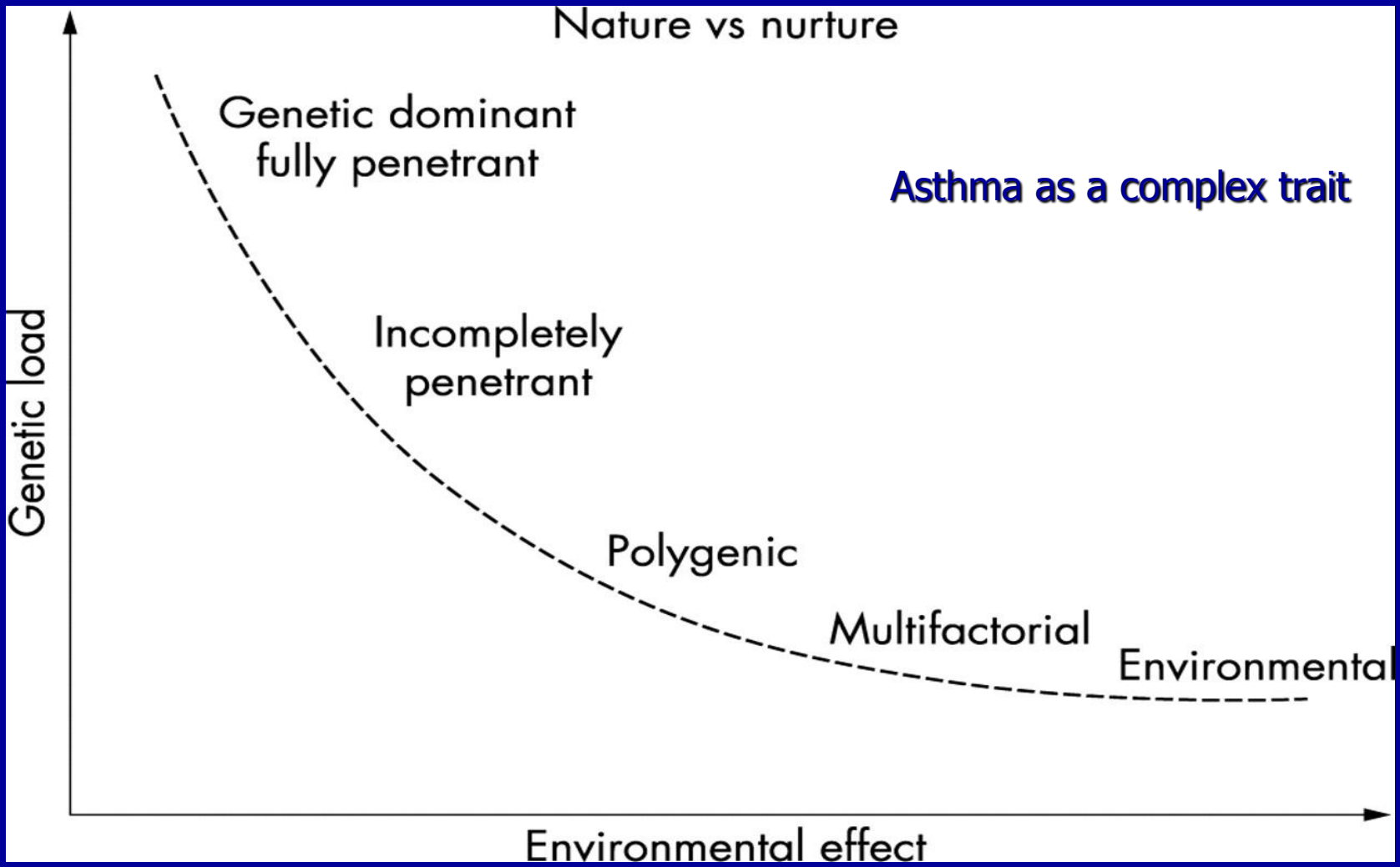
- ISAAC phase III conducted 8-10 years later confirmed the high prevalence of asthma symptoms in some of developing country centers

- A stabilization or decrease on asthma prevalence was observed in the majority of centers in industrialized countries

- The moderate or high prevalence of asthma in some developing countries is already being reflected by a significant demand for health services

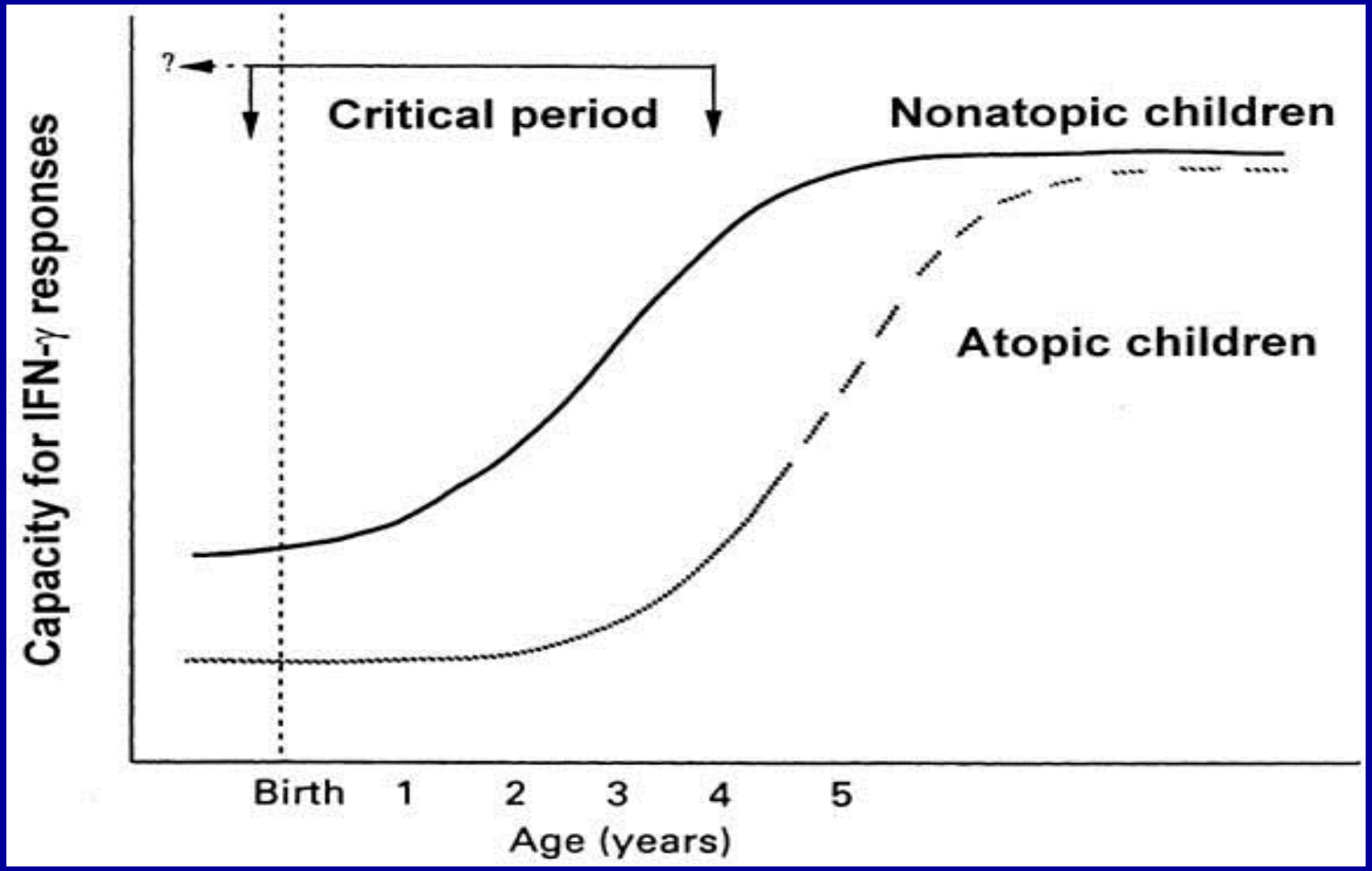
- Asthma, from childhood to adulthood in several developing countries is the first cause of consultations for chronic respiratory disease in primary healthcare settings (WHO report 2004)

Gene By Environment Interactions, a Key feature of Asthma Genetic (Weiss ST, 2004)

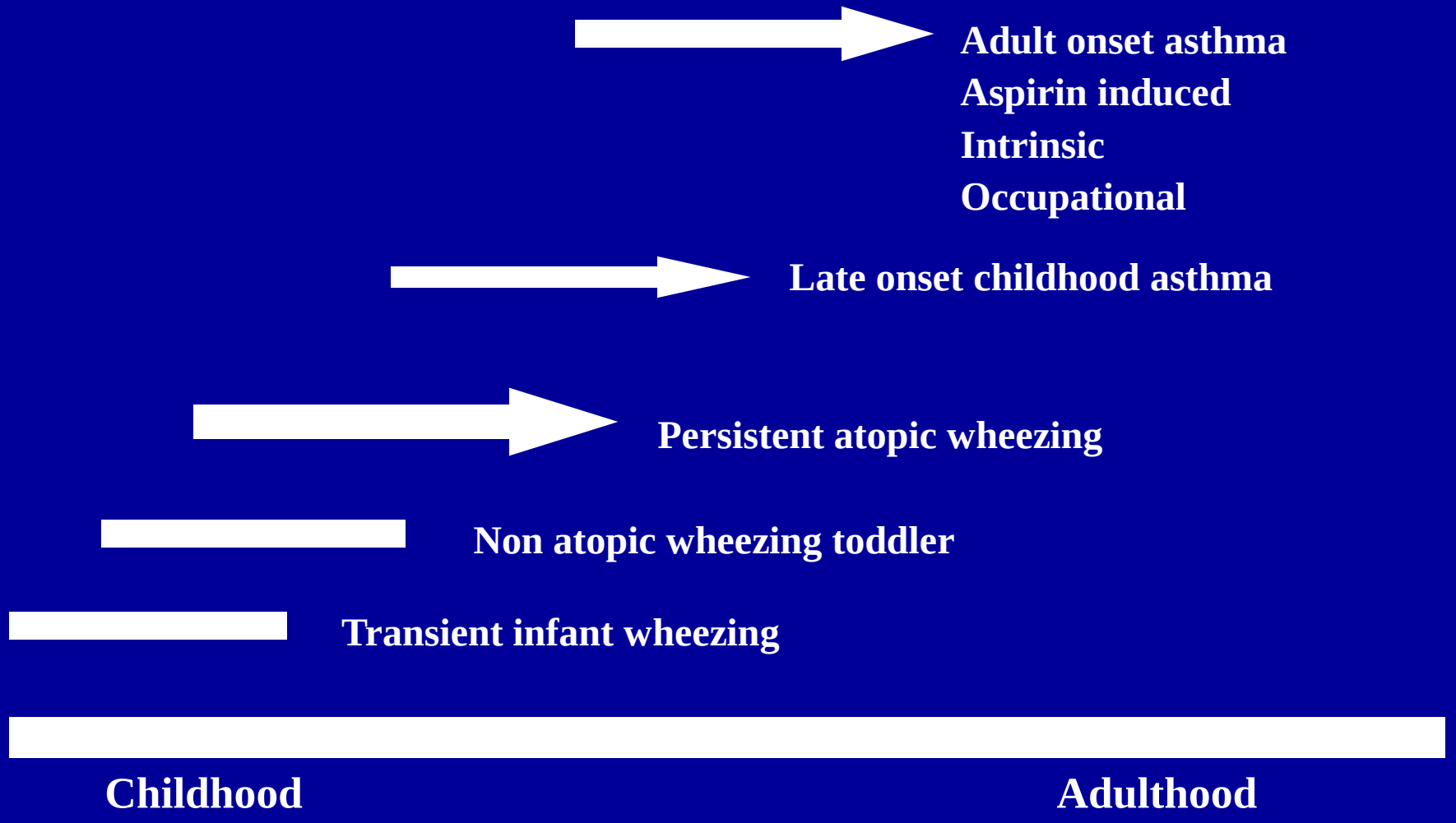


Atopic immune systems don't mature normally

(Lemanske R, JACI 109(6)



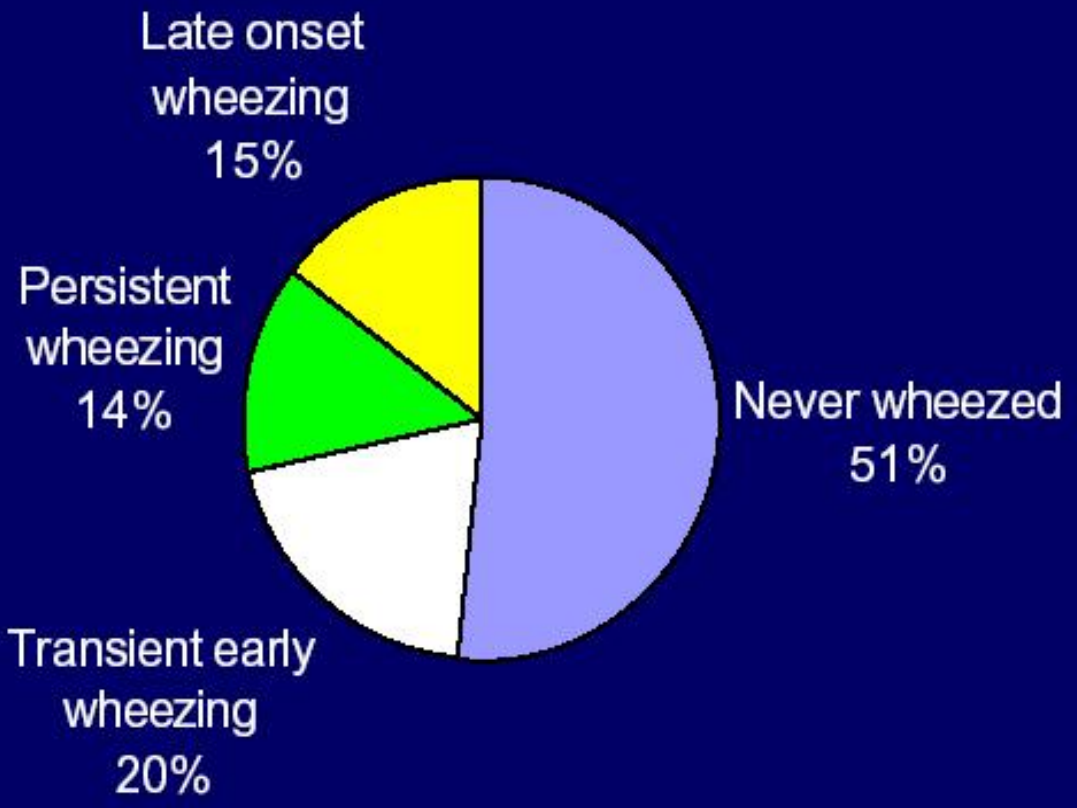
Asthma Phenotype



Adapted from Bel EH Curr Opin Pulm Med 2004

- Despite the fact that certain levels of allergens may prove to be protective, allergen exposure is still the major risk factor for the development of allergy.
- In the absence of allergens, no allergy develops, and above and allergen-specific threshold, the risk of sensitization increase in parallel with exposure.
- To measure allergen in environment is important to establish dose-response relationships between exposure on the one hand and sensitization and clinical allergy on the other hand.

Wheezing is Common in Early Life



N=1246 newborns
Tucson Children's Respiratory Study

Martinez FD et al NEJM 1995;332:133

Transient vs. Persistent Wheezers

Transient Wheezers

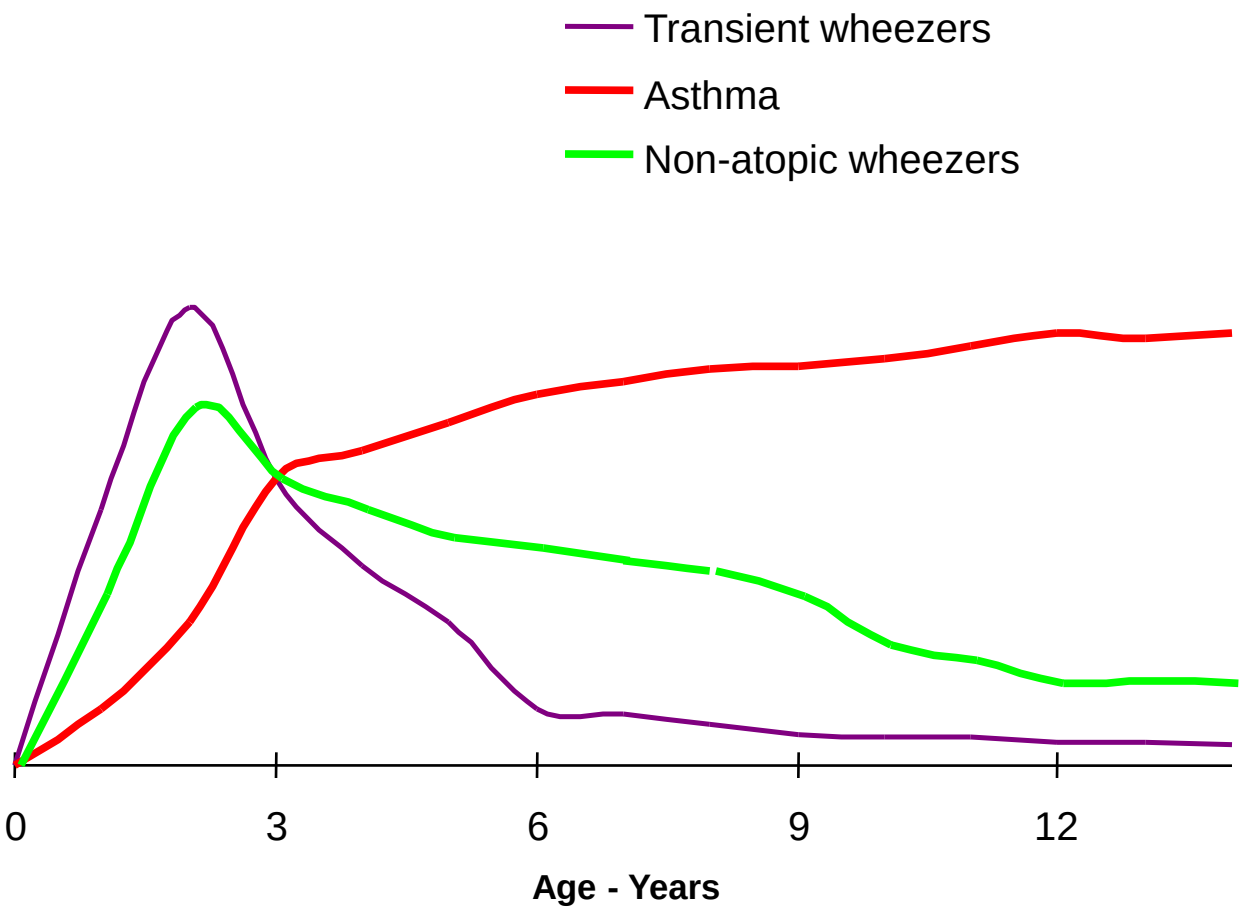
- Diminished lung function at birth, at 6, 13 & 16 yrs of age
- Mother who smoked
- Mothers without asthma
- Normal IgE levels
- Negative skin tests

Persistent Wheezers

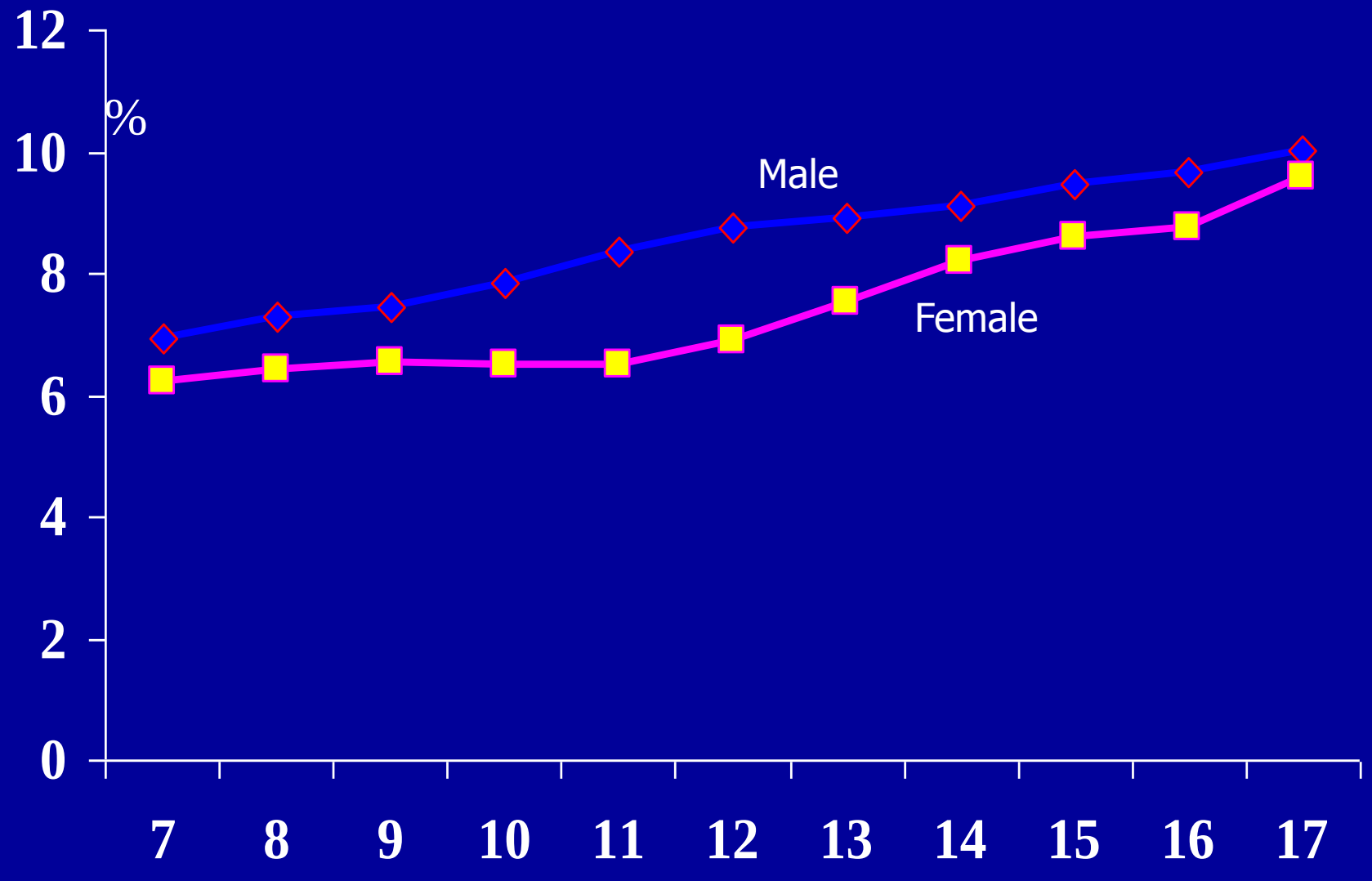
- Normal lung function at birth but diminished at 6, 13 & 16 yrs of age
- Mothers with asthma
- Elevated IgE levels at 9 months and 6 yrs
- Positive skin tests at 6 yrs of age

Tucson Children's Respiratory Study

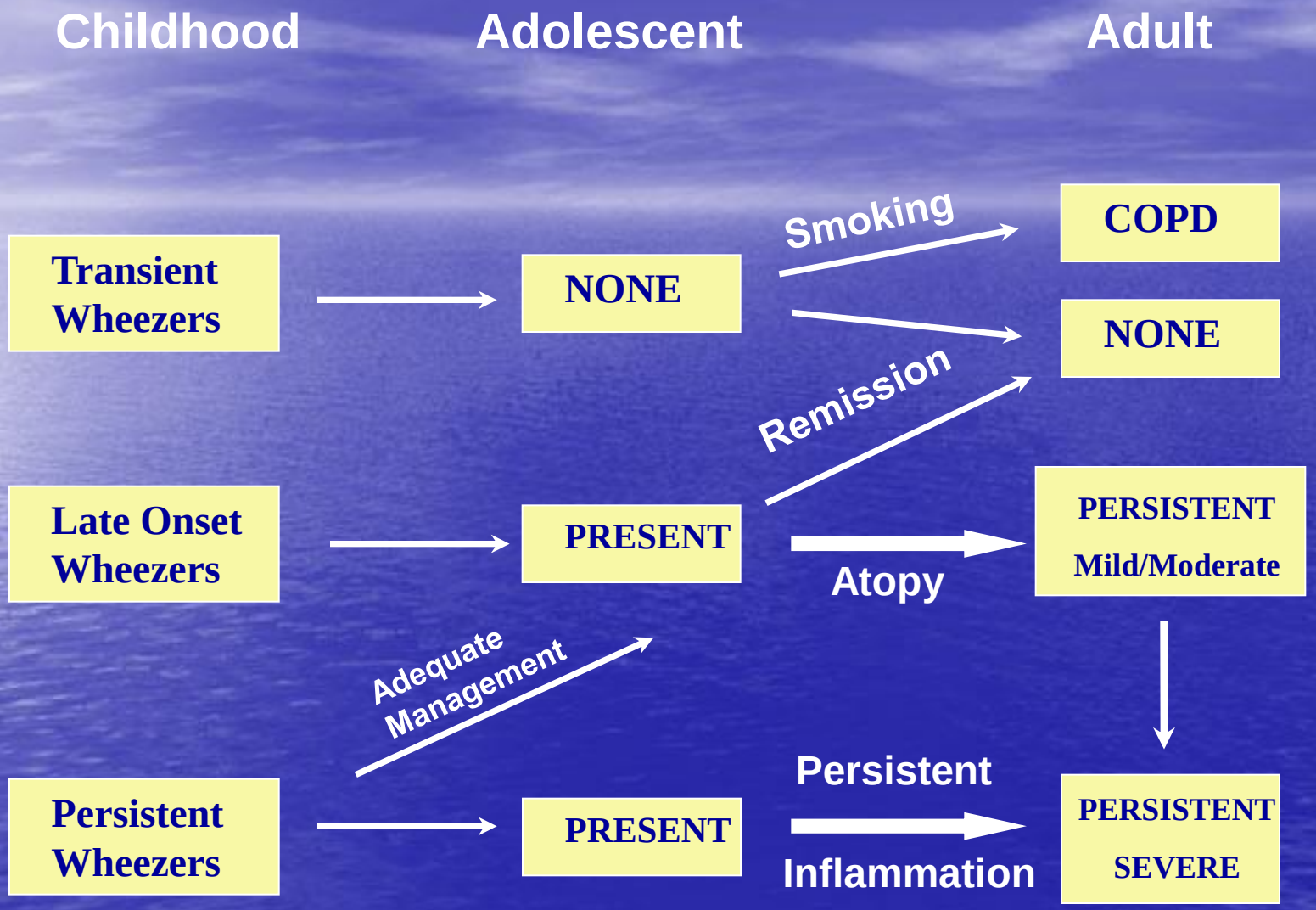
Prevalence – Wheezing Evolution



Asthma Prevalence in Schoolchildren (5.386)



Nunes C et al RPIA, 1996


Childhood
Adolescent
Adult
Transient Wheezers
NONE
Smoking
COPD
NONE
Late Onset Wheezers
PRESENT
Remission
Atopy
PERSISTENT Mild/Moderate
Persistent Wheezers
PRESENT
Adequate Management
Persistent Inflammation
PERSISTENT SEVERE

Asthma predictive index

Major criteria

Parental history of physician diagnosed asthma

Physician diagnosed asthma with atopic dermatitis

Minor criteria

Wheezing apart colds
Blood eosinophilia ≥ 4%
Physician-diagnosed allergic rhinitis

The child must have a history of early frequent wheezing during first 3 years of life plus one major criterion or two minor criteria

Adapated from Castro Rodrigues et al. Am J Respir Crit Care Med 2000;162:1403-6

Predictors of persistence and severity of childhood asthma

More severe and frequent wheezing episodes during preschool age
Onset during school age
Family history of asthma and allergy
Elevated serum IgE
Early development of positive skin test results
Early development of bronchial hyperresponsiveness
Frequency of respiratory infections
Lack of contact with older children
Parenting difficulties
Greater childhood psychological risk

- Strong oxidative stress in children with asthma and the oxidant/antioxidant imbalance increases with asthma severity.

  (Ercan et al. JACI 2006;118:1097-104)

- Early deterioration on lung function, high IgE levels, and persistent cough/mucus hypersecretion are strong markers of moderate/severe asthma.

  (de Marco et al JACI 2006;117:1249-56)

Asthma evolution

We could estimate 2 out of 3 children with asthma outgrow their symptoms

Risk factors for asthma persisting into adulthood

- **Female**
- **Eczema**
- Onset after **age** of 3 years
- **Severe** disease
- **Parental history** of atopy / asthma

- High endotoxin exposition, pet ownership, atopy and wheezing in high-risk infants has no effect on aeroallergen sensitisation or wheezing during infancy

  (Campo et al. JACI 2006;118:1271-8)

- House dust avoidance and dietary fatty acid modification in the first 5 yrs of life has no effect to prevent the onset of asthma, eczema or atopy

  (Marks et al JACI 2006;118:53-61)

Persistence of Asthma from Childhood to Adulthood

- 613 N. Zealand children followed from age 3 yrs to 26

- At age 26,
  - 42% no symptoms and no challenged wheezing
  - 31% transient or intermittent wheezing
  - 12% relapsing symptoms (wheezing stopped after childhood, then recurred)
  - 15% persistent wheezing.

N Engl J Med 2003; 349:1414

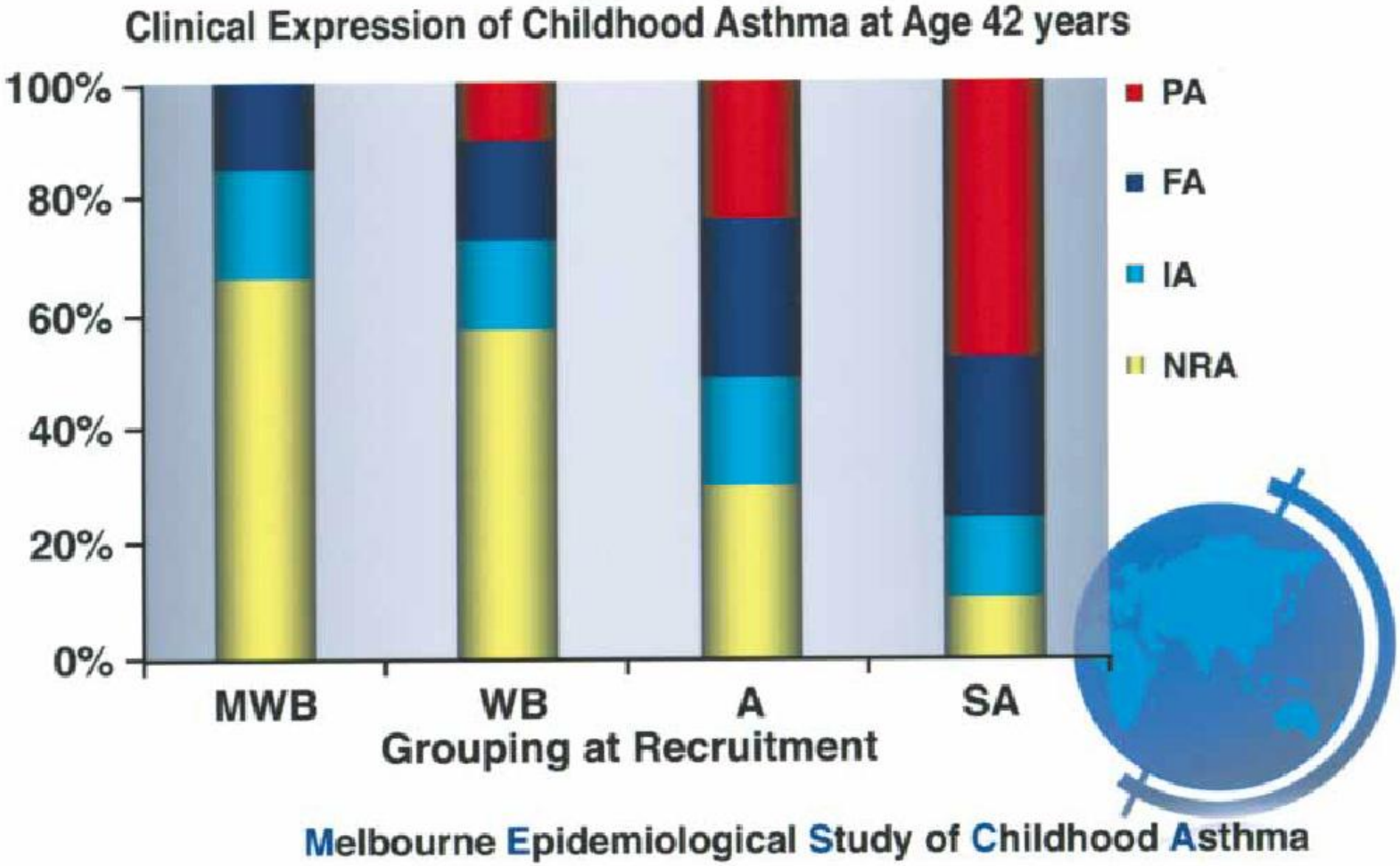
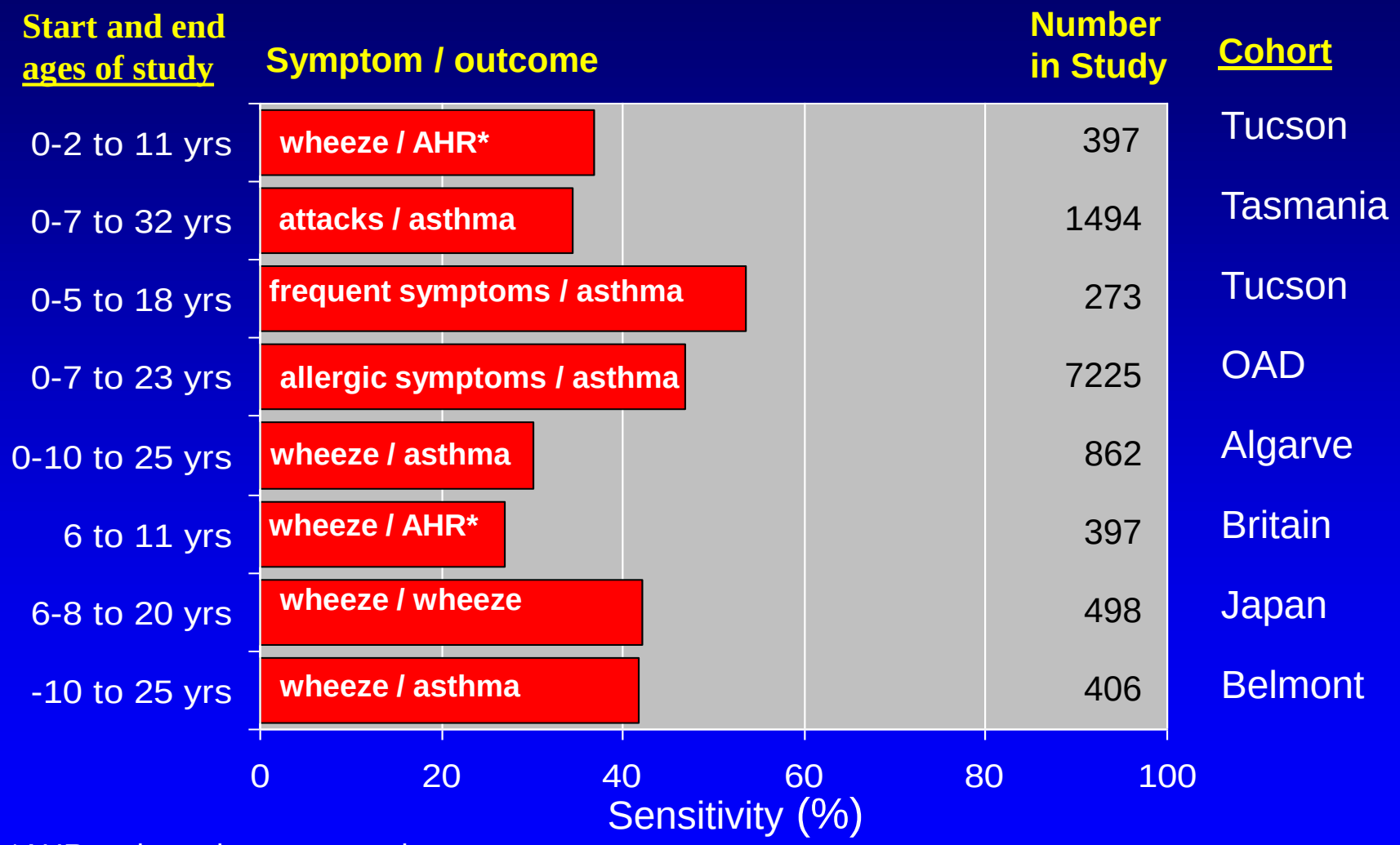


FIG 1. Histogram showing pattern of asthma at age 42 years in subjects from original recruitment groups. *MWB*, Mild wheezy bronchitis; *WB*, wheezy bronchitis; *A*, asthma; *SA*, severe asthma; *NRA*, no recent asthma; *IA*, infrequent episodic asthma; *FA*, frequent episodic asthma; *PA*, persistent asthma.

Phelan JACI, 2002

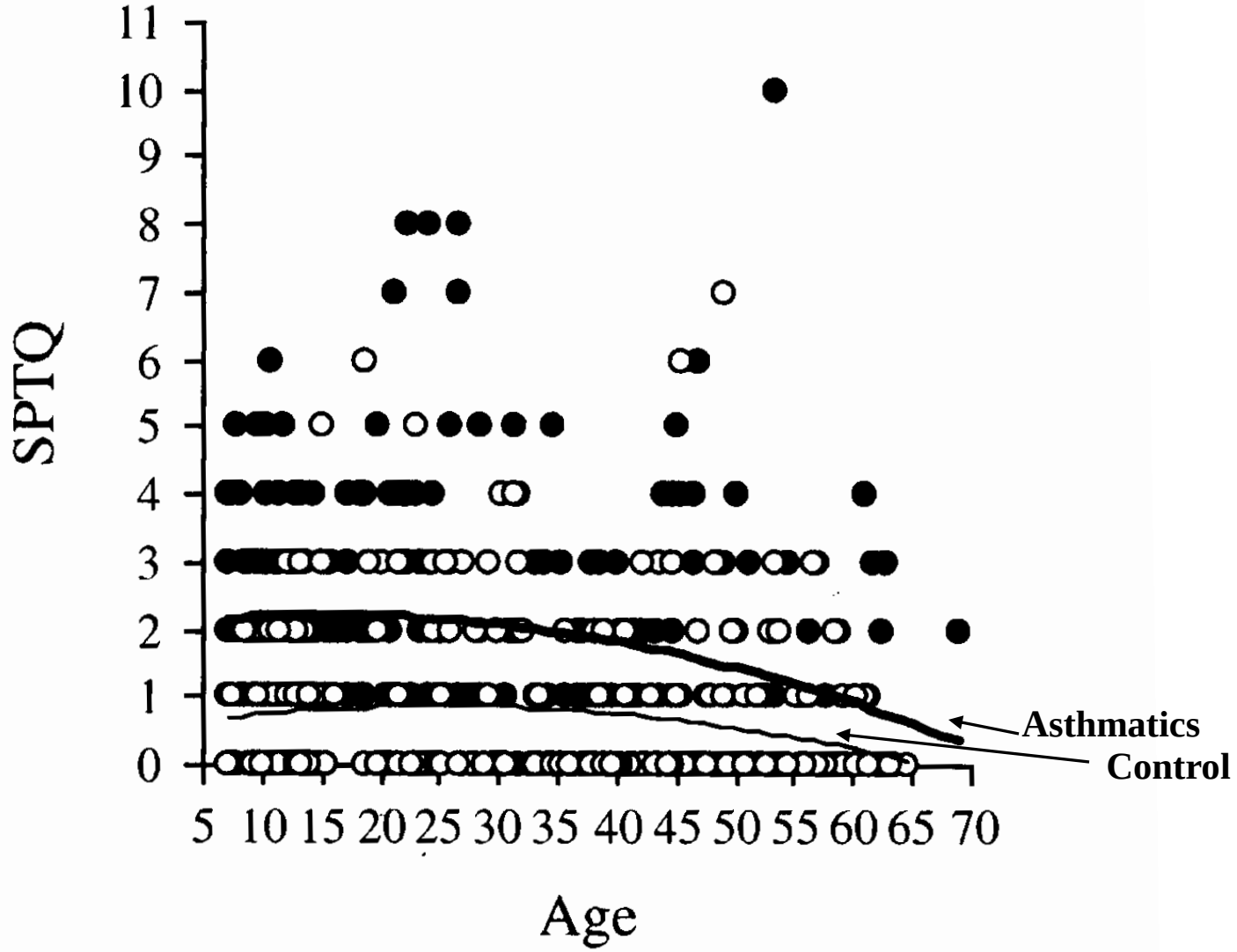
Sensitivity of Early Symptoms for Predicting Later Asthma



*AHR = airway hyperresponsiveness

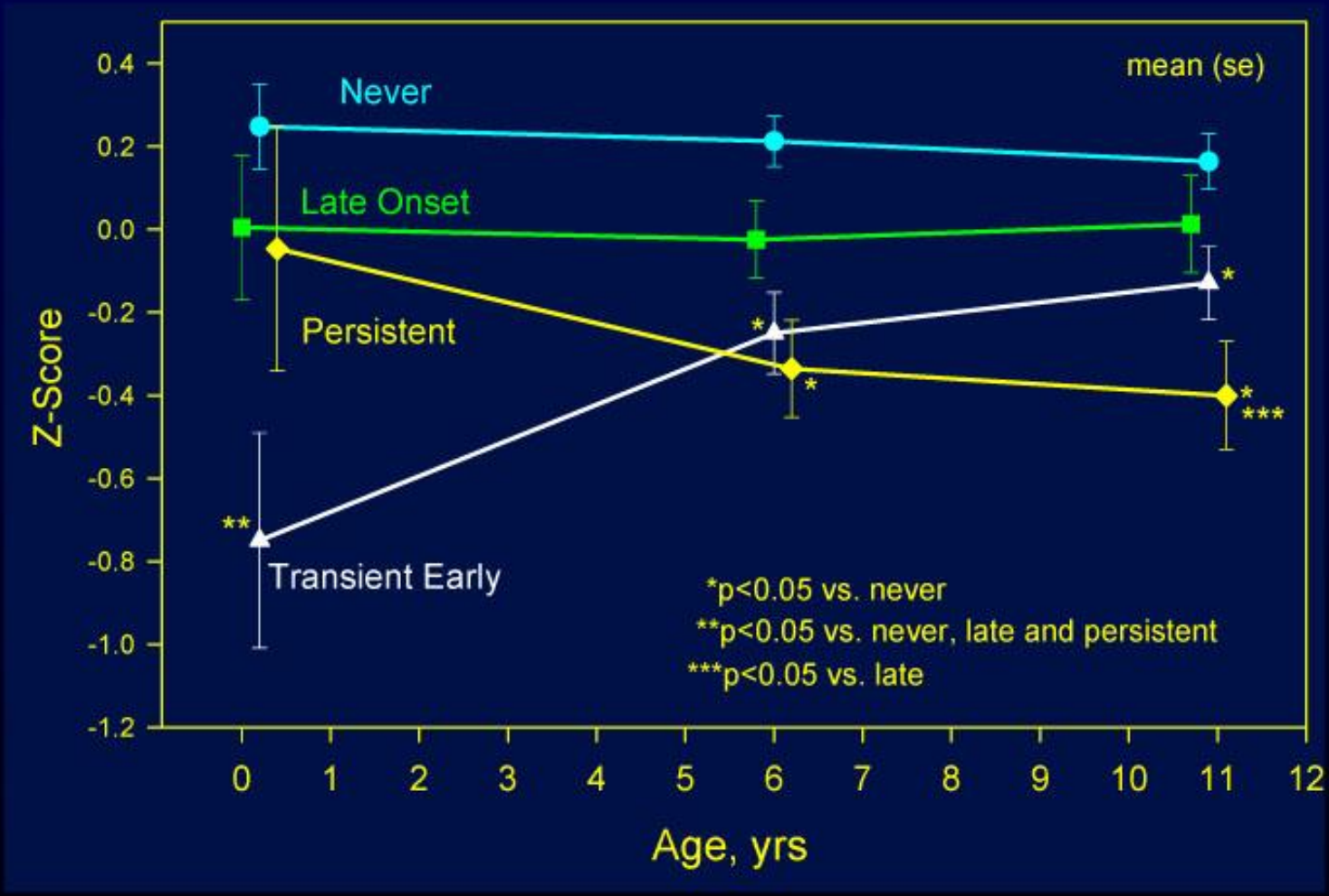
Adapted from Peat JK, Toelle BG, Mellis CM. JACI 2000

Aeroallergen Sensitisation throughout age



Oryszczin et al EGEA JACI 2007; 119:57-63

Lung Function in Children: "Natural History"



Childhood Asthma Research and Education Network. Tucson Children's Respiratory Study.

- Reduced lung function at birth was associated with an increased risk of asthma at 10 yrs

(Haland et al. N Engl J Med 2006;355:1682-9)

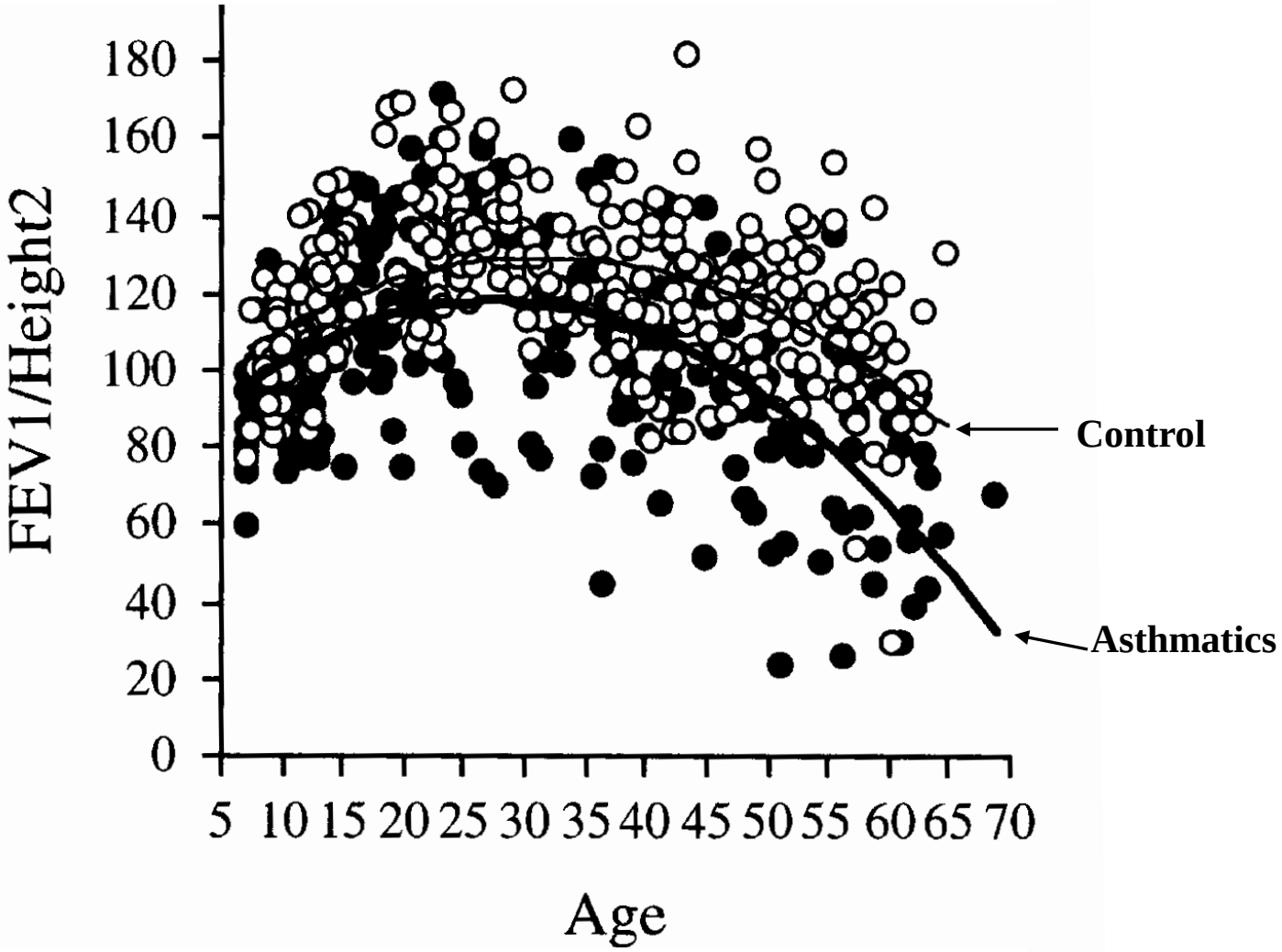
- Chronic course of asthma with airway hyper-responsiveness and impairment at school age is determined by continuing allergic airway inflammation beginning in the first 3 yrs of life

(Illi et al Lancet 2006;368:763-70)

FEV_1 / FVC ratio is diminished in children with asthma because of slower FEV_1 and greater FVC development with age

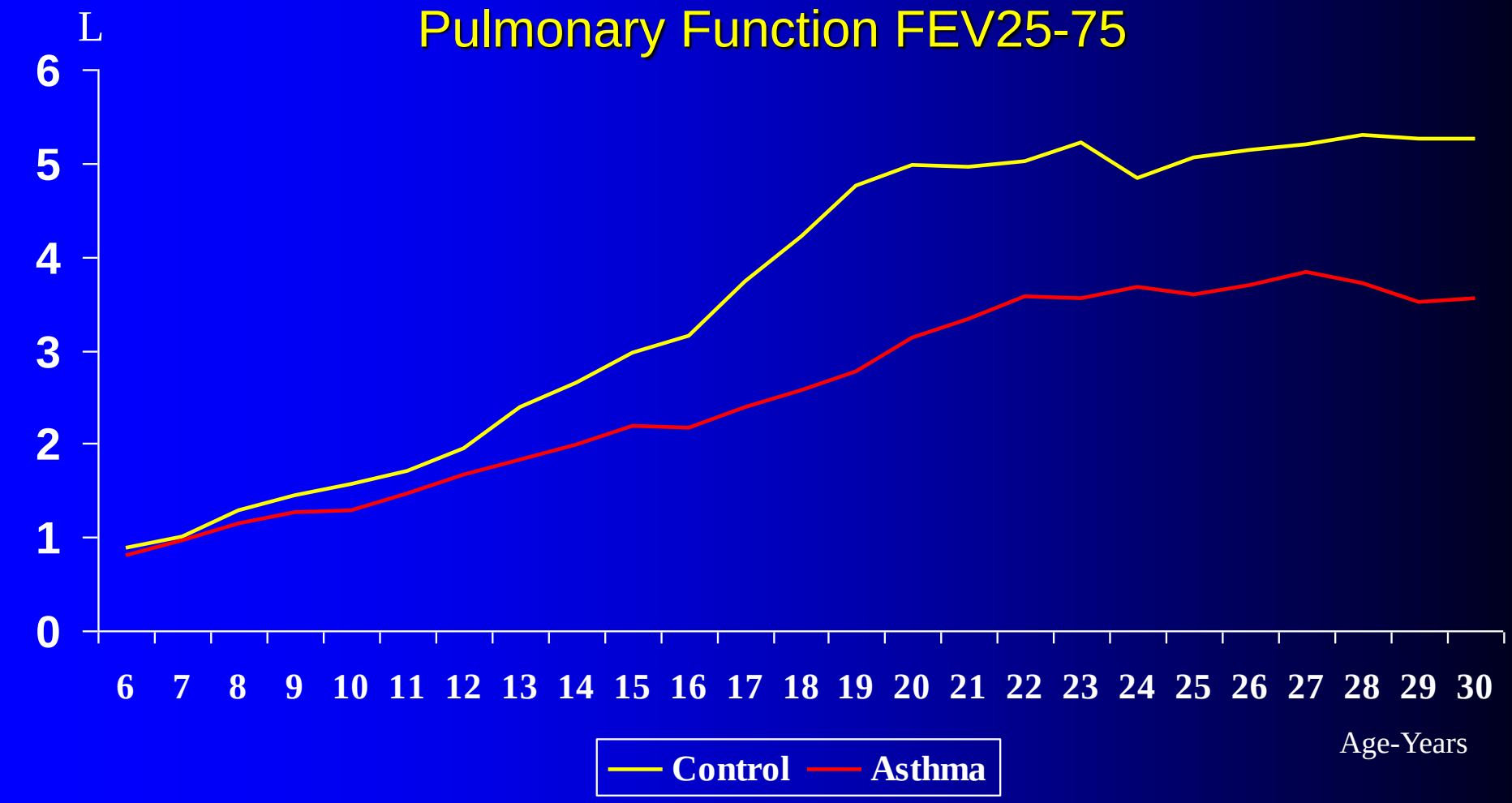
NHBLI - CAMP Research

Fev_1 versus height throughout age



Oryszczin et al EGEA JACI 2007; 119:57-63

Cohort of 165 asthmatics children versus 148 non-asthmatics during 20 years

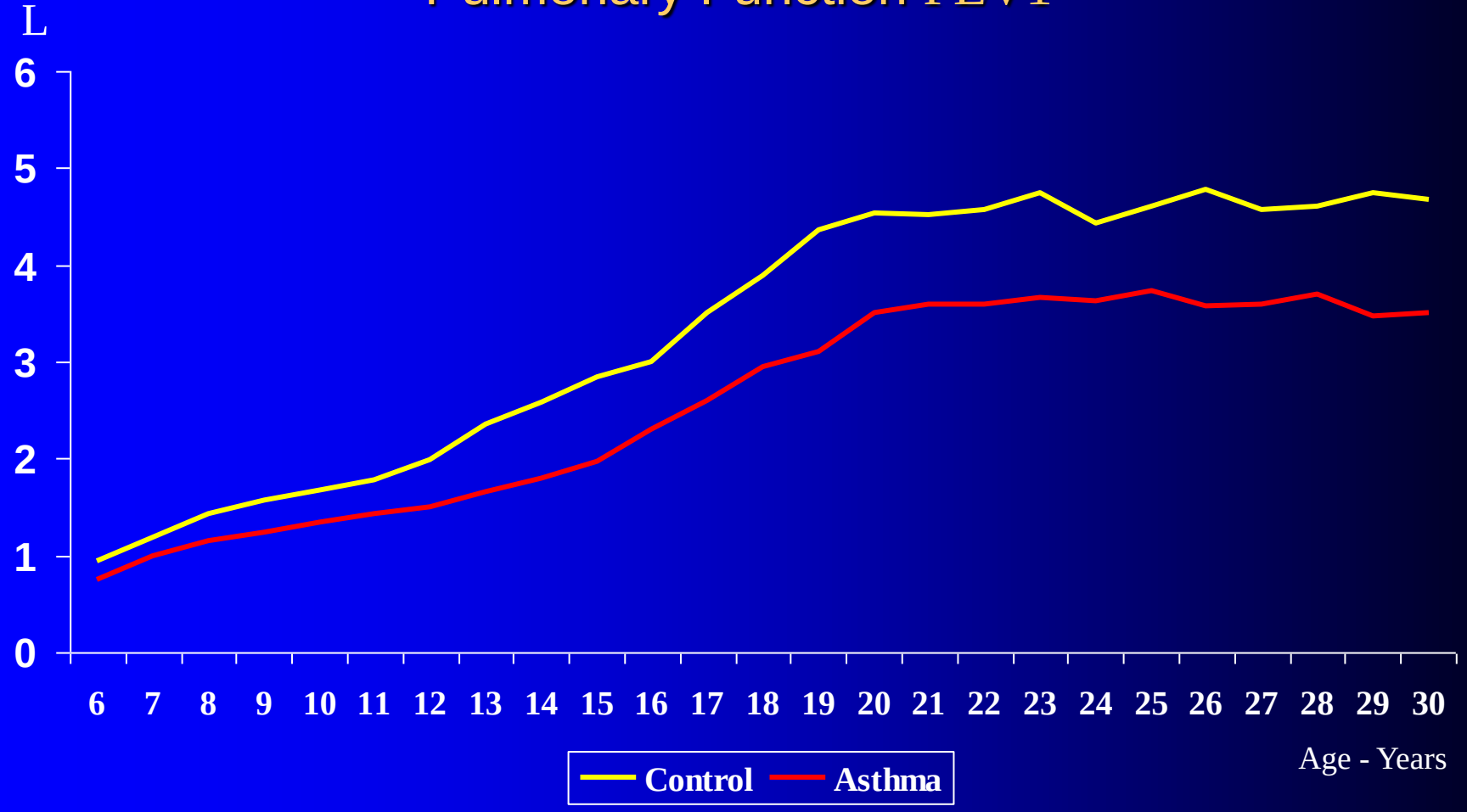


Nunes C et al JIACI, 2002

Cohort of 165 asthmatics children

versus 148 non-asthmatics during 20 years

Pulmonary Function FEV1



Nunes C et al JIACI, 2002

FIG 2. FEV_1 percent predicted at ages 7, 10, 14, 21, 28, 35, and 42 years in subjects in their recruitment groups. *C*, Control; *MWB*, mild wheezy bronchitis; *WB*, wheezy bronchitis; *A*, asthma; *SA*, severe asthma.

Phelan JACI, 2002

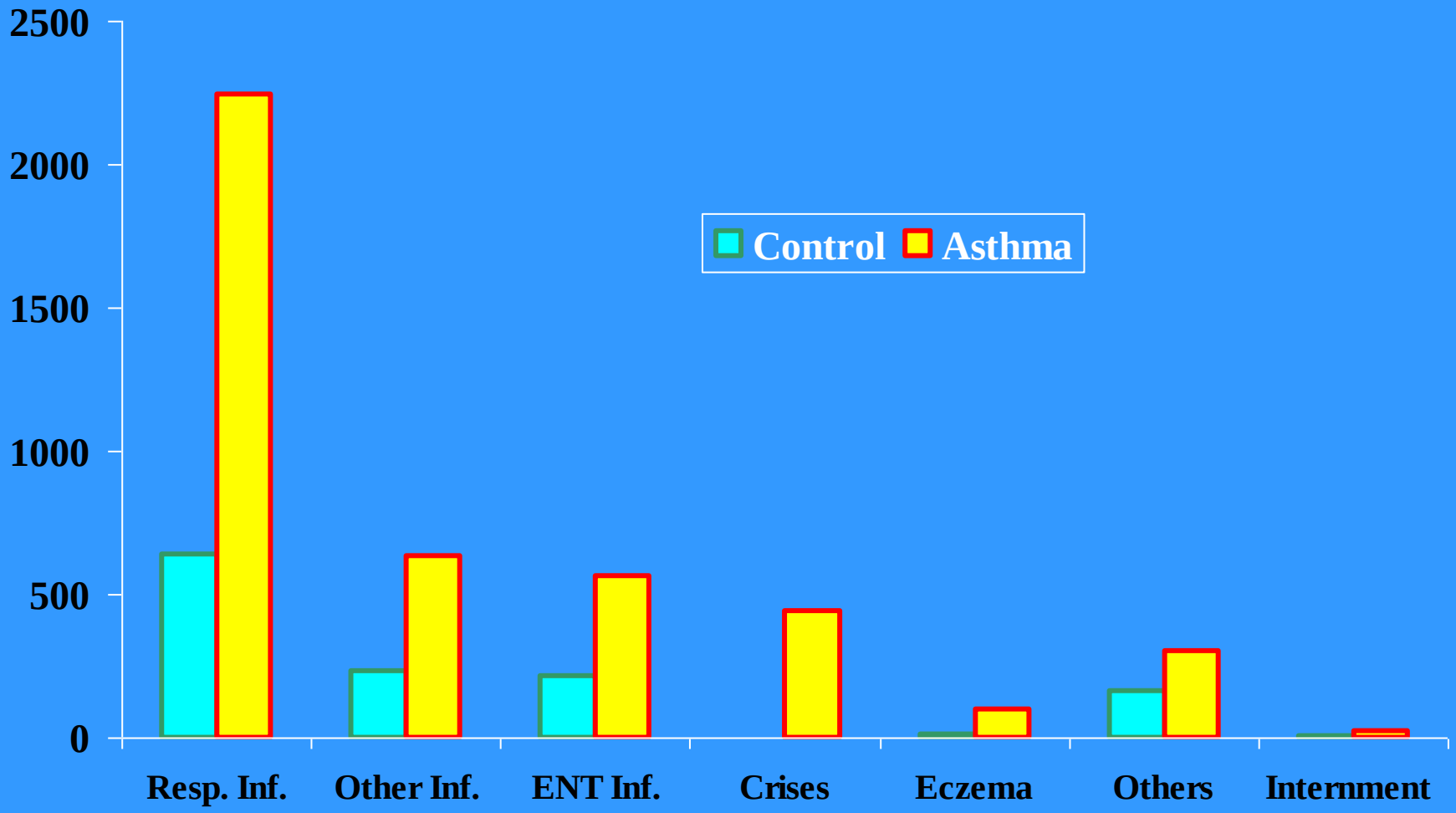
Visits per year/sex/age

Cohort of 165 asthmatics children during 20 years

Morbidity	Male	Female	
Hospitalisations	0.17	0.09	P<0.0.1
Asthma Crises	2.46	1.95	P<0.0.1
Respiratory Inf.	12.18	10.27	P<0.0.5
ENT Infections	2.73	2.90	NS
Other Infections	3.03	3.33	NS
Eczema	0.57	0.43	NS
Others	1.52	1.51	NS

Nunes C et al JIACI, 2002

Clinical observations of a cohort 165 asthmatics versus 148 non-asthmatics during 20 years



Nunes C et al JIACI, 2002

- **In outpatients with moderate and severe asthma the annual mean is 7.4 visits per year. This mean is 3.4 fold of the general population**

- **There is a annual mean of 3.7 visits in mild asthma**

- **There is an annual mean of 0.7 visits to emergency rooms**

- **A mean of 0.04 internments per asthmatic/year**

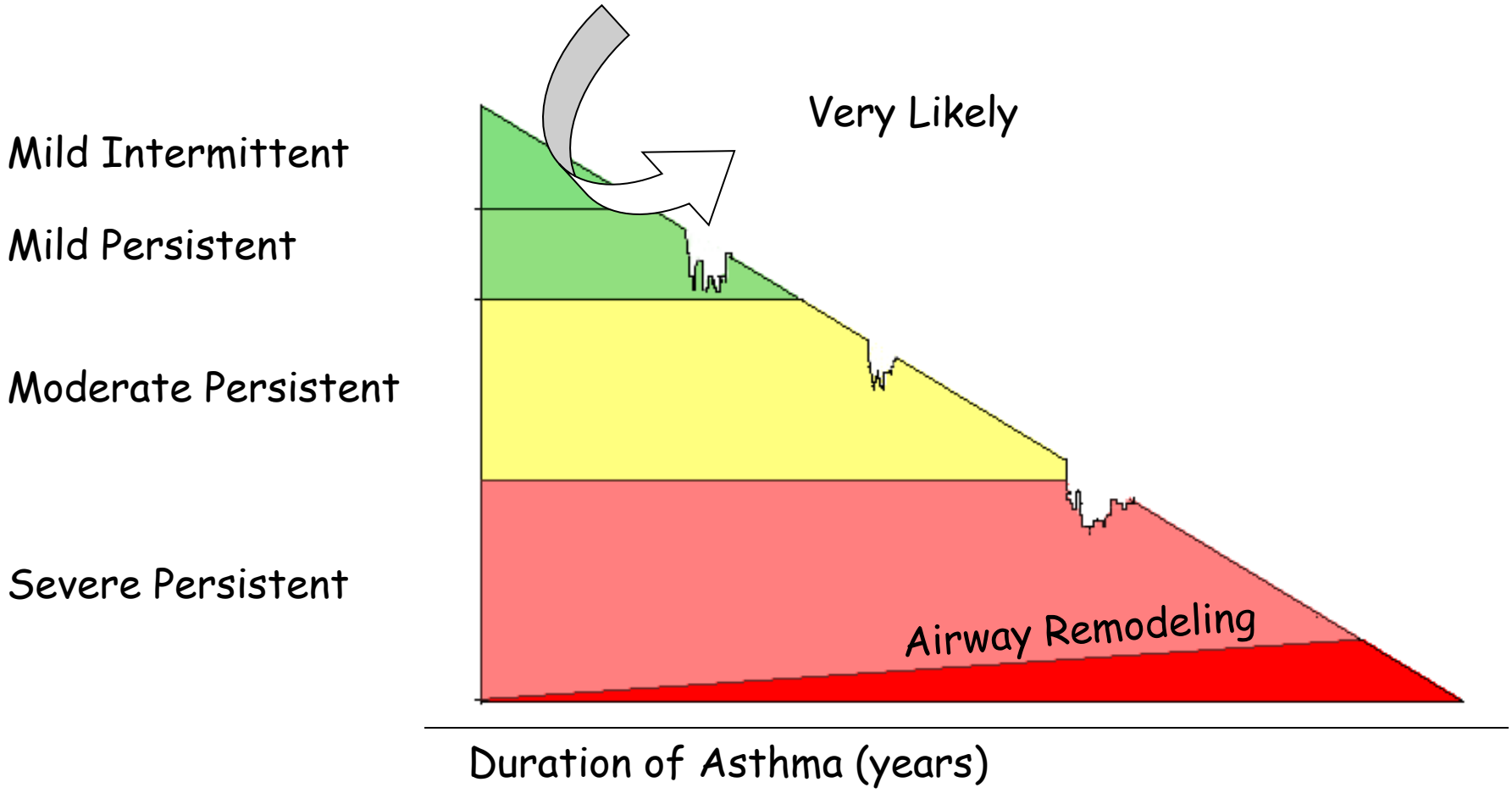
Nunes et al RPIA 2004;12:114-128

Psychological disorders often present in children and adolescents with asthma

	With acute asthma	Asymptomatic
Depression	86.4 %	47.7 %
Anxiety	36.4 %	45.5 %
Overprotection	37.0 %	29.5 %
Isolation	47.0 %	41.7 %
Dependence	85.6 %	47.2 %
Defective Perception	35.2 %	38.6 %

Revino MB ACAI 2006, P124

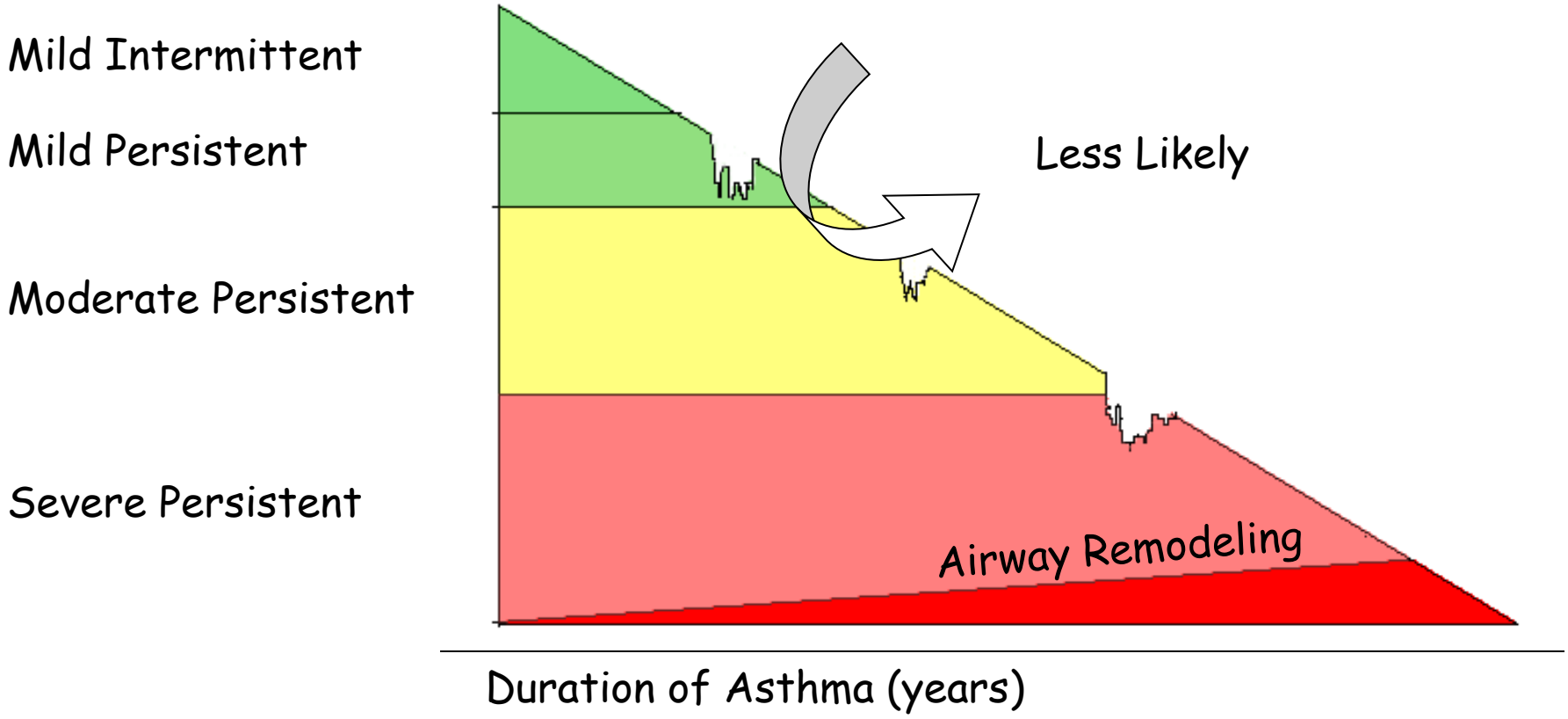
Who Has Asthma Remissions ?



Adapted from: Szefler SJ. Advances in Pediatrics 2000; 47: 273-308

Guerra S et al Am J Resp Crit Care Med 2004; 170: 78-85

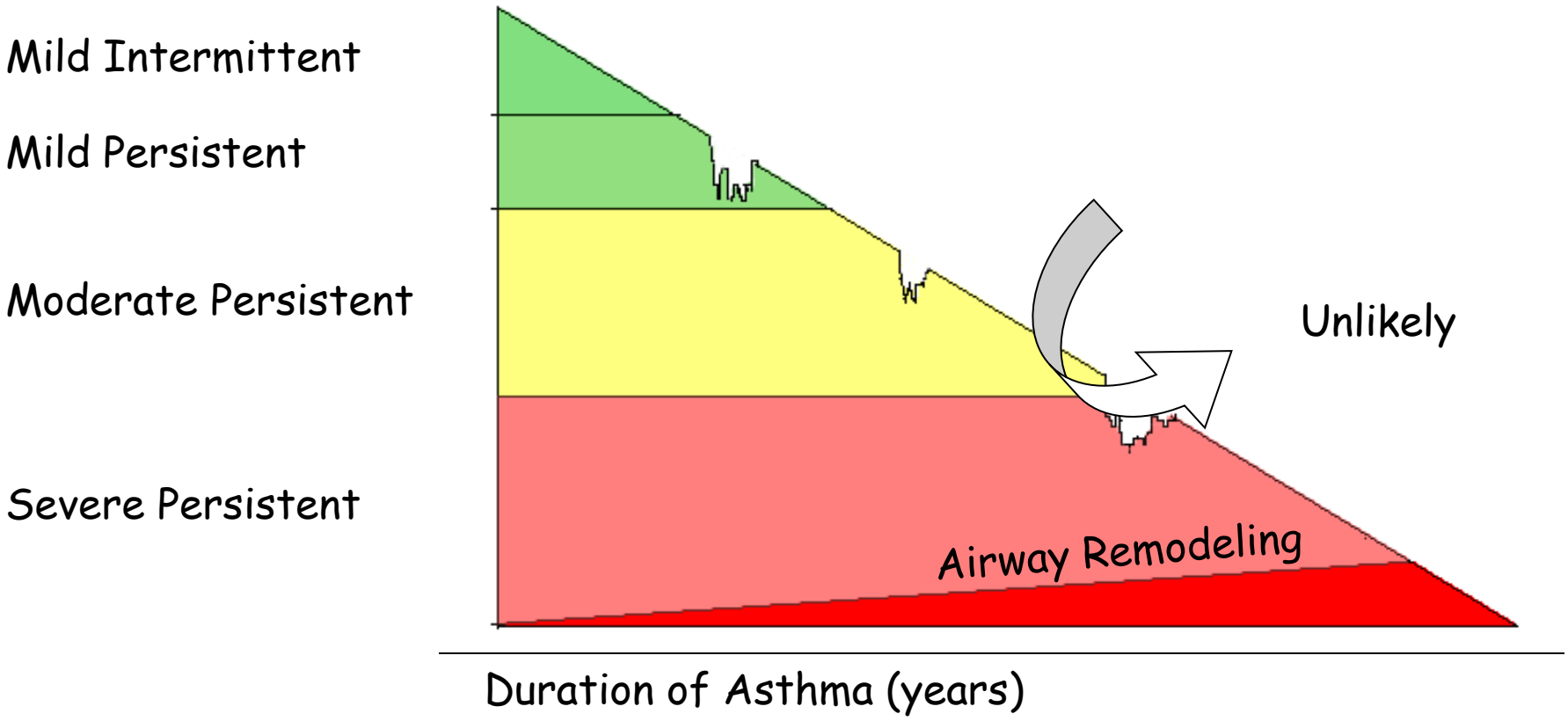
Who Has Asthma Remissions ?



Adapted from: Szefler SJ. Advances in Pediatrics 2000; 47: 273-308

Guerra S et al Am J Resp Crit Care Med 2004; 170: 78-85

Who Has Asthma Remissions ?



Adapted from: Szefler SJ. Advances in Pediatrics 2000; 47: 273-308

Guerra S et al Am J Resp Crit Care Med 2004; 170: 78-85

Conclusions

- **Early intervention with inhaled corticosteroids in childhood asthma reduces morbidity but does not alter the natural history of asthma**
- **Symptom questionnaires are predictive of subsequent asthma episodes in people older than 10 years old, but not in young children**
- **In children with asthma, FEV_1/FVC is a more reliable inclusion criterion for clinical studies as well as an assessment measure for clinical control**

- **Evaluation and management of severe asthma in children include verification of the diagnosis, assessment for coexisting illnesses, and identification of effective treatment strategies directed to adherence, medication delivery, and combination therapy**

- **Responsiveness to asthma treatment is heterogeneous even among patients with asthma of similar severity. This heterogeneity calls attention to the importance of assessing control and adjusting treatment accordingly**

- **We are now moving toward an individualized approach to asthma therapy and searching for biomarkers and genetics as a resource to guide treatment**